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World Journal of Clinical Pediatrics
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
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EDITORIAL

Reducing childhood obesity through coordinated care: Development of a park prescription program

Sarah E Messiah, Sandy Jiang, Jack Kardys, Eric Hansen, Maria Nardi, Lourdes Forster

Sarah E Messiah, Division of Community-Based Research and Training, Mailman Center for Child Development, Department of Pediatrics, Miller School of Medicine, University of Miami, Miami, FL 33130, United States

Sarah E Messiah, Sandy Jiang, Department of Public Health Sciences, Miller School of Medicine, University of Miami, Miami, FL 33130, United States

Jack Kardys, Eric Hansen, Maria Nardi, Miami Dade County Department of Parks, Recreation and Open Spaces, Miami, FL 33128, United States

Lourdes Forster, Department of Pediatrics, Miller School of Medicine, University of Miami, Miami, FL 33130, United States

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Correspondence to: Sarah E Messiah, MPH, PhD, Research Associate Professor and Co-Director of the Division of Community-Based Research and Training, Mailman Center for Child Development, Department of Pediatrics, Miller School of Medicine, University of Miami, 1580 NW 10th Avenue, Miami, FL 33130, United States. smessiah@med.miami.edu
Telephone: +1-305-2431943
Fax: +1-305-2438475

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Abstract

Major hindrances to controlling the current childhood obesity epidemic include access to prevention and/or treatment programs that are affordable, provide minimal barriers for participation, and are available to the general public. Moreover, successful childhood obesity prevention efforts will require coordinated partnerships in multiple sectors such as government, health care, school/afterschool, and the community but very few documented sustainable programs currently exist. Effective, community-based health and wellness programs with a focus on maintaining healthy weight *via* physical activity and healthy eating have the potential to be a powerful referral resource for pediatricians and other healthcare professionals who have young patients who are overweight/obese. The Miami Dade County Department of Parks, Recreation and Open Spaces in partnership with the University of Miami UHealth Systems have created a "Park Prescription Program (Parks Rx 4Health™)" that formally coordinates pediatricians, families, parents, caregivers, and child/adolescents to provide daily obesity-prevention activities. This Parks Rx 4Health™ program that we describe here allows UHealth pediatricians to seamlessly refer their overweight and obese patients to Fit2Play™, an evidence-based, park-based afterschool health and wellness program. Measurable outcomes that include body mass index, blood pressure, fitness, and nutrition knowledge are being collected at baseline and at 3-and 6-mo after referral to document patient progress. Results are then shared with the referring physician so they can follow up with the patient if necessary. Identifying successful

models that integrate primary care, public health, and community-based efforts is important to accelerating progress in preventing childhood obesity. Effective, community-based health and wellness programs with a focus on physical activity and nutrition education could be a powerful referral resource for pediatricians who have obese patients.

Key words: Obesity; Overweight; Prevention; Community-based; Children; Adolescents; Primary care

Core tip: Childhood obesity continues to be a vexing clinical and public health challenge and is an epidemic that will not be solved in silos. Instead, coordinated, collective partnerships in multiple sectors such as government, health care, school/afterschool, the family, and the community give the most promise for sustainability of healthy weight in children and adolescents. The described Parks Rx 4Health™ program will enhance care coordination among pediatricians, families and community-based providers to encourage and monitor overweight/obese youth. It will be increasingly important to capitalize on existing resources such as local park systems to conduct prevention efforts to lower current obesity and related comorbidity trends.

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INTRODUCTION

The United States (US) Department of Health and Human Services' Healthy People 2020 Nutrition and Weight Status health indicator's goal is to "promote health and reduce chronic disease risk through the consumption of healthful diets and achievement and maintenance of healthy body weights"[1]. This initiative identifies the reduction of overweight/obesity during childhood as 1 of 10 leading public-health priorities, yet the prevalence of childhood overweight/obesity in the US continues to be a vexing public health and clinical issue, especially among ethnic minorities and low income underserved subgroups who are at increased risk for adult onset type 2 diabetes and cardiovascular disease[2,3]. For obesity prevention efforts to be successful will require coordinated, collective partnerships in multiple sectors such as government, health care, school/afterschool, workplace, and the community, yet very few sustainable programs currently exist[4].

While coordination of care for childhood obesity prevention efforts are desperately needed, they are severely lacking. Primary care providers (PCPs, such as physicians, physician's assistants, nurse practitioners, and/or registered nurses working in a primary care setting) and professionals working in out-of-school/afterschool-based settings have important roles in meeting national and international obesity prevention goals. PCPs traditionally measure patients' growth and development and treat obesity and health-related conditions, but there is a recognized need to expand these roles to include advocacy, counseling, and referring patients and their families to community-based resources, and communicating with these community-based referrals about patient participation and progress[5,6].

The institute of medicine (IOM) in its 2012 report "Accelerating progress in obesity prevention"[7] includes the goal to "expand the role of health care providers in obesity prevention". Health care providers/PCPs have a role in the following strategies recommended by the IOM to achieve this goal: (1) strategy 4-1: Provide standardized care and advocate for healthy community environments; (2) strategy 4-2: Ensure coverage of, access to, and incentives for routine obesity prevention, screening, diagnosis, and treatment; and (3) strategy 4-3: Encourage active living and healthy eating[7]. Similarly, the US preventive services task force recommendation statement says "PCPs should offer or refer children aged 6 years and older to intensive counseling and behavioral interventions to promote improvements in weight status"[8].

While the physician's role in the identification and recruitment of children and families into obesity prevention or treatment interventions is often cited as important, the literature is limited in terms of existing models that are effective and sustainable. Published studies include primarily family-based counseling and treatment programs, lasting from eight weeks to a few months and include group education sessions for parents and children, home visits, follow-up telephone calls, automated messages, and/or other family-oriented activities[4,9]. Very few incorporate any technology enhancements (*e.g.*, computer/tablet Parks Rx 4Health™ registration, tablet/phone data entry capabilities, healthy text messaging programs) that encourage bi-directional communication between PCPs, families and community-based providers to track progress and attendance, and are designed for low income, ethnic minority groups in particular[10,11]. Yet studies report that parents perceived the community-based program as an extension of their pediatrician's care due to the physician-referral of the program, and follow-up monitoring and care with patients[4].

Park-based afterschool programs have the potential to be an ideal setting for childhood obesity-prevention PCP referrals. How the existence of community parks and their health and wellness programming is related to overall physical activity levels and health of its residents is just now gaining attention in the literature[12]. Another

area of interest nationally is the concept of a "park prescription" program that links the healthcare system and public lands, such as local parks, to create healthier people[13,14]. However, none of these programs to date have: (1) linked PCPs to evidence-based programming in childhood obesity prevention efforts; and (2) have incorporated technology to create bidirectional communication between PCPs and community providers to track patient progress.

To answer the need for affordable and accessible obesity prevention and treatment programs in the community, the University of Miami Miller School of Medicine's (UMMSM) Department of Pediatrics and the Miami Dade County Department of Parks, Recreation and Open Spaces (MDPROS) have collaborated over the past 8 years to successfully develop "Fit2Play™", a 10-mo (entire school year) afterschool health and wellness program that is available to over 1500 low income, urban and suburban children annually at 35 parks in Miami Dade County (approximately 48% Hispanic, approximately 48% non-Hispanic black, mean age 9.3 years). Fit2Play™ provides the ideal PCP-referral given its (1) evidence-based results[15-17]; (2) accessibility; it is offered in multiple locations (35 park locations all over the county); (3) affordability (can be free or sliding scale based on household income but not to exceed $35/wk, which is considerably less than comparable non-evidence based programs offered locally); and (4) acceptability and endorsement by our UMMMSM physicians for referrals. We describe below the formal Park Prescription (Parks Rx 4Health™) model that has been developed from this Fit2Play™ evidence-based work.

STUDY METHODS

Study design

We are currently/prospectively conducting a Parks Rx 4Health™ pilot study that will include a total of 50 families who visit UMMSM Pediatric Clinics (general pediatrics or pediatric endocrinology) and are referred to, and enrolled in the Fit-2-Play™ afterschool program. During this pilot phase, the program is free to families that participate and is financially underwritten and trademarked by MDPROS. This study has been approved by the University of Miami Institutional Review Board. We describe the methods for this program in detail below.

Participants

The UMMSM Pediatric Clinics serve a very rich racially and ethnically diverse population of overweight/obese patients (approximately 1 out of every 3 and 1 out of every 2 ethnic minority patients are overweight/obese). Pediatricians ask patients if they are interested in participating in the Park Rx program if they meet the following inclusion criteria: (1) Child is between the ages of 6 and 14; (2) child body mass index (BMI) percentile is $\geqslant 85^{th}$ %ile for age and sex[18], is physically inactive, has systolic and/or diastolic pre-hypertension or hypertension, or has a strong family history of type 2 diabetes and/or cardiovascular disease; (3) parent is willing to enroll their child in a Fit-2-Play™ program that is located close to their child's school or home and have them attend 5 d/wk (transportation provided); and (4) parent consent for child to participate. If a child has a medical condition that excludes them from the physical fitness testing component of the study then they are not referred to Fit-2-Play™.

PROCEDURES

Initial referral process

Pre-Parks Rx 4Health™ program roll out focus groups among pediatricians identified the initial referral process as a critical point of buy-in for medical team members. They stated that if they had to pick just one key strategy that would increase program success, it would be that the in-house clinical referral process must be (1) seamless; (2) simple; and (3) short (no more than 1 min). Hence, an official Park Prescription website "landing page" was developed (Available from: URL: http://www.miamidade.gov/parks/rx4health.asp) that was loaded on all desktop computers in each patient room. This site can also be accessed *via* tablet, mobile phone, or laptop computer. This page gives specific information on park location, times, and how to live a heart-healthy life. Once the parent chooses the most convenient park location, the physician and family fill out a brief online registration form together (Available from: URL: http://www.miamidade.gov/parks/rx4-contact-form-youth-um.asp) that includes basic patient information. This preliminary registration form is sent electronically to the MDPROS wellness team (a centralized team of 6 health and wellness specialists/coaches). In turn, this team (1) within 24 h verifies that patient has been registered with Fit2Play™ at the pre-identified park; (2) calls and emails/texts each parent with a welcome message; and (3) provide further assistance necessary to complete the registration process. Parents leave the pediatrician's office with additional materials describing the details of the program and MDPROS Health and Wellness staff contact information.

Tracking of patients throughout their enrollment in Fit2Play™

All Park Prescription children have a baseline, 3- and 6-mo assessment battery completed (measurements described in detail below) by the park health and fitness team. In addition, children and parents receive encouraging text messages and emails from both their pediatricians and park coaches as they meet program milestones. Daily attendance is also recorded.

Description of Fit2Play™ afterschool program physical activity and health and wellness/nutrition education components

Fit2Play™ includes (1) 50-60 min of physical activity that incorporates multiple sports (soccer, kickball, flag


Parks Rx 4Health

Health, wellness and fitness report card

Patient's ID# _____ Physician's name _____

Measures	Baseline/Date	Lates/Date
Height	____ / ____	____ / ____
Weight	____ / ____	____ / ____
Blood pressure	____ / ____	____ / ____
Pulse	____ / ____	____ / ____
Circumference measure		
Midarm	____ / ____	____ / ____
Waist	____ / ____	____ / ____
Hip	____ / ____	____ / ____
Skinfold measure		
Tricep	____ / ____	____ / ____
Bicep	____ / ____	____ / ____
Subscapular	____ / ____	____ / ____
Suprailiac	____ / ____	____ / ____
Flexibility		
Sit and reach	____ / ____	____ / ____

Testing and measures - comments

Program attendance - comments

Comments

Figure 1 Park Rx 4Health™ participant health report card.

football, dodgeball) and activities from Sports, Play and Active Recreation for Kids[19,20], an evidenced-based, outcome oriented structured active recreation program for children with a focus on developing and improving motor skills, movement knowledge, and social and personal skills; and (2) a health and wellness/nutrition education component where children participate in 30 min education lessons 1-2/times per week that incorporate EmpowerMe4Life[21], a nutrition education curriculum grounded in the American Heart Association's scientific recommendations in promoting heart-healthy lifestyles. This curriculum promotes being several health messages (physical activity, nutrition, sleep, screen time) and has been expanded over the years to include modules for younger (ages 6-9) and older (ages 10-14) participants that include more in-depth materials.

Closing the communication loop between pediatricians and community-based providers

Every three months, pediatricians receive a patient "report card" (Figure 1) on primary clinical outcome measurements including height, weight and blood pressure. MDPROS Park Health and Wellness staff also include attendance numbers for the pediatrician's review. MDPROS Parks Rx 4Health™ software is pre-programmed to assist with a 6-mo pediatrician follow-up visit and sends pediatrician, parent and park staff scheduling reminders. This entire referral and follow-up process is shown visually in Figure 2.

MEASURES

Individual-level measures

MDPROS Parks Rx 4Health™ software is programmed to collect/track the following measures on the children referred to Fit2Play™:

Demographic questionnaire: A baseline questionnaire captures (1) age, sex, and race/ethnicity for children and parents; (2) parent medical history; and (3) any other relevant medical and/or personal history (*e.g.*, previous sports injuries, allergies); all of the following measures are taken at baseline and at the follow-ups.

Height and weight: Height (by stadiometer) and weight (by digital scale) are converted to age and sex adjusted BMI scores and percentiles[18,22].

Waist and hip circumference: Waist and hip circumferences are measured to the nearest 0.1 cm using a non-stretchable plastic tape measure by a standard method[23]. Waist circumference is measured over the

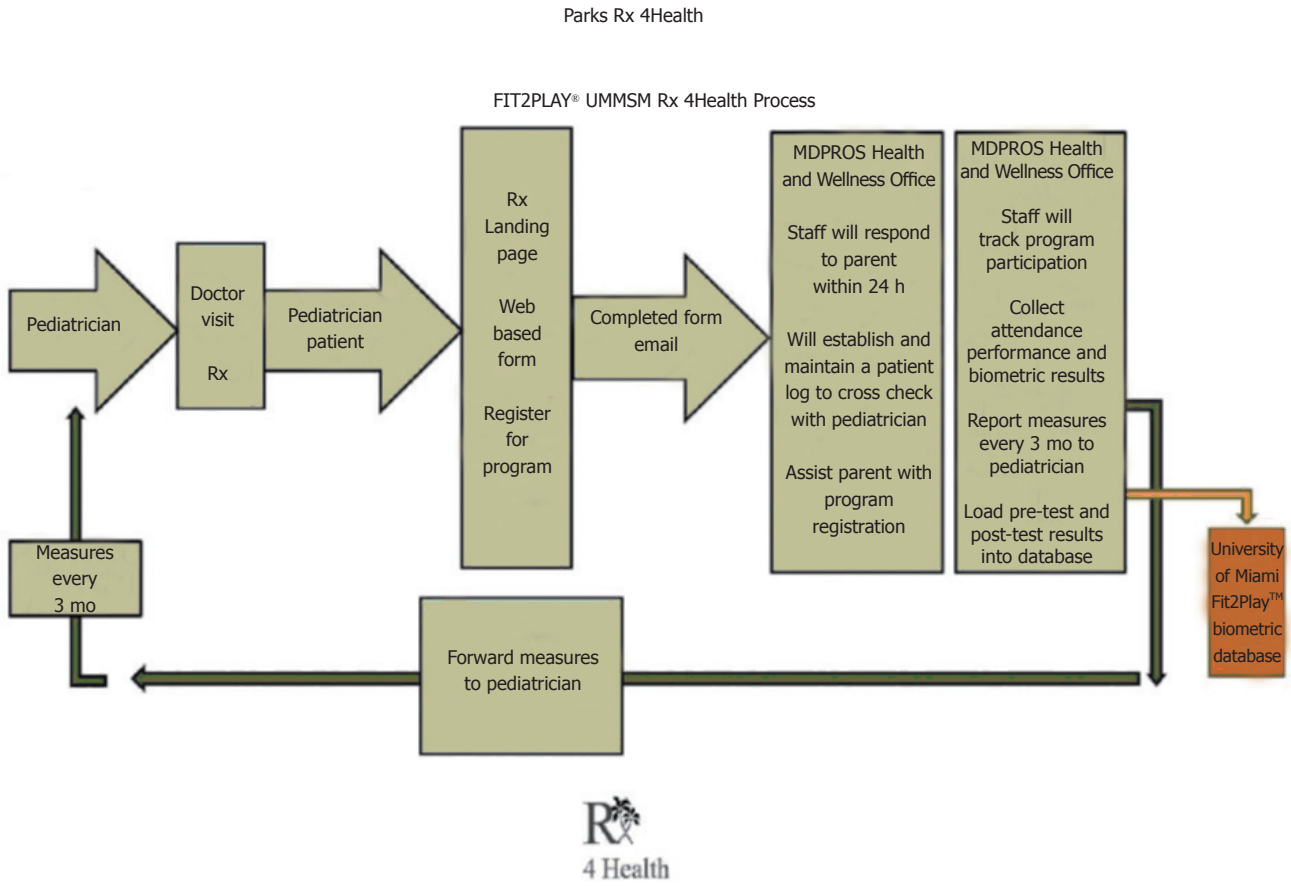

Figure 2 Park Rx 4Health™ project flow.

navel at the end of gentle exhalation and hip circumference is measured at the maximum circumference over the buttocks. A total of three waist and hip circumference measures are taken for each child and the average used for the analysis.

Skinfold measurements: Bicep, triceps, subscapular, and suprailiac skinfold thicknesses are measured to the nearest 0.1 mm following standard procedures[22]. These 4 thickness values are combined and analyzed using the Durnin formula to estimate percent body fat[24].

Blood pressure: Blood pressure is taken using the American Heart Association Guidelines[25]. Each child has a total of 3 blood pressure measurements taken where the first one is dropped and the second two are averaged for analysis[26].

Physical fitness: The following battery of physical fitness tests[27] is conducted: (1) Sit and Reach[28]. The child sits on the floor with legs extended straight in front. Feet are placed against the front of the test box and are approximately 6 inches apart. The subject extends the arms forward, placing the index fingers of both hands together with knees straight. The score is the most distant point reached by the fingertips in the best of 3 trials; (2) Progressive Aerobic Cardiovascular Endurance Run (PACER) test[29]. The PACER test is a maximal aerobic fitness test and is a timed fitness run test. The test involves continuous running between the two lines in time to recorded beeps. The time between recorded beeps decrease each minute (level) requiring an increase in pace. The subjects continue until they are unable to keep pace with the beeps. Participants are compared to established national standards; (3) Timed Sit-ups[27]. For the sit-up test the child lies with knees bent and arms across the chest. The participant will complete as many sit-ups as possible in the 60 s allotted time period; (4) Timed Push-ups[27]. For the push-up test the participant completes as many push-ups as possible in the 60 s allotted time period; and (5) 400 Meter Run[27]. Shorter distance runs are included as options for younger children. Younger children can be prepared to run the mile (6-7 year olds - ¼ mile; 8-9 years old - ½ mile).

Mental health measures: The following 3 assessments are administered at initial enrollment and at the end of the school year or at the 6-mo follow-up only; (1) Rosenberg Self Esteem Scale[30], a simple 10 item questionnaire asking participants on a 4-level Likert Scale about how they feel about themselves. Self-esteem is one measure of a children's overall mental health; (2) Social Anxiety Scale for Adolescents[31], a 22-item questionnaire that assesses participant's level of social anxiety (how much they worry about what others

Table 1 Abbreviated reach, effectiveness/efficacy, adoption, implementation, and maintenance item(s) and methods/approach/measure

Study topic area: Childhood obesity prevention *via* coordination of care, Parks Rx 4Health™	Study setting: Pediatric Primary Care Clinics, MDPROS-based afterschool Fit2Play™ program
Dimensions/item	Method/approach/measure
Reach	
Characteristics of participants compared to non-participants or to target population	Proportion of family/patient referrals who register for Fit2Play™, continue to participate for entire 6 mo Proportion of pediatricians who make referrals *via* Parks Rx 4Health™
Effectiveness	
Measure of primary outcome with or w/o comparison to a public health goal	Proportion of youth participants who improve in above listed individual measures (BMI, BP, fitness, *etc.*)
Measure of broader outcomes (*e.g.*, other outcomes, measure of life improvements, or potential negative outcome)	Mean improvement of cardiovascular health, physical activity levels, anthropometrics; satisfaction with Parks Rx 4Health™ program
Adoption-setting level	
Characteristics of settings participating (comparison and intervention) compared to either: non participants or relevant resource data	Overall satisfaction with Parks Rx 4Health™ program (pediatrician referral process, Fit2Play™ program, family/child Fit2Play™ participants/completers *vs* non-completers)
Use of qualitative methods to understand adoption at setting level	Focus group with pediatricians, park coaches and children; process evaluation with pediatricians, park coaches and parents
Implementation	
Percent of perfect delivery (adherence or consistency)	Pediatrician and Parent Satisfaction Survey, Parks Rx 4Health™ adherence measure
Adaptations made to intervention during study	Focus groups with pediatricians and park coaches at end of study
Maintenance - individual level	
Measure of primary outcome at follow-up after final intervention contact	Proportion of children participants who continue in Fit2Play™ Proportion of pediatricians who make Parks Rx 4Health™ referrals
Qualitative data to understand long -term effects	Pediatrician, Family and Park Health and Wellness Coaches Satisfaction Survey
Maintenance - setting level	
Program is ongoing at ⩾ 6 mo post-study funding	Proportion of pediatricians using Parks Rx 4Health™ 3-mo post-pilot phase
Some measure/discussion of alignment to organization mission or sustainability	Adoption of Parks Rx 4Health™ program by the National Recreation and Park Association, promotion by the American Academy of Pediatrics

MDPROS: Miami Dade County Department of Parks, Recreation and Open Spaces; BMI: Body mass index.

think of them, *etc.*). Social anxiety disorder is common among youth, often emerging during adolescence and the benefits of participating in a park-based group afterschool program have not been previously described; and the (3) pediatric Quality of Life Inventory ™[32] that assesses how the participant currently feels about their overall quality of life. The utility of pediatric quality of life measurement in population health outcome evaluation from the perspective of children in large pediatric populations has several distinct benefits beyond the clinical setting but has been largely unexplored in a park-based setting.

Process measures

Process measures are a priority as they are key in tracking the uptake of implementation (Table 1). Data are collected from pediatricians, park health and wellness specialists/coaches, and families (parents and child participants) by observations, self-report satisfaction surveys, focus groups, questionnaires and process surveys.

It is critical that obesity prevention coordination efforts are guided by a clear framework. The reach, effectiveness/efficacy, adoption, implementation, and maintenance (RE-AIM) framework, highly compatible with development of community-based public health interventions[33-37] is used to guide our integration and dissemination of the Parks Rx 4Health™ program. The dimensions of the framework, (1) reach (the absolute number, proportion, and representativeness of individuals who are willing to participate); (2) effectiveness (impact of an intervention on outcomes, including potential negative effects, quality of life, and economic outcomes); (3) adoption (absolute number, proportion, representativeness of settings and intervention agents willing to initiate a program); (4) implementation (intervention agents' fidelity to various elements of an intervention's protocol including consistency of delivery as intended, intervention time and cost); and (5) maintenance (extent to which a program/policy becomes institutionalized or part of the routine organizational practices and policies, but also has individual-level outcomes) all have applicability to the Parks Rx 4Health™ program.

RE-AIM was initially designed to help evaluate interventions and public health programs, to produce a more balanced approach to internal and external validity, and to address key issues important for dissemination and generalization[33]. RE-AIM has been applied to policies[34,35] and community-based multilevel interventions[36], and to reduce health disparities in previous studies[37]. Within this framework, it has been recommended that childhood obesity interventions use multiple disciplines and perspectives in creating and implementing programs, integrate research and practice partnerships, and assess the potential of intervention

strategies to reduce health disparities[36,37]. To date, the complexity of the community-based childhood obesity prevention intervention implementation process has not been well-studied or understood, especially in highly diverse communities. This is true particularly in low resource setting and for populations traditionally underrepresented in obesity prevention research, for which dissemination and implementation may not be a simple process, particularly when multiple entities are involved (PCPs, community-based programs, families)[37].

Data analysis

Proportions and means are the primary scales of the dependent outcomes used to evaluate program outcomes. While not the only statistical approach available, we chose to use the generalized linear model (GZLM) to model the impact of the Parks Rx 4Health™ program for all the dependent effects. We chose this specific approach because much like the general linear model that allows for variation in type and scale characteristics of the independent effects, the GZLM extends this versatility to include various types of dependent variables. Rather than applying different statistical techniques based on the scale properties of the dependent variables (*e.g.*, analysis of variance for continuous data, contingency tables for proportion, *etc.*), the GZLM model accounts for the scale type of the dependent variable *via* model specification. The relationship between the independent variables and the dependent outcomes are specified by way of a link function that defines the functional form of this relationship (*e.g.*, when the dependent variable is a proportion, a logistic link function might be used). Through different specifications of the link and probability functions, one generalized model is used to examine the statistical relationships between the design parameters (*i.e.*, independent variables) and the dependent variables, regardless of their scale properties. Additionally, statistical consideration is given to repeated measures which needs to be considered in the current Park Rx 4Health model. One of the major benefits of the program to pediatricians is that they can track how their patient is doing in the program throughout the school year and thus they request multiple data collection time points. Although an additional independent factor (*i.e.*, time) can be included in the GZLM (*i.e.*, generalized mixed model), the results may be better interpreted when analyzed as separate short and long-term models. This is an important issue in the current model, because the time lapse between the pre- and post-test measurement will vary by patient, and thus the introduction of an interim value may be important.

Measures taken at baseline will be included in the GZLM as covariates to insure pretest balance and as a control on regression to the mean. In studies involving weight loss or change, initial weight is a covariate that is often included in the statistical model since weight gain or loss is correlated with initial values. This dictates a statistical approach to the data analysis which accounts for the difference scores from baseline to post-treatment measurements as the dependent outcome using the baseline measurement as the covariate. SAS and JMP (SAS Institute, Cary, NC) are the primary statistical software packages used for all analyses.

Quality control

To ensure Park Rx program quality control, the following strategies are implemented: (1) MDPROS field staff are properly trained in standardized Parks Rx 4Health™ methods of outcome measures and data collection; (2) activities, personnel, data and the database are well-organized and maintain proper documentation; and (3) all required reports to physicians are delivered in a timely manner. Appropriate data safety checks are conducted prior to, during, and after the completion of data collection activities such as adding upper and lower bounds to the possible ranges of outcome variables to decrease the incidence of data entry error. Prior to the initiation of any data collection, pilot runs involving measurement and data collection and entry mockups are used to establish process capability. Finally, MDPROS field teams conduct weekly field audits to ensure that all Parks Rx 4Health™ data are recorded correctly and completely.

Lessons learned

There have been many important lessons learned as we continue in our roll out pilot phase of the UMMSM-MDPROS Parks Rx 4Health™ program. At both a pre- and 4-mo follow-up focus group, our pediatrician team emphasized the importance of (1) a seamless and quick referral process and (2) receiving follow-up information on their patients to keep them engaged in the program. Because it is typical for a pediatrician to see their patients only once a year, the Parks Rx 4Health™ program provides a significant incentive for their participation to learn about not only if they are consistently engaging in a healthy weight program, but they are gaining health benefits as well.

Another critical lesson learned is the importance of fluid team communication among the clinical, research and parks team members. During the first week of Parks Rx 4Health™ roll out, the pediatrician team was experiencing a technical difficulty with the web-based registration form. This was quickly resolved by the MDPROS team through one simple telephone call. Communication between MDRPOS staff and Parks Rx 4Health™ families and their children is also a critical component of program success. Parents like to hear their children are enjoying the program, and improving their health, as supported by their family pediatrician. Our Parks Rx 4Health™ children like to hear they are doing well and enjoy being encouraged daily to pursue personal health goals.

Future plans

Our UMMSM-MDPROS Parks Rx 4Health™ program will begin Phase Ⅱ with summer 2016 referrals for the

2016-2017 school year. Additional components that will be included in this phase are (1) a 2-min video loop that will play in all patient rooms for parents/families to view that will feature children participating in Fit2Play™ and describe their experiences during the program; (2) weekly nutrition and health and wellness materials that will go home on Fridays with Parks Rx 4Health™ participants. Each week will feature one key nutrition and/or physical activity message; (3) the expansion of the UMMSM-MDPROS Parks Rx 4Health™ website to include supplemental health and wellness materials and resources for families to access at any time; (4) family-based activities on weekends and after hours that both parents and children can participate in as a family. This is one of the major advantages of conducting such a program in a large urban parks system; the variety of activities available at minimum to no-cost while enjoying nature and the outdoors; and (5) the option of a consultation visit with a UMMSM faculty member to discuss family health and wellness goals and strategies to meet these goals.

Another area of scientific interest to the team is the contribution of genetics *vs* environment to the current childhood obesity epidemic, particularly because our patient population is so ethnically diverse and most have family origins from outside the United States. Genome-wide association studies in pediatric populations have produced evidence to indicate a genetic component involvement in the occurrence and development of obesity[38-41]. In particular, the fat mass and obesity-associated gene (*FTO*) has received increased attention for being associated with the development of obesity[42]. A recent meta-analysis of 12 studies (that included 5000 cases and 9853 controls) has shown that the FTO rs9939609 polymorphism is associated with the increased risk of obesity among children and adolescents[43]. However, the major proportion of study subjects were Caucasian, and FTO polymorphism have actually been shown to not affect BMI or the risk of obesity in African Americans[41], a population who has been consistently shown to be at greater risk for obesity *vs* Caucasians[2,3]. Given that the overwhelming majority of Park Rx 4Health patients are not Caucasian, and about half are non-Hispanic black, one must consider that the patient's environment is having a greater impact on their weight than their genetic predisposition. For example, studies have shown that physical activity (*vs* sedentary behavior) counters the genetic predisposition to obesity[44]. These findings have major implications to the Park Rx 4Health program because its referral program Fit2Play™ has daily non-stop physical activity as its cornerstone. So, perhaps if we do capture patients with a genetic predisposition to obesity we can influence a gene-environment interaction by keeping them consistently physically active during the pediatric years. While the literature on obesity-related gene-environment interactions is still immature, it will no doubt be an area of much scientific inquiry in the future as obesity continues to spread around the globe.

Park Rx 4Health™ impact

Our UMMSM-MDPROS Parks Rx 4Health™ program described here will move us closer to accomplishing the following Healthy People goals set by the State of FL: Goal 1: Help all children meet their full potential ("making sure children develop healthfully with regard to height, weight, *etc.*); Goal 2: Reduce mortality and morbidity in children (particularly from such chronic diseases as type 2 diabetes and cardiovascular disease); and Goal 3: Reduce disparities in child health outcomes[1]. Moreover, Section 4004(i) of the Affordable Care Act requires the Department of Health and Human Services to provide guidance to States regarding preventive and obesity-related services available to individuals enrolled in Medicaid/Children's Health Insurance Program[45]. It also requires States to design public awareness campaigns to educate Medicaid enrollees, as well as those with other insurance carriers on the availability and coverage of such services. The Park Rx 4Health™ program described here can help close the gap between patient needs and prevention service providers[46].

CONCLUSION

Identifying successful models that integrate primary care, public health and community-based efforts is important to accelerating progress in preventing childhood obesity. Effective, community-based health and wellness programs with a focus on physical activity and nutrition education could be a powerful referral resource for pediatricians who have obese patients.

REFERENCES

1 **Office of Disease Prevention and Health Promotion**. Disability and Health. Available from: URL: http://www.healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=9

2 **Ogden CL**, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA* 2014; **311**: 806-814 [PMID: 24570244 DOI: 10.1001/jama.2014.732]

3 **Ogden CL**, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity among adults: United States, 2011-2012. *NCHS Data Brief* 2013; **(131)**: 1-8 [PMID: 24152742]

4 **Vine M**, Hargreaves MB, Briefel RR, Orfield C. Expanding the role of primary care in the prevention and treatment of childhood obesity: a review of clinic- and community-based recommendations and interventions. *J Obes* 2013; **2013**: 172035 [PMID: 23710345 DOI: 10.1155/2013/172035]

5 **Krebs NF**, Jacobson MS. Prevention of pediatric overweight and obesity. *Pediatrics* 2003; **112**: 424-430 [PMID: 12897303 DOI: 10.1542/peds.112.2.424]

6 **Barlow SE**, Dietz WH, Klish WJ, Trowbridge FL. Medical evaluation of overweight children and adolescents: reports from pediatricians, pediatric nurse practitioners, and registered dietitians. *Pediatrics* 2002; **110**: 222-228 [PMID: 12093999]

7 **Committee on Accelerating Progress in Obesity Prevention and Institute of Medicine**. Accelerating progress in obesity prevention: Solving the weight of the nation. Washington, DC: National Academies Press, 2012

8 **Barnes M**. Solving the problem of childhood obesity within a generation. Whitehouse Task Force on Childhood Obesity, 2010

9 **Perrin EM**, Finkle JP, Benjamin JT. Obesity prevention and the primary care pediatrician's office. *Curr Opin Pediatr* 2007; **19**:

354-361 [PMID: 17505200 DOI: 10.1097/MOP.0b013e328151c3e9]
10 **Gance-Cleveland B**, Gilbert LH, Kopanos T, Gilbert KC. Evaluation of technology to identify and assess overweight children and adolescents. *J Spec Pediatr Nurs* 2010; **15**: 72-83 [PMID: 20074114 DOI: 10.1111/j.1744-6155.2009.00220.x]
11 **Khaylis A**, Yiaslas T, Bergstrom J, Gore-Felton C. A review of efficacious technology-based weight-loss interventions: five key components. *Telemed J E Health* 2010; **16**: 931-938 [PMID: 21091286 DOI: 10.1089/tmj.2010.0065]
12 **West ST**, Shores KA, Mudd LM. Association of available parkland, physical activity, and overweight in America's largest cities. *J Public Health Manag Pract* 2012; **18**: 423-430 [PMID: 22836533 DOI: 10.1097/PHH.0b013e318238ea27]
13 **Institute at the Golden Gate**. Park Prescriptions. Profiles and resources for good health from the great outdoors. [retrieved 2016 Jan 9]. Available from: URL: http://www.parksconservancy.org/assets/programs/igg/pdfs/park-prescriptions-2010.pdf
14 **National Recreation and Park Association**. Park Prescriptions. [retrieved 2016 Jan 9]. Available from: URL: http://www.nrpa.org/Grants-and-Partners/Recreation-and-Health/Park-Prescriptions/
15 **Messiah SE**, Diego A, Kardys J, Kirwin K, Hanson E, Nottage R, Ramirez S, Arheart KL. Effect of a park-based after-school program on participant obesity-related health outcomes. *Am J Health Promot* 2015; **29**: 217-225 [PMID: 24460001 DOI: 10.4278/ajhp.120705-QUAN-327]
16 **Haney K**, Messiah SE, Arheart KL, Hanson E, Diego A, Kardys J, Kirwin K, Nottage R, Ramirez S, Somarriba G, Binhack L. Park-based afterschool program to improve cardiovascular health and physical fitness in children with disabilities. *Disabil Health J* 2014; **7**: 335-342 [PMID: 24947575 DOI: 10.1016/j.dhjo.2014.02.006]
17 **Messiah SE**, Arheart KL, Somarriba G, Diego A, Kardys J, Kirwin K, Hansen E, Nottage R, Ramirez S, Armstrong JH. How one of our nation's greatest resources can help children maintain healthy weight and cardiovascular fitness: It starts in the parks (Feature platform presentation to the American Public Health Association Meeting; 2014 Nov 15-19. LA: New Orleans, 2014)! Available from: URL: http//xueshu.baidu.com/s?wd=paperuri:(2f915938159918c25434e347a6ea8330)&filter=sc_long_sign&sc_ks_para=q=How+One+of+our+Nation's+Greatest+Resources+Can+Help+Children+Maintain+Healthy+Weight+and+Cardiovascular+Fitness:+It+Starts+in+the+Parks!&tn=SE_baiduxueshu_c1gjeupa&ie=utf-8&sc_us=17266751060184562072
18 **Kuczmarski RJ**, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Wei R, Curtin LR, Roche AF, Johnson CL. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11* 2002; **(246)**: 1-190 [PMID: 12043359]
19 **McKenzie TL**, Sallis JF, Rosengard P. Beyond the stucco tower: Design, development, and dissemination of the SPARK physical education programs. *Quest* 2009; **61**: 114-127 [DOI: 10.1080/00336297.2009.10483606]
20 **Sallis JF**, McKenzie TL, Alcaraz JE, Kolody B, Faucette N, Hovell MF. The effects of a 2-year physical education program (SPARK) on physical activity and fitness in elementary school students. Sports, Play and Active Recreation for Kids. *Am J Public Health* 1997; **87**: 1328-1334 [PMID: 9279269 DOI: 10.2105/AJPH.87.8.1328]
21 **Alliance for a Healthier Generation**. [accessed 2016 Mar 8]. Available from: URL: http: //www.healthiergeneration.org
22 **Centers for Disease Control and Prevention**. National Health and Nutrition Examination Survey. Anthropometry Procedures Manual. 2007. Available from: URL: http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf
23 **Chumlea NC**, Kuczmarski RJ. Using a bony landmark to measure waist circumference. *J Am Diet Assoc* 1995; **95**: 12 [PMID: 7798573 DOI: 10.1016/S0002-8223(95)00003-8]
24 **Durnin JV**, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *Br J Nutr* 1974; **32**: 77-97 [PMID: 4843734 DOI: 10.1079/BJN19740060]
25 **Urbina E**, Alpert B, Flynn J, Hayman L, Harshfield GA, Jacobson M, Mahoney L, McCrindle B, Mietus-Snyder M, Steinberger J, Daniels S. Ambulatory blood pressure monitoring in children and adolescents: recommendations for standard assessment: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee of the council on cardiovascular disease in the young and the council for high blood pressure research. *Hypertension* 2008; **52**: 433-451 [PMID: 18678786 DOI: 10.1161/HYPERTENSIONAHA.108.190329]
26 **National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents**. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 2004; **114**: 555-576 [PMID: 15286277]
27 **President's Council on Physical Fitness and Sports**. 1985 National School Population Fitness Survey. Washington, DC: US Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, 1986
28 **Rosenberg M**. Society and the adolescent self-image. Princeton, NJ: Princeton University Press, 1965
29 **La Greca AM**, Lopez N. Social anxiety among adolescents: linkages with peer relations and friendships. *J Abnorm Child Psychol* 1998; **26**: 83-94 [PMID: 9634131]
30 **Varni JW**, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* 2001; **39**: 800-812 [PMID: 11468499]
31 **Castro-Piñero J**, Chillón P, Ortega FB, Montesinos JL, Sjöström M, Ruiz JR. Criterion-related validity of sit-and-reach and modified sit-and-reach test for estimating hamstring flexibility in children and adolescents aged 6-17 years. *Int J Sports Med* 2009; **30**: 658-662 [PMID: 19585399 DOI: 10.1055/s-0029-1224175]
32 **Léger LA**, Lambert J. A maximal multistage 20-m shuttle run test to predict VO2 max. *Eur J Appl Physiol Occup Physiol* 1982; **49**: 1-12 [PMID: 7201922 DOI: 10.1007/BF00428958]
33 **Gaglio B**, Shoup JA, Glasgow RE. The RE-AIM framework: a systematic review of use over time. *Am J Public Health* 2013; **103**: e38-e46 [PMID: 23597377 DOI: 10.2105/AJPH.2013.301299]
34 **Glasgow RE**, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health* 1999; **89**: 1322-1327 [PMID: 10474547 DOI: 10.2105/AJPH.89.9.1322]
35 **Jilcott S**, Ammerman A, Sommers J, Glasgow RE. Applying the RE-AIM framework to assess the public health impact of policy change. *Ann Behav Med* 2007; **34**: 105-114 [PMID: 17927550 DOI: 10.1007/BF02872666]
36 **Glasgow RE**, Dickinson P, Fisher L, Christiansen S, Toobert DJ, Bender BG, Dickinson LM, Jortberg B, Estabrooks PA. Use of RE-AIM to develop a multi-media facilitation tool for the patient-centered medical home. *Implement Sci* 2011; **6**: 118 [PMID: 22017791 DOI: 10.1186/1748-5908-6-118]
37 **Glasgow RE**, Askew S, Purcell P, Levine E, Warner ET, Stange KC, Colditz GA, Bennett GG. Use of RE-AIM to Address Health Inequities: Application in a low-income community health center based weight loss and hypertension self-management program. *Transl Behav Med* 2013; **3**: 200-210 [PMID: 23750180 DOI: 10.1007/s13142-013-0201-8]
38 **Dina C**, Meyre D, Gallina S, Durand E, Körner A, Jacobson P, Carlsson LM, Kiess W, Vatin V, Lecoeur C, Delplanque J, Vaillant E, Pattou F, Ruiz J, Weill J, Levy-Marchal C, Horber F, Potoczna N, Hercberg S, Le Stunff C, Bougnères P, Kovacs P, Marre M, Balkau B, Cauchi S, Chèvre JC, Froguel P. Variation in FTO contributes to childhood obesity and severe adult obesity. *Nat Genet* 2007; **39**: 724-726 [PMID: 17496892 DOI: 10.1038/ng2048]
39 **Loos RJ**, Bouchard C. FTO: the first gene contributing to common forms of human obesity. *Obes Rev* 2008; **9**: 246-250 [PMID: 18373508 DOI: 10.1111/j.1467-789X.2008.00481.x]
40 **Liu C**, Mou S, Cai Y. FTO gene variant and risk of overweight and obesity among children and adolescents: a systematic review and meta-analysis. *PLoS One* 2013; **8**: e82133 [PMID: 24278475 DOI: 10.1371/journal.pone.0082133]
41 **Scuteri A**, Sanna S, Chen WM, Uda M, Albai G, Strait J, Najjar S,

Nagaraja R, Orrú M, Usala G, Dei M, Lai S, Maschio A, Busonero F, Mulas A, Ehret GB, Fink AA, Weder AB, Cooper RS, Galan P, Chakravarti A, Schlessinger D, Cao A, Lakatta E, Abecasis GR. Genome-wide association scan shows genetic variants in the FTO gene are associated with obesity-related traits. *PLoS Genet* 2007; **3**: e115 [PMID: 17658951 DOI: 10.1371/journal.pgen.0030115]

42 **Frayling TM**, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, Perry JR, Elliott KS, Lango H, Rayner NW, Shields B, Harries LW, Barrett JC, Ellard S, Groves CJ, Knight B, Patch AM, Ness AR, Ebrahim S, Lawlor DA, Ring SM, Ben-Shlomo Y, Jarvelin MR, Sovio U, Bennett AJ, Melzer D, Ferrucci L, Loos RJ, Barroso I, Wareham NJ, Karpe F, Owen KR, Cardon LR, Walker M, Hitman GA, Palmer CN, Doney AS, Morris AD, Smith GD, Hattersley AT, McCarthy MI. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* 2007; **316**: 889-894 [PMID: 17434869 DOI: 10.1126/science.1141634]

43 **Quan LL**, Wang H, Tian Y, Mu X, Zhang Y, Tao K. Association of fat-mass and obesity-associated gene FTO rs9939609 polymorphism with the risk of obesity among children and adolescents: a meta-analysis. *Eur Rev Med Pharmacol Sci* 2015; **19**: 614-623 [PMID: 25753879]

44 **Andreasen CH**, Stender-Petersen KL, Mogensen MS, Torekov SS, Wegner L, Andersen G, Nielsen AL, Albrechtsen A, Borch-Johnsen K, Rasmussen SS, Clausen JO, Sandbaek A, Lauritzen T, Hansen L, Jørgensen T, Pedersen O, Hansen T. Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. *Diabetes* 2008; **57**: 95-101 [PMID: 17942823 DOI: 10.2337/db07-0910]

45 Medicaid.gov. Keeping American healthy. [accessed 2016 Jan 20]. Available from: URL: http://www.medicaid.gov/medicaid-chip-program-information/by-topics/quality-of-care/reducing-obesity.html

46 **Barlow SE**. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 2007; **120** Suppl 4: S164-S192 [PMID: 18055651]

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EDITORIAL

Transitioning antimicrobials from intravenous to oral in pediatric acute uncomplicated osteomyelitis

Nathan Batchelder, Tsz-Yin So

Nathan Batchelder, Tsz-Yin So, Department of Pharmacy, Moses H. Cone Memorial Hospital, Greensboro, NC 27401, United States

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Correspondence to: Tsz-Yin So, BCPS, PharmD, Pediatric Clinical Pharmacist, Department of Pharmacy, Moses H. Cone Memorial Hospital, 1200 N. Elm Street, Greensboro, NC 27401, United States. jeremy.so@conehealth.com
Telephone: +1-336-8326166
Fax: +1-336-8327198

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Abstract

Osteomyelitis is a bone infection that requires prolonged antibiotic treatment and potential surgical intervention. If left untreated, acute osteomyelitis can lead to chronic osteomyelitis and overwhelming sepsis. Early treatment is necessary to prevent complications, and the standard of care is progressing to a shorter duration of intravenous (*IV*) antibiotics and transitioning to oral therapy for the rest of the treatment course. We systematically reviewed the current literature on pediatric patients with acute osteomyelitis to determine when and how to transition to oral antibiotics from a short *IV* course. Studies have shown that switching to oral after a short course (*i.e.*, 3-7 d) of *IV* therapy has similar cure rates to continuing long-term *IV* therapy. Prolonged *IV* use is also associated with increased risk of complications. Parameters that help guide clinicians on making the switch include a downward trend in fever, improvement in local tenderness, and a normalization in C-reactive protein concentration. Based on the available literature, we recommend transitioning antibiotics to oral after 3-7 d of *IV* therapy for pediatric patients (except neonates) with acute uncomplicated osteomyelitis if there are signs of clinical improvement, and such regimen should be continued for a total antibiotic duration of four to six weeks.

Key words: Antimicrobials; C-reactive protein; Intravenous; Oral; Osteomyelitis; Pediatrics

Core tip: When is an appropriate time to switch to oral antibiotics is a challenging question surrounding the treatment of acute uncomplicated osteomyelitis in pediatrics. With improvements in disease management and antibiotic therapy, the standard of care is progressing to a shorter duration of intravenous antibiotics and transitioning to oral therapy for the rest of the treatment course. This review aims to evaluate the current literature in order to help clinicians make sound decisions on when and how to transition from intravenous antibiotics to oral therapy in pediatric patients with acute uncomplicated osteomyelitis.

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INTRODUCTION

Osteomyelitis is an infection of the bone. These infections can spread to the bone numerous ways including trauma, cellulitis, septic arthritis, or bacteremia. Acute osteomyelitis in children is most commonly hematogenous in origin[1]. In high-income countries, acute osteomyelitis occurs in about 8 of 100000 children per year, but it is considerably more common in low-income countries[2]. Boys are two times more prone to acute osteomyelitis than girls[2]. While *Kingella kingae* is the most common causative organism of acute osteomyelitis below the age of 4 years[3], *Staphylococcus aureus* (*S. aureus*) is the predominant pathogen in older children, followed by *Streptococcus pyogenes*[2,4].

Osteomyelitis can be classified into three separate categories: Acute, subacute, and chronic. Osteomyelitis is considered as acute if the duration of illness is less than two weeks; subacute, if the duration is two weeks to three months; and chronic, if the duration is longer than three months[5]. Clinical manifestations of osteomyelitis can vary depending on the location of the infected bone, but since the majority of osteomyelitis in children affects the bones of the legs, a classic sign is limping or an inability to walk[6]. Other symptoms include fever, focal tenderness, visible redness, or swelling around the infected area[6]. If physical examination suggests bone involvement, then further studies are necessary. Radiograph can show signs of osteomyelitis two to three weeks after symptom onset so an early negative radiograph cannot rule out acute osteomyelitis[6]. Magnetic resonance imaging remains the most useful imaging method for diagnosing osteomyelitis, but it presents other problems such as an increase in cost and the potential requirement of sedation in pediatric patients[6].

Elevations in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) also have high sensitivities for diagnosis[6]. Both CRP and ESR are strong markers of systemic inflammation in the body, but CRP has a much shorter half-life which makes it more useful in acute osteomyelitis[6,7]. A CRP level of 2 mg/dL and above has been found to be sensitive in the diagnosis of osteomyelitis, and this level tends to descend quickly during the early treatment phase if the proper antibiotic is used[7].

The role of surgery in pediatric patients with acute osteomyelitis is not well understood because of the lack of randomized trials regarding this subject. Questions remain about the overall need for surgical intervention other than biopsy to diagnose osteomyelitis and help guide antimicrobial treatment. Conservative treatment is effective up to 90% of the time in acute osteomyelitis if it is diagnosed early in the course of illness[8,9]. Therefore, the general recommendation for acute osteomyelitis requires a prolonged course of antibiotics. In the past, four to six weeks of antibiotic therapy delivered through the intravenous (*IV*) route was the standard of care and often required the placement of a peripherally inserted central catheter (PICC) for medication administration. PICC's are effective for delivering high concentrations of antibiotics for serious infections but have several downfalls including the risk of developing other infections, thrombotic events, and mechanical complications[10]. Because of these potential problems, many clinicians have started looking into transitioning to oral antibiotics sooner. This review aims to evaluate the current literature in order to help clinicians make sound decisions on when and how to transition from *IV* antibiotics to oral therapy in pediatric patients with acute uncomplicated osteomyelitis, defined as osteomyelitis without any open wounds, fractures or adjacent joint infection and with clinical symptoms of less than 2 wk[11].

RESEARCH

MEDLINE/PubMed searches were performed by the investigators to identify all literature published over the past two decades since 1996 that addressed antibiotic management for osteomyelitis in pediatric patients. The searches were done on PubMed (http://www.ncbi.nlm.nih.gov). One set was created using the Medical subject heading (MeSH) terms "pediatric" OR "children", "osteomyelitis", "antibiotic", "intravenous", and "oral". Combining the five sets with the Boolean "AND" function yielded 61 citations. We included article types consisting of only clinical trials, journal articles, reviews, and systematic reviews. We limited our search to articles that had full text and excluded abstracts only, case reports, incomplete reports, and letters from our review.

LITERATURE EVALUATION

One of the first studies that evaluated early transition of antibiotics to oral therapy in pediatric patients with acute osteomyelitis was by Peltola *et al*[12] in 1997. This was a prospective study with the purpose of simplifying treatment of confirmed acute staphylococcal osteomyelitis in fifty children between the ages of three months and fourteen years[12]. The majority of patients were diagnosed with plain osteomyelitis without adjacent joint infection. Sixty-two percent of the patients underwent no surgery or only needle aspiration as a diagnostic tool during the treatment period[12]. Patients received either 37.5 mg/kg every 6 h of cephradine or clindamycin at 10 mg/kg every 6 h intravenously. This

cohort had an average baseline CRP level of around 7 mg/dL which continued to rise on the first couple of days and then started to decline after the antibiotic had started clearing the infection[12]. After three to four days of therapy, the antibiotic was switched to oral for a total treatment duration of three to four weeks[12]. These children had an average hospitalization of eleven days, and their CRP (*i.e.*, < 2 mg/dL) and ESR (*i.e.*, < 20 mm/h) normalized within nine days and twenty-nine days, respectively[12]. The results showed that early transition to oral antibiotics within four days did not cause any treatment failure or long-term sequelae in this cohort of pediatric patients with acute uncomplicated osteomyelitis[12]. This study was one of the first looking at a short duration of *IV* antibiotics and was able to assess several outcomes, but the results might be limited by its small sample size.

Another prospective, randomized study on the treatment of acute osteomyelitis in pediatric patients was performed in 2010[13]. One hundred and thirty-one children aged three months to fifteen years were randomized to receive either two to four days of *IV* treatment followed by oral antibiotics for either twenty or thirty days[13]. The majority of the diagnosed osteomyelitis pertained to the long bones of the lower extremity that were caused by methicillin-susceptible *S. aureus* (MSSA)[13]. Dosing of antibiotics used were clindamycin 40 mg/kg per day divided into four doses or cephradine 150 mg/kg per day divided into four doses[13]. Majority of the children went through diagnostic aspiration; only 24% of the patients did not undergo any surgery[13]. The primary outcome was the comparison of full recovery from acute osteomyelitis between the 20-d and 30-d groups[13]. CRP levels were monitored and showed an elevation on the first two days of treatment with an average baseline of 9.9 mg/dL, but this inflammatory marker began to trend down as the antibiotic course progressed with the majority of CRP levels being less than 2 mg/dL by day nine[13]. The data of this study showed excellent results for both groups, and they found that there were not any significant radiological, hematological, or clinical differences between the groups[13]. The authors concluded that a shorter 20-d course of antibiotics with only two to four days of *IV* therapy are enough for the treatment of acute osteomyelitis if the child is clinically improving and the CRP has gone down to below 2 mg/dL within seven to ten days[13]. A strength of this study is its design giving it valuable internal validity, but some children received other antibiotic in addition to the recommended agents and the treatment duration was not always the exact twenty or thirty days.

A study by Arnold *et al*[14] specifically looked at CRP levels as a marker to help clinicians decide on when to step down to oral therapy for acute bacterial osteoarticular infections. This study consisted of a primary chart review of 194 children from one month to eighteen years old with either acute bacterial arthritis (n = 32), acute bacterial osteomyelitis (n = 113), or both (n = 49)[14]. Surgical intervention was not discussed in this study. These subjects' CRP averaged at 9.1 ± 7.4 mg/dL on admission and 2.0 ± 1.8 mg/dL when the patients were transitioned to oral antibiotics[14]. The mean duration of *IV* therapy was 1.7 wk and the mean duration of total antibiotic course was 7.1 wk[14]. The most common organism causing the infection was MSSA[14]. Out of the 194 patients, all but one were successfully treated with step-down oral therapy after having clinical improvement and an elevated CRP that had decreased below 3 mg/dL[14]. The child who failed therapy was thought to have had a fragment of infected bone in the joint space that was not removed at the time of initial surgical debridement[14]. This study was able to maintain the sequence of events as a retrospective study, but capturing the information from a chart review might have led to limitations regarding data collection.

A systematic review from 2002 evaluated the appropriate duration of *IV* antibiotics for acute hematogenous osteomyelitis due primarily to *S. aureus* in children aged three months to sixteen years[10]. Two hundred and thirty children were included in this review that compared clinical cure rates at six months in patients who received seven days or less of *IV* therapy to those who received greater than one week of *IV* therapy[10]. Thirty to around ninety percent of the patients underwent surgical intervention. In most cases, it was not stated whether these procedures were for diagnostic or therapeutic purposes. The patients' CRP levels were not reported in this study. No significant difference was observed between the groups in regards to the total duration of antibiotic treatment[10]. The cure rates between the groups were statistically insignificant (P = 0.224) as the cure rate for the shorter *IV* therapy group was 95.2% (95%CI: 90.4-97.7) and the other group had a cure rate of 98.8% (95%CI: 93.6-99.8)[10]. The authors of this systematic review concluded that the efficacy is similar between a short and long course of *IV* antibiotics for the treatment of acute uncomplicated osteomyelitis in pediatric patients, and it is appropriate to switch to oral for the rest of the treatment course after seven days of *IV* antibiotics[10]. This systematic review had a good sample size, but it only looked at cohort studies and did not include results from any randomized controlled trials.

Since that time, more trials and reviews had shown similar results in that a short course of *IV* antibiotics with a transition to oral therapy did not show any differences in clinical outcomes compared to long courses of *IV* antibiotics even when the short course of *IV* therapy was given for less than one week[15-18]. For example, a prospective, bi-center study collected data on seventy consecutive children aged two weeks to fourteen years[15]. These children did not have any underlying disease or medical condition predisposing them to infection[15]. All of the cases were found to be from *S. aureus* and the median duration of hospital stay was five days[15]. Surgical intervention was not discussed in

this study. The outcomes showed that 59% of children were converted to oral therapy after three days and 86% after five days of *IV* antibiotics[15]. This study revealed that a prolonged fever (*i.e.*, > 3-5 d) and an elevated initial CRP (*i.e.*, > 10 mg/dL) resulted in patients requiring longer *IV* treatment probably because the clinicians did not want to switch to oral agents when there were persistent elevations in the inflammatory markers[15]. This study demonstrated that in otherwise healthy patients, three weeks of total antibiotic therapy should be appropriate if the patients have already finished five days or less of *IV* treatment[15]. The authors also concluded that temperature and CRP were the best quantitative measurements for monitoring and assessing patients' response to therapy[15].

Another large retrospective study was performed by Zaoutis *et al*[19] that aimed to compare the treatment failure rate between patients two months to seventeen years old (n = 1969) discharged with *IV* and oral antibiotics. One thousand and twenty-one patients had a central venous catheter placed for long-term *IV* therapy and 948 patients received oral therapy at discharge[19]. The two groups were virtually identical in terms of demographic characteristics, which included 37% of the subjects in the *IV* therapy group and 33% in the oral therapy group who had undergone a surgical procedure for diagnostic or treatment purposes[19]. The median length of stay in the hospital prior to discharge was five days for the *IV* group and four days for the oral group[19]. The primary outcome of the study was treatment failure defined as re-hospitalization within six months with an assigned diagnosis or procedure code consistent with osteomyelitis[19]. The treatment failure was 5% in the prolonged *IV* group and 4% in the oral group (OR = 0.77, 95%CI: 0.49-1.22)[19]. The authors concluded that early transition to oral therapy did not increase the risk of treatment failure[19]. A limitation of this large retrospective study is the possibility that some patients might have been admitted to other hospitals not included in this study for treatment failure or complications.

Similarly, a systematic review in 2013 assessed a primary outcome of cure rates in protracted treatment compared to a shorter duration of antibiotic therapy[18]. The results stemmed from six randomized controlled trials and twenty-eight observational studies[18]. Most of the studies included did not mention the use of surgical procedures for treatment, except for one randomized controlled trial that included 12 children who went through surgical drainage. The majority of the randomized controlled trials focused on the choice of antibiotic or total duration of treatment[18]. The bulk of the observational studies addressed the duration of *IV* treatment and were split into two groups: Short duration which consisted of all studies that had less than seven days of *IV* antibiotic therapy and long duration which included all studies that had seven days or greater of *IV* antibiotic therapy[18]. The success rate of the short-duration group ranged from 77%-100% and that of the long-duration group ranged from 80%-100%[18]. This 2013 review concluded that acute uncomplicated osteomyelitis in children greater than three months old can be treated with three to four days of *IV* antibiotics and be transitioned to oral if the child is clinically improving[18]. The authors classified the strength of their recommendations as weak because the review was derived from observational studies and a small number of randomized controlled trials with important limitations in regards to lack of blinding, small sample size, or a prolonged recruitment period.

A recent retrospective study published in 2015 evaluated the clinical outcome of 2060 children who were either discharged with *IV* or oral antibiotic[1]. The majority of patients were male, aged five to thirteen years, Caucasians, and had osteomyelitis of the leg, foot, or ankle. One thousand and five children received oral antibiotics at discharge and the remaining 1055 children received antibiotics *via* a PICC line[1]. The baseline characteristics showed that 17.1%, 39%, 13.5%, and 16.7% of participants underwent arthrocentesis, osteotomy, incision and drainage, and arthrotomy, respectively[1]. This study did not report on the participants' CRP levels. The median length of stay in the hospital was six days for both groups before being discharged with either an oral or *IV* antibiotic[1]. This study showed that treatment failure was 5% in patients discharged with oral antibiotic therapy and 6% in the group who received antibiotics through a PICC at discharge with no statistical significance (P = 0.77)[1]. A high frequency of PICC-related adverse outcomes requiring ED visits or re-hospitalization was observed in the *IV* group compared to the oral group[1]. Despite of the limited data on treating young children less than five years of age with oral therapy, this large retrospective study showed that there was not any clinically relevant difference in treatment efficacy between *IV* and oral therapy in this age group[1]. This study also looked to see if the isolation of MRSA as the cause of osteomyelitis had an impact on the effect of the treatment route, but the results did not show any difference either[1].

Dartnell *et al*[7] performed the largest systematic review on this controversy to date which included over 12000 cases of pediatric patients with acute osteomyelitis. The majority of patients presented with acute osteomyelitis of the lower extremity and initially had localized pain and fever[7]. This systematic review discussed the role of surgery, but it did not mention the overall percentage of patients in the cohort who had such intervention[7]. The initial average CRP level was elevated at 8.5 mg/dL and resulted in a peak level around day two of treatment[7]. Twelve of the included studies were described as prospective, but there was only one randomized controlled study which made statistical analysis of all these studies combined not achievable[7]. This review concluded that short-term parenteral medication is acceptable in cases of osteomyelitis when the patients do not show any signs of complications and exhibit clinical improvement and

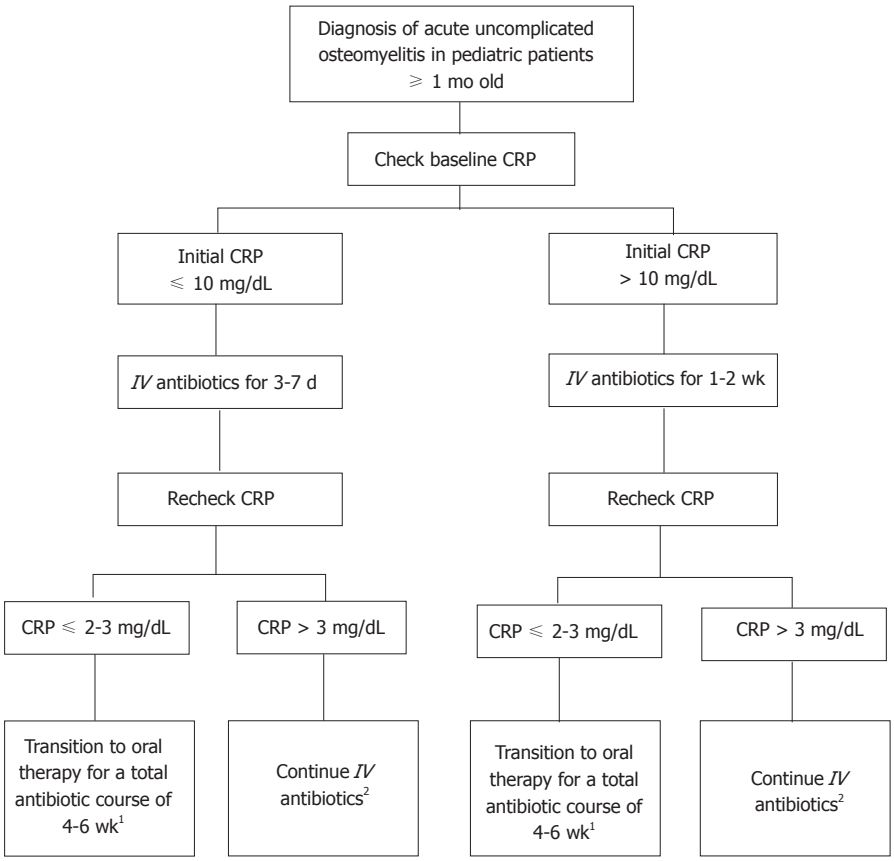

Figure 1 Proposed algorithm of the transition to oral antibiotics from intravenous therapy for pediatric patients with acute uncomplicated osteomyelitis. [1]Patient must be afebrile, have remarkably improved focal tenderness, and tolerate oral medication. If they do not meet these criteria, continue *IV* therapy until these criteria are met; [2]Consider rechecking CRP level in 3-7 d and re-evaluating the appropriateness of continuing *IV* therapy *vs* switching to an oral antibiotic for a total antibiotic course of 4-6 wk (note: The method used in this scenario has not yet been clinically studied and validated). CRP: C-reactive protein; IV: Intravenous.

normalization of hematological markers within the first few days of *IV* therapy provided that the oral antibiotic is effective, the microorganism isolated is susceptible to the administered drug, and the correct dose is used[7]. The authors also added that there is an increasing evidence that long-term *IV* therapy can do more harm than good and can lead to complications that may arise from extended *IV* treatment[7]. This systematic review did include some reports from developing countries which provided useful information, but it might lack external validity when trying to extrapolate the data to developed countries.

There is an ongoing study by Grimbly *et al*[2] that aims to evaluate the literature looking for evidence to support the optimal duration of treatment for both parenteral and oral therapy when managing acute osteomyelitis in children less than eighteen years of age[2]. The authors will conduct a comprehensive review of approximately 3400 studies; these studies will be limited to randomized and quasi-randomized controlled trials found through multiple database searches that compare an *IV* antibiotic course of less than seven days to that greater than seven days[2]. Studies included will describe the antibiotics used as well as the route and duration for at least a three-month timespan[2]. The primary outcome of this study will be the success of the treatment options by the end of therapy defined by resolution of symptoms which include pain, local tenderness, swelling, and gait abnormalities[2]. One of the secondary outcomes will be looking at surgical intervention. The results of this study will surely add to the strength of the current evidence for the early transition of antibiotics to oral in pediatric patients with acute uncomplicated osteomyelitis. Table 1 summarizes all the aforementioned studies.

CLINICAL APPLICATION

After reviewing the available literature, we recommend managing pediatric patients with acute uncomplicated osteomyelitis initially with *IV* antibiotics. Their fever curve, site tenderness, clinical status, and CRP level should be closely monitored. If there are improvements in these infection markers, the *IV* therapy can then be transitioned to oral because the latter has been shown to be just as efficacious as *IV* therapy in treating acute uncomplicated osteomyelitis. A baseline CRP level should be obtained in the patients before starting an antibiotic. After the first several days (*i.e.*, 3-7 d) of *IV* therapy, we suggest rechecking a CRP level; and if the CRP level is less than 2-3 mg/dL, the clinicians can then consider transitioning to oral antibiotics (Figure

Table 1 Published studies evaluating the transition of antibiotics from intravenous to oral for acute uncomplicated osteomyelitis in the pediatric population

Ref.	Study type	Population	Objective	Results	Conclusion
Peltola *et al*[12]	Prospective	50 children (3 mo to 14 yr)	Determined the full recovery rate and remaining health of patients transitioned to oral antibiotics at 12 mo from hospital discharge	100% had full recovery	Treatment of pediatric osteomyelitis can be simplified and costs reduced by switching to oral early on in the treatment course
Le Saux *et al*[10]	Systematic review (12 prospective studies)	230 children (3 mo to 16 yr)	Compared the cure rates at 6 mo for *IV* therapy ≤ 7 d and > 7 d	95.2% - ≤ 7 d (P = 0.224) 98.8% - > 7 d (P = 0.248)	Similar cure rates between groups Increased morbidity and cost associated with long-term *IV* therapy
Prado *et al*[17]	Retrospective	70 children (< 15 yr)	Assessed the efficacy of the transition to oral antibiotic after 7 d of *IV* therapy	No child had a complication from treatment	Seven days of an *IV* antibiotic for the initial treatment phase of acute osteomyelitis was effective in the majority of children
Zaoutis *et al*[19]	Retrospective cohort	1969 children (2 mo to 17 yr)	Compared the treatment failure rate between patients discharged with *IV* and oral antibiotics	5% - *IV* group 4% - Oral group OR = 0.77, 95%CI: 0.49-1.22	Early transition to oral therapy did not increase the risk of treatment failure
Jagodzinski *et al*[15]	Prospective cohort	70 children (≤ 16 yr)	Determined the parameters for prolonged *IV* antibiotic therapy of > 6 d	Fever > 38.4 °C for 3 to 5 d Admission CRP > 10 mg/dL	3-5 d of *IV* antibiotic therapy followed by oral therapy for 3 wk is sufficient for uncomplicated osteoarticular infections
Peltola *et al*[13]	Prospective randomized	131 children (3 mo to 15 yr)	Compared 20-d *vs* 30-d treatment with *IV* therapy for the first 2-4 d	98.5% had full recovery	Most childhood osteomyelitis can be treated for a total antibiotic course of 20 d with only 2-4 d of *IV* therapy
Dartnell *et al*[7]	Comprehensive systematic review (132 studies)	> 12000 children (< 18 yr)	Reviewed the different features of osteomyelitis to formulate a recommendation on treatment	Short course of *IV* therapy is acceptable	Clinical improvements of tenderness, normal temperature, and normalized CRP (< 2 mg/dL) are good indicators for converting *IV* antibiotics to oral[1]
Arnold *et al*[14]	Chart review	194 children (1 mo to 18 yr)	Evaluated if CRP is a good marker to use for transitioning therapy to oral	99.5% success rate	CRP (*i.e.*, < 3 mg/dL) is a useful tool along with other clinical findings to help transition to oral therapy
Liu *et al*[16]	Retrospective	95 children (≤ 17 yr)	Compared recurrence rates of osteomyelitis at discharge with *IV* or oral therapy	0% - Oral 9% - Intravenous (P = 0.59)	Early transition to oral antibiotics may offer similar recurrence rates of osteomyelitis
Howard-Jones *et al*[18]	Systematic review (28 observational and 6 randomized)	Approximately 3000 children (< 18 yr)	Compared cure rates between shorter and longer durations of *IV* therapy	77%-100% - Short duration 80%-100% - Long duration	Early transition to oral therapy after 3-4 d of intravenous therapy is as effective as longer courses[1]
Keren *et al*[1]	Retrospective cohort	2060 children (2 mo to 18 yr)	Compared therapy failure between PICC administered antibiotics and oral antibiotics	5% - Oral route 6% - PICC route OR = 1.06, 95%CI: 0.70-1.61	No advantage of antibiotics *via* PICC line Increased complications with PICC line

[1]Does not apply to neonates. CRP: C-reactive protein; IV: Intravenous; PICC: Peripherally inserted central catheter.

1). However, if the CRP is still above 2-3 mg/dL at that time, *IV* antibiotics should be continued and the CRP can be rechecked in a few more days. If the CRP level continues to increase from baseline by the fourth day of treatment, then this should alert the clinician that the patients may have developed some complications from the infection and thus may require thorough re-evaluation, a longer course of *IV* antibiotic, and/or a surgical intervention[10].

Some patients, however, may not be good candidates for switching over to oral antibiotics after a short *IV* course. If the child has fevers persisting for more than three to five days after starting treatment, then *IV* antibiotics should be continued for a longer course. Also, if the initial CRP is above 10 mg/dL, which usually correlates to a more severe and potentially complicated osteomyelitis, a longer duration of *IV* therapy may be necessary[7,15]. This clinical practice has not been studied in neonates with acute uncomplicated osteomyelitis; as a result, this population should continue receiving a longer-term of *IV* antibiotics to ensure that the infection is treated properly. Besides neonates, patients with complicated osteomyelitis such as bone fracture, bacteremia, abscess, growth arrest, or chronic infection also should not transition to oral therapy early. Patients with other comorbid conditions such as diabetes mellitus, sickle-cell disease, or children who are immuno-compromised should consider receiving a longer course

of *IV* antibiotics due to their clinical condition predisposing them to a more serious infection. Finally, patients who have a history of osteomyelitis or recent treatment failure for acute osteomyelitis should also consider a longer duration of *IV* therapy until studies are performed to evaluate the appropriateness of early transition of antibiotics to oral in this population.

Several practical advantages of a shorter course of *IV* antibiotic exist, and they include a shorter hospital stay, decreased morbidity from *IV* lines, and more cost effectiveness[12]. A common issue causing longer hospital stay is that the patients continue to have an *IV* line in place preventing discharge. Transitioning to oral therapy when clinically ready will help shorten hospitalization. Switching to oral therapy can also decrease the risk of complications related to long-term *IV* antibiotic administration. Most complications from *IV* lines are not serious, but they do result in significant increase in emergency department or clinic visits, or even hospital readmissions[14]. These complications, as a result, can increase cost burden for the healthcare system. Considering the cost of *IV* antibiotic treatment *vs* oral, there is a huge difference between the two[5]. In summary, since there are not any clinical differences observed in the early transition to oral antibiotics, clinicians can surely consider such practice in their pediatric patients with acute uncomplicated osteomyelitis.

CONCLUSION

Clinicians should consider transitioning antibiotic from *IV* to oral in pediatric patients with acute osteomyelitis when there is a downward trend in their fever curve, improved tenderness in the affected area, a reduction in CRP, and overall clinical improvement. These recommendations only pertain to patients with acute uncomplicated osteomyelitis that are responding well to early *IV* treatment. Questions relating to this clinical practice that still need to be answered include the appropriateness of such early transition in neonates and if specific organisms direct such transitions from *IV* to oral therapy.

REFERENCES

1 **Keren R**, Shah SS, Srivastava R, Rangel S, Bendel-Stenzel M, Harik N, Hartley J, Lopez M, Seguias L, Tieder J, Bryan M, Gong W, Hall M, Localio R, Luan X, deBerardinis R, Parker A. Comparative effectiveness of intravenous vs oral antibiotics for postdischarge treatment of acute osteomyelitis in children. *JAMA Pediatr* 2015; **169**: 120-128 [PMID: 25506733 DOI: 10.1001/jamapediatrics.2014.2822]

2 **Grimbly C**, Odenbach J, Vandermeer B, Forgie S, Curtis S. Parenteral and oral antibiotic duration for treatment of pediatric osteomyelitis: a systematic review protocol. *Syst Rev* 2013; **2**: 92 [PMID: 24099135 DOI: 10.1186/2046-4053-2-92]

3 **Chometon S**, Benito Y, Chaker M, Boisset S, Ploton C, Bérard J, Vandenesch F, Freydiere AM. Specific real-time polymerase chain reaction places Kingella kingae as the most common cause of osteoarticular infections in young children. *Pediatr Infect Dis J* 2007; **26**: 377-381 [PMID: 17468645 DOI: 10.1097/01.inf.0000259954.88139.f4]

4 **Jaberi FM**, Shahcheraghi GH, Ahadzadeh M. Short-term intravenous antibiotic treatment of acute hematogenous bone and joint infection in children: a prospective randomized trial. *J Pediatr Orthop* 2002; **22**: 317-320 [PMID: 11961446]

5 **Krogstad P**, Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL. Osteomyelitis. Pediatric infectious diseases. 6th ed. Philadelphia: Saunders, 2009: 725-742

6 **Peltola H**, Pääkkönen M. Acute osteomyelitis in children. *N Engl J Med* 2014; **370**: 352-360 [PMID: 24450893 DOI: 10.1056/NEJMra1213956]

7 **Dartnell J**, Ramachandran M, Katchburian M. Haematogenous acute and subacute paediatric osteomyelitis: a systematic review of the literature. *J Bone Joint Surg Br* 2012; **94**: 584-595 [PMID: 22529075 DOI: 10.1302/0301-620X.94B5.28523]

8 **Vaughan PA**, Newman NM, Rosman MA. Acute hematogenous osteomyelitis in children. *J Pediatr Orthop* 1987; **7**: 652-655 [PMID: 3429648 DOI: 10.1097/01241398-198707060-00004]

9 **Cole WG**, Dalziel RE, Leitl S. Treatment of acute osteomyelitis in childhood. *J Bone Joint Surg Br* 1982; **64**: 218-223 [PMID: 6802854]

10 **Le Saux N**, Howard A, Barrowman NJ, Gaboury I, Sampson M, Moher D. Shorter courses of parenteral antibiotic therapy do not appear to influence response rates for children with acute hematogenous osteomyelitis: a systematic review. *BMC Infect Dis* 2002; **2**: 16 [PMID: 12181082 DOI: 10.1186/1471-2334-2-16]

11 **Bachur R**, Pagon Z. Success of short-course parenteral antibiotic therapy for acute osteomyelitis of childhood. *Clin Pediatr* (Phila) 2007; **46**: 30-35 [PMID: 17164506 DOI: 10.1177/0009922806289081]

12 **Peltola H**, Unkila-Kallio L, Kallio MJ. Simplified treatment of acute staphylococcal osteomyelitis of childhood. The Finnish Study Group. *Pediatrics* 1997; **99**: 846-850 [PMID: 9190554]

13 **Peltola H**, Pääkkönen M, Kallio P, Kallio MJ. Short- versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood: prospective, randomized trial on 131 culture-positive cases. *Pediatr Infect Dis J* 2010; **29**: 1123-1128 [PMID: 20842069 DOI: 10.1097/INF.0b013e3181f55a89]

14 **Arnold JC**, Cannavino CR, Ross MK, Westley B, Miller TC, Riffenburgh RH, Bradley J. Acute bacterial osteoarticular infections: eight-year analysis of C-reactive protein for oral step-down therapy. *Pediatrics* 2012; **130**: e821-e828 [PMID: 22966033 DOI: 10.1542/peds.2012-0220]

15 **Jagodzinski NA**, Kanwar R, Graham K, Bache CE. Prospective evaluation of a shortened regimen of treatment for acute osteomyelitis and septic arthritis in children. *J Pediatr Orthop* 2009; **29**: 518-525 [PMID: 19568027 DOI: 10.1097/BPO.0b013e3181ab472d]

16 **Liu RW**, Abaza H, Mehta P, Bauer J, Cooperman DR, Gilmore A. Intravenous versus oral outpatient antibiotic therapy for pediatric acute osteomyelitis. *Iowa Orthop J* 2013; **33**: 208-212 [PMID: 24027485]

17 **Prado S MA**, Lizama C M, Peña D A, Valenzuela M C, Viviani S T. Short duration of initial intravenous treatment in 70 pediatric patients with osteoarticular infections. *Rev Chilena Infectol* 2008; **25**: 30-36 [PMID: 18273522]

18 **Howard-Jones AR**, Isaacs D. Systematic review of duration and choice of systemic antibiotic therapy for acute haematogenous bacterial osteomyelitis in children. *J Paediatr Child Health* 2013; **49**: 760-768 [PMID: 23745943 DOI: 10.1111/jpc.12251]

19 **Zaoutis T**, Localio AR, Leckerman K, Saddlemire S, Bertoch D, Keren R. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. *Pediatrics* 2009; **123**: 636-642 [PMID: 19171632 DOI: 10.1542/peds.2008-0596]

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FRONTIER

Critical evaluation of unscientific arguments disparaging affirmative infant male circumcision policy

Brian J Morris, John N Krieger, Jeffrey D Klausner

Brian J Morris, School of Medical Sciences, University of Sydney, Sydney, New South Wales 2006, Australia

John N Krieger, Section of Urology, VA Puget Sound Health Care System and School of Medicine, University of Washington, Seattle, WA 98195, United States

Jeffrey D Klausner, Division of Infectious Diseases, Department of Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA 90095, United States

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Correspondence to: Brian J Morris, DSc, PhD, Professor Emeritus, School of Medical Sciences, University of Sydney, Building F13, Sydney, New South Wales 2006, Australia. brian.morris@sydney.edu.au
Telephone: +61-2-93513688
Fax: +61-2-93512227

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Abstract

We evaluate recent claims opposing infant male circumcision, a procedure now supported by the evidence-based policy of the American Academy of Pediatrics. We find those criticisms depend on speculative claims about the foreskin and obfuscation of the strong scientific evidence supporting pediatric policy development. An argument that circumcision should be delayed to allow a boy to make up his own mind as an adult fails to appreciate the psychological, scheduling and financial burdens later circumcision entails, so reducing the likelihood that it will occur. In contrast, early infant circumcision is convenient, safer, quicker, lower risk, healing is faster, cosmetic outcome is routinely good and the lifetime benefits accrue immediately. Benefits include reduction in urinary tract infections, inflammatory skin conditions, foreskin problems, and, when older, substantial protection against sexually transmitted infections and genital cancers in the male and his female sexual partners. Some authorities regard the failure to offer parents early infant circumcision as unethical, just as it would be unethical to fail to encourage the vaccination of children. In conclusion, the criticisms of evidence-based infant male circumcision policy are seriously flawed and should be dismissed as unhelpful to evidence-based development and implementation of pediatric policy intended to improve public health and individual wellbeing.

Key words: Male circumcision; Policy; American Academy of Pediatrics; Newborn; Foreskin

Core tip: This article critically assesses an extensive compendium of detailed arguments criticizing the American Academy of Pediatrics policy in support of infant male circumcision. The article we assess is by an historian, Robert Darby, who is opposed to infant circumcision. It should be recognized that the American Academy of Pediatrics policy on infant male circumcision was developed on the basis of the latest scientific evidence. The policy reported that benefits exceed

risks and recommended unbiased education of parents and providers, as well as facilitation of access and improvement in affordability by increased third party insurance coverage. We present the scientific evidence undermining Darby's arguments. Our evaluation leads us to conclude that the criticisms by Darby should be dismissed as unreliable.

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INTRODUCTION

We evaluate very extensive criticisms[1] of the American Academy of Pediatrics (AAP) infant male circumcision (IMC) policy that found benefits of IMC substantially outweigh the risks[2]. The 34-page article asserts that, "the AAP's conclusion is untenable", because no consideration was given to broader risks than surgical complications. In essence, it argues that IMC is unethical because of: (1) supposed long-term risks resulting from loss of the foreskin; (2) that only the owner of the foreskin should decide whether he wishes to be circumcised; and (3) a claim that since the foreskin is, "erotogenic", circumcision diminishes sexual pleasure for the man.

In the interests of medical decision-making, public health policy and the rights of parents to receive accurate information to facilitate decision-making about the circumcision of a baby boy, the numerous criticisms of the AAP's policy deserve an appropriate critical response.

CENTRAL ARGUMENTS

The fundamental thesis underlying the criticisms is the statement that, "we can be confident that the average individual would be far more relaxed about losing his tonsils or appendix than an erotogenic feature of his genitals". That generalization is not supported by current medical or biological evidence.

The article cites previous criticisms of the AAP's policy[3,4], without noting detailed responses by the AAP[5] and academic experts[6] disputing those criticisms.

OTHER POLICY STATEMENTS

Outdated, non-evidence-based, IMC policy statements are cited. One, by the Royal Australasian College of Physicians[7], was found to contain fundamental flaws and failed to accurately review the literature[8].

Besides the AAP policy, evidence-based policy statements have been produced by the Centers for Disease Control and Prevention (CDC)[9] and the Circumcision Academy of Australia (CAA)[10]. Each found that benefits of IMC greatly exceed risks.

FORESKIN ANATOMY AND FUNCTION

Opponents are concerned about, "the anatomy or functions of the foreskin"[1]. Leaving speculation aside, survey evidence suggests a foreskin may make it easier for a woman to bring a man to orgasm manually, but little else[11]. A prepuce may be "healthy" and "visible", but whether it is "functional" depends on what use it is put to (discussed later). Rather than being, "of great significance to most males", strong scientific evidence indicates the foreskin poses a health risk from minor and major conditions, including genital cancers, urinary tract infections (UTI), human immunodeficiency virus (HIV) infection and other sexually transmitted infections (STIs)[2,9,12].

Foreskin removal by circumcision is referred to in the article as, "amputation"[1]. Since the medical definition of amputation is the removal of a limb, digit or the entire penis, that term is misused and inaccurate.

The article claims, "recent research", shows that the foreskin, "contains one of the densest concentrations of nerve endings in the body", citing 16-19 year-old publications[1]. In fact, current research shows that sensory nerve endings in the foreskin are actually lower in number and smaller in size than those in other glaborous (hairless) tissues[13]. The article further claims, "the foreskin is an ingenious piece of biological engineering, the functions of which are primarily erotic", that, "its specialized web of nerve endings convey fine touch sensations" and that its, "mechanical action in sliding back and forth stimulates and lubricates the glans, thus facilitating sexual activity of all kinds". Instead of citing experimental evidence from the peer-reviewed literature, it cites a book written to discredit circumcision[14].

A 300 year-old book is cited in claiming the importance of the foreskin was well understood up until the late nineteenth century. The article argues that subsequent Victorian "mistakes" about the foreskin, "have been corrected by recent research". However, two of the three publications used as support[15,16] contain serious flaws[17,18] undermining their conclusions. The third, a small telephone survey of 109 men $\geqslant$ 3 mo after circumcision[19], was too small to make accurate conclusions about sexual dysfunction, these apparently being related to diabetes or older age. Owing to phimosis, which is common in uncircumcised men, 50% of the men experienced pain during intercourse prior to circumcision, falling to 6.5% after circumcision.

SEXUAL PLEASURE INVOLVES THE GLANS

The claim that special sensory receptors in the foreskin

make it, "the principal sensory platform of the penis"[1] is no longer tenable. A recent systematic review of all histological and anatomical data on sensory receptors in the penis, including changes during puberty, concluded that, contrary to the article's claim, the foreskin has no role in sexual sensation[20]. Nerve endings involved in sexual pleasure reside in the glans, the underside being particularly sensitive. Stimulation of the exposed glans is the source of sexual sensations during sexual activity[20]. In support, a detailed systematic literature review[21], a meta-analysis of sexual dysfunction in men[22], two randomized controlled trials (RCTs)[23,24] and a large United Kingdom study[25] found male circumcision has no adverse effect on sexual function, sensitivity or sensation. Recent sensitivity testing of different penile sites dismissed the claim that the foreskin is the most sensitive part of the penis[26].

OTHER CLAIMS

The article maintains that the foreskin serves as a valve to, "let urine out" while, "blocking the entry of dirt", that it provides lubrication, that it protects the glans, the latter apparently being, "an internal organ" that is, "easily irritated" and, "eventually desensitized, if it is exposed to the abrasion of clothes, *etc.*", and that the foreskin is a, "slack tissue" somehow needed for erection[1]. Anecdotes and the author's own highly criticized[27] monograph disputing Victorian ideas[28] are used as "evidence". Scientific support for these claims is lacking.

HIGH STAKES IN THE HARM QUESTION

The statement, "if it were proved that one value of the foreskin was to enhance genital sensation and function (foreskin removal) would undoubtedly be counted as a harm"[1] has been disproved by multiple studies[20-26]. Overall, sexual function, sensation and pleasure are either the same or better after circumcision[20-26]. Instead of scientific studies, support is drawn from historical anecdotes, outmoded opinion pieces by opponents, and discredited or weak publications considered above. There may be some (not "many"), "circumcised men who resent their condition". Apart from very rare cases of damage to the penis from an inexperienced operator, any resentment is likely a result of some men with sexual dysfunctions believing claims by circumcision opponents attributing these to their IMC. Other men may read the claims and think they might be missing out on something important by lacking a foreskin.

Rather than ask why, "most men throughout the world have neither been circumcised as children nor elected the operation for themselves as adults", the article should have considered why many men are circumcised. A recent study that determined circumcision prevalence in all 237 countries and territories in the world estimated a global circumcision prevalence of 38%[29], which is high for an elective procedure. Of these, 62% were for religious reasons. Barriers to getting circumcised at a later age are substantial[30], as discussed later.

The article calls for, "advocates to prove that circumcision is both necessary and harmless". That has been accomplished. Extensive reviews of the medical literature, by the AAP[2], CDC[9], and CAA[10], have established that benefits of IMC greatly exceed risks. A CDC study of 1.4 million circumcisions in the United States found the adverse event frequency was 0.4% for IMC, but was 10-20 times higher in older children and men[31]. The vast majority of adverse events were minor and easily treatable with complete resolution.

LEGAL CHALLENGES

The article refers to, "several judgments" by "courts in Europe"[1]. There was only one such judgment. That decision, by a regional court in Cologne, was overturned by legislation enacted by the German Federal Parliament[32]. The German ethics council lent its support to circumcision of boys[33]. The article then cites a, "law reform report from Australia" that calls for, "strict regulation and partial prohibition". That report was written by a graduate student and placed on the Tasmanian Law Reform Institute website in 2012. A critical evaluation of the report by a lawyer, ethicist and medical experts found it had no basis in law, ethics or medicine[34]. The report appears to have been ignored by the Tasmanian Government.

IS CIRCUMCISION REALLY A MEDICAL ANOMALY?

Another claim is that circumcision, "requires special rules". The article did not consider the favorable risk: benefit to be sufficient reason to advocate prophylactic circumcision. It considered vaccination not to be a reasonable comparison, "because the nature, extent, risks and costs of the protection gained or claimed are quite different" and, "vaccination does not entail surgical removal of a significant body part"[1]. While vaccinations protect against many infectious diseases and cancers, IMC is a one-time intervention that provides life-long protection against a wide array of adverse medical conditions, many unrelated to infectious agents. The number of children who need to be vaccinated to prevent one infection[35] is greater than the number of boys who need to be circumcised to prevent adverse medical conditions resulting from failure to circumcise[12].

The article overstates the risks of circumcision. Apart from invoking the disproven belief that, "the foreskin has sexual functions", it suggests "many people" value the foreskin for various, "personal reasons". It cites a sexually explicit website that promotes foreskin use in sexual activities such as "docking", engaged in by some men who have sex with men. The article also cites posts

on, "Internet dating sites" and, "the distress many men feel" at having been circumcised when young. Neither represents scientific evidence.

In contradiction to a 2002 paper by circumcision opponents listing criteria that should be met before childhood circumcision would be permissible, the AAP policy states the, "best interests" of the individual and "public health justifications" are served by ensuring a baby boy is circumcised[2]. The position that circumcision is, "impermissible because it was performed on a minor without consent" does not acknowledge that the same applies to childhood vaccinations.

The claim that, "the human rights cost to the individual exceed the proven public health benefit; and the diseases from which circumcision might provide protection could be avoided through appropriate behavioral choices or otherwise managed without surgery" is not supported by evidence.

For example, circumcision is the only way to prevent balanoposthitis, which only occurs in uncircumcised males, and to reduce balanitis, which is twice as common in the uncircumcised[12].

Condoms, when used correctly and consistently, provide only partial protection against STIs, *e.g.*, 80% against HIV in a Cochrane meta-analysis[36]. However, seven RCTs (two in the United States, one in England and four in sub-Saharan African countries) found, "little clinical evidence of real-world effectiveness of interventions promoting condom use for dual protection" against HIV, but 42% effectiveness in syphilis reduction[37]. It should be noted that, unlike condoms, circumcision is a one-time intervention that provides a lifetime of protection. Condom use should nevertheless be encouraged. Together each confer greater protection than either alone.

Phimosis can be managed using steroid creams, but this requires twice-daily administration for many weeks, the creams are effective for only a portion of cases, have side-effects and, unlike circumcision, do not protect against STIs[38,39] and UTIs[40].

While circumcision does remove, "a genital feature", absence of a foreskin is preferred by most women[11,41-47]. Reasons included esthetics, better hygiene, reduced risk of infection, easier and less traumatic vaginal (or anal) penetration during intercourse, and greater overall sexual pleasure[11,44,45,48]. A large clinical trial found far more men reported an improvement in their sexual experience after having been circumcised, with few stating sex was worse[24]. A possible explanation might be that after circumcision the shaft of the penis makes closer contact with the walls of the vagina during intercourse.

The three studies cited in the article to support a premise that, "circumcision is not ordinary medical treatment"[1] were selective citations of reports by circumcision opponents. The one by Frisch *et al*[49] has been severely criticized[21,50]. The one by O'Hara *et al*[51] was a "preliminary" survey by lay anti-circumcision activists of women, "recruited through … an announcement in an anti-circumcision newsletter". Those authors acknowledged this was a "shortcoming". They stated, "this study has some obvious methodological flaws" and that, "it is important that these findings be confirmed by a prospective study of a randomly selected population of women". Since then a RCT has been conducted[45], and most of the female participants reported a better sexual experience after their male partner had been circumcised.

The claim that the foreskin is as important as the female breast is implausible. The breast is a highly visible female accouterment providing, through its milk, critical nutrition and immune protection for the newborn. In contrast, the foreskin may only be seen when a male exposes his penis. In comparing penile cancer and breast cancer prevalence, the article misleadingly cites lifetime risk for breast cancer (1 in 10), but annual incidence of penile cancer (1 in 100000) rather than lifetime risk (approximately 1 in 1000)[2,9,52].

The article argues that, "it is impossible to identify a single [boy] who died because he had not been circumcised"[1]. A large CDC study reported higher rate of serious adverse events in boys not circumcised[31]. Apart from gangrene, a potential consequence of paraphimosis, these included several types of STIs, which can lead to death[2,9,12,39,52]. UTIs, which is ten times more prevalent in uncircumcised boys[40], can result in potentially fatal complications such as meningitis and sepsis[53]. Deaths from circumcision do occur after initiation ceremonies in sub-Saharan Africa involving non-medical operators. But the claim of 117 deaths in the United States per year from circumcision is fanciful. That figure is based on the false assumption by Daniel Bollinger that the well-known sex difference in infant mortality is entirely a consequence of IMC. A similar sex-difference is seen in countries with low circumcision prevalence[54]. Deaths from medical circumcision in the United States are exceedingly rare[31].

BIOETHICS AND AUTONOMY

The ethics of IMC has been debated extensively. Scholarly assessments suggest circumcision of male minors is ethical[34,55-60]. Given the wide-ranging protection against multiple medical conditions and infections, including STIs in boys who become sexually active early, it has been argued that it would be unethical to leave boys uncircumcised[34,58]. Article 24(3) of the United National Convention on the Rights of the Child has been construed as mandating circumcision, since not circumcising boys should be deemed as prejudicial to their health[58].

In contrast to the claim about tattooing, piercing and genital cutting of girls[1], there are sound medical reasons why IMC should be regarded quite differently. While IMC has cosmetic benefits, it is not merely, "a cosmetic procedure". It provides life-long medical

benefits.

A view expressed that, "the experts are unable to agree"[1], represents obfuscation of the AAP's advice that, "parents should, weigh health benefits and risks in light of their own religious, cultural, and personal preferences, as the medical benefits alone may not outweigh these other considerations for individual families"[2]. All evidence-based policy statements support IMC on medical grounds[2,9,10,61]. As with childhood vaccination, parental consent is required. Moreover, the supposition, "if the risk/benefit equation is only slightly tilted (AAP) or equally balanced"[55] is not supported by the scientific evidence. Draft CDC recommendations state, "In a comprehensive risk-benefit analysis of [IMC] based on reviews of the literature and meta-analyses, it is estimated that over a lifetime, benefits exceed risks by a factor of 100:1"[9]. This risk-benefit analysis cited by the CDC found that the foreskin contributes to adverse medical conditions in half of uncircumcised males during their life-time[12]. Thus the data refute the assertion that a, "situation of uncertainty" exists.

The article rejects parental choice, saying that, "it does not logically follow that parents are the appropriate party to make the proverbial circumcision decision", because, "from the child's point of view" a decision made by others, "denies him autonomy and choice in a matter affecting an intimate part of his own body". An argument that a child has a right to, "bodily integrity" follows the line espoused by circumcision opponents that IMC should be banned, discouraged or at least delayed until the boy is old enough to decide for himself[62-64]. Ethics authorities have refuted this opinion[56-60,65,66]. It has been argued that being circumcised boosts autonomy more than constraining it[67]. The, "circumcision decision" is one of many decisions that a parent must make in the interests of the health of their male child. The AAP recommends that early in a pregnancy the medical practitioner should provide parents with unbiased education about risks and benefits of IMC so they have adequate opportunity to choose what is in the child's best interests should they have a boy[2].

THE BEST TIME TO CIRCUMCISE

Cogent arguments favor early parent-approved IMC over delaying circumcision until the male is old enough to decide for himself[30]. Circumcision in infancy is easier, lower-cost, more convenient, usually involves local anesthesia, healing is quick and cosmetic outcome is good as stitches are not required. In contrast, circumcision of older boys or adults is more difficult technically, poses a higher risk of adverse events[31], is more expensive, and, although can be done using local anesthesia, some operators prefer that general anesthesia be used, so further adding to cost. It means taking time off work or school, and is associated with psychological issues, including fear of pain, unfounded concern about diminished sexual pleasure, of having to undergo an operation, peer pressure not to get circumcised, sexual abstinence until healing is complete, which the man and/or his sexual partner may find unacceptable, and, when sutures are used, a cosmetic result that can be inferior to that achieved by IMC, which does not require sutures[30]. It also means years of not having been protected from adverse medical conditions that affect uncircumcised boys. Taken together, those observations provide a strong case favoring early infancy as being the best time to circumcise[30]. In light of all of this, the argument that the, "decision should still be left to the owner of the foreskin" is likely to mean circumcision will not occur, even if the older male wants to be circumcised. This probably represents the outcome desired by circumcision opponents.

While children and infants, "lack the power to make rational choices and must therefore be guided by adults"[1], it is untrue that, "circumcision is not something that has to be done before a person is capable of rational thought". Although, "children are not sexually active and thus not at risk of disease"[1], circumcision confers multiple benefits in infancy and childhood that are not related to sexual activity.

Benefits include strong protection against UTIs[40] that are common in infancy[68] and can result in permanent kidney damage[53,69-73]. Early IMC prevents phimosis, which affects 10% of uncircumcised older boys and young men[74]. Paraphimosis is less common, but can lead to penile gangrene and auto-amputation of the penis[75]. Circumcision protects against inflammatory skin conditions (balanitis and balanoposthitis) that occur in 10% of uncircumcised boys and men[30]. Uncircumcised adolescents and men have inferior penile hygiene owing to the proliferation of bacteria and accumulation of smegma under the foreskin[76-80]. The thin, fragile foreskin is easily torn and trauma due to zipper injuries can occur[81].

HUMAN PAPILLOMAVIRUS

The article disputes claims that uncircumcised men are more likely to harbor oncogenic human papillomavirus (HPV) types[1]. In doing so the references cited[82,83] are misinterpreted, as explained previously[38]. The article fails to cite extensive evidence contradicting the author's skepticism. That includes ignoring RCTs that found circumcision strongly protects men against ongogenic HPV acquisition and improves HPV clearance[84-89]. There is also RCT evidence of reduced low-risk HPV types that cause genital warts[90].

The claim that, "the development of safe, effective vaccines is rapidly making the question of circumcision irrelevant", fails to appreciate that the two current HPV vaccines do not target all of the 14 or more prevalent oncogenic HPV types, whereas circumcision offers approximately 50% protection against all oncogenic HPV types. Thus circumcision and vaccination re-

present synergistic approaches to countering the HPV epidemic[91].

The article skirts the fact that by partially protecting against oncogenic HPV types and various other STIs male circumcision provides a range of benefits to women. Virtually all cases of cervical cancer are caused by oncogenic HPVs. The risk of cervical cancer is much lower in the female sexual partners of circumcised men[92]. While over 70% of girls in early adolescence have received HPV vaccination in Australia[93], vaccine uptake in the United States has been much lower[94].

Policy recommendations of the AAP and CDC recognize cervical cancer prevention as an important benefit of IMC[2,9]. Yet, the article inaccurately states that circumcision of boys has, "zero benefit" to, "reduce the risk of cervical cancer in future female sexual partners"[1].

OTHER STI, INCLUDING HIV

Well-designed large RCTs provide the cleanest picture of the risks and benefits of circumcision compared to retrospective or observational studies. This is because confounding and bias are minimized. Three RCTs convincingly demonstrated that MC protects against heterosexual HIV infection in men[95-97]. The trials went on to demonstrate protection against other STIs such as oncogenic types of HPV[84-89], genital herpes (HSV-2)[87,98-100], *Trichomonas vaginalis* (*T. vaginalis*)[101] and *Mycoplasma genitalium* (*M. genitalium*)[102]. In addition, RCT data confirms the protective effect of MC in the female partners against oncogenic HPV types[103-105], HSV-2[106], *T. vaginalis*[107], *M. genitalium*[108], bacterial vaginosis[78,107] and genital ulceration[107]. The consistency in efficacy estimates between trials provides increased confidence in the benefits.

The claim that, "the major benefits claimed (reduced risk of STIs, HIV and various cancers) can be obtained in adulthood"[1] fails to acknowledge that the likelihood an adolescent or adult male will seek a circumcision for himself is low. Thus, parents' decision to circumcise a newborn son will ensure he has the lifelong benefits circumcision provides. Programs to encourage circumcision have been suggested by the CDC for high-risk population groups in the United States[9]. The WHO and other bodies have supported the implementation of such programs in sub-Saharan Africa since 2007. Although the article concedes that circumcision, "provides some degree of protection against HIV in certain risk situations and epidemiological environments", it then states, "there is no proof that it provides any overall protection against other STIs"[1], citing an article containing a series of meta-analyses[109]. Those meta-analyses were criticized[38]. They contained extensive flaws, data manipulation, failed to include numerous studies, including high-quality RCT data, and used uncommon statistical approaches[38].

It then states, "most [STIs] are readily curable with antibiotics", failing to realize that many common STIs (HIV, HPV and HSV-2) are viruses that cannot be cured. That exposes a lack of medical knowledge by the historian author.

WHY IS THERE OPPOSITION TO MALE CIRCUMCISION?

The article refers to a man who suffered the consequences of a botched IMC[110]. Such occurrences are exceedingly rare in the current era for circumcision performed by experienced medical professionals. The AAP policy recommends provider training to help ensure good outcomes. At the population level the frequency and severity of medical conditions arising from failure to circumcise greatly exceed that of adverse events arising after IMC[12].

The existence of, "a vigorous, community-based anti-circumcision movement in places where the practice remains common", as evidence, "circumcision is harmful and thus wrong" can be said of other fringe groups opposed to beneficial public health policies such as vaccination and water fluoridation.

FORESKIN RESTORATION AND PARTIALISM

The article cites dated opinion pieces containing anecdotes and speculation about, "serious psychological dysfunction", caused by IMC, in claiming, "some [men] resent [their IMC] sufficiently to attempt foreskin restoration"[1]. Rather than this being, "proof that they believe they have suffered sufficient harm to warrant a complex and laborious project", these men may have formed a misguided belief, as discussed earlier. Following online instructions about "restoration" of a pseudo-foreskin seems ill-advised. Not only is the process cumbersome and protracted, but has led to genital mutilation[111]. A recent meta-analysis found that sexual dysfunctions in men are common, irrespective of their circumcision status[22]. Moreover, a study prompted by reports by proponents of, "foreskin restoration", stated that there is a, "disparity between the mythology and medical reality of circumcision regarding male sexuality"[112].

A psychopathology term that fits the sexual obsession with the prepuce is termed "partialism" (see the American Psychiatric Association's Diagnostic and Statistical Manual 5th Revision (DSM-5)[113] under "Paraphilia not Otherwise Specified" (ICD-10 code CM F65.9) in the sexual and gender Identity Disorders Section). A diagnosis is made for paraphilia if, "the behavior, sexual urges, or fantasies cause clinically significant distress or impairment in social, occupational,

or other important areas of functioning". The definition of partialism is, "exclusive focus on part of the body"[114].

After "foreskin restoration", claimed benefits of, "increased sensitivity" in reality are more likely a result of the friction of the foreskin, whether intact or newly created, on the moist or sweaty glans and undersurface of the prepuce in the un-aroused state and would obviously, in the "re-uncircumcised" penis, have nothing to do with an increase in touch receptors, as in most instances nerves tend not to regenerate. Moreover, in RCTs, follow-up of young healthy men after circumcision found they experienced no decrease in sensitivity during sexual intercourse[23,24].

A detailed professional analysis of psychiatric aspects in eight patients seeking prepuce restoration noted several psychological disorders[115]. These included narcissistic and exhibitionistic body image, depression, major defects in early mothering and ego pathology. These men had a preoccupation with their absent foreskin and represented a subgroup within the community of men who have sex with men[115]. Of the 1200 members of one organization devoted to foreskin restoration, 80% were homosexual, 10% were bisexual and 10% were heterosexual. The overall membership comprised 65% who were uncircumcised, 30% who were circumcised and 5% who were partially circumcised. Although many were happy with the result, thus justifying to themselves the decision to undertake this procedure, others disliked their new genital status, even choosing to undergo re-circumcision[116].

CONCLUSION

Criticisms of the AAP policy statement supporting IMC fail to withstand scrutiny. The Hippocratic Oath states, "I will prevent disease whenever I can, for prevention is preferable to cure"[117,118]. Disease prevention is central to affirmative IMC policy recommendations. Given the immediate and lifelong protections and very low risk of adverse events, failure to recommend IMC or to suggest circumcision should be delayed seems unethical. We do not think the one-sided arguments opposing IMC are naïve. Rather, they involve deliberate obfuscation in support of an underlying agenda aimed at stopping IMC. We trust that our critical evaluation will set the record straight in the best interest of pediatrics, preventive medicine and individual wellbeing.

REFERENCES

1 **Darby R**. Risks, benefits, complications and harms: neglected factors in the current debate on non-therapeutic circumcision. *Kennedy Inst Ethics J* 2015; **25**: 1-34 [PMID: 25843118 DOI: 10.1353/ken.2015.0004]

2 Circumcision policy statement. American Academy of Pediatrics. Task Force on Circumcision. *Pediatrics* 1999; **103**: 686-693 [PMID: 10049981 DOI: 10.1542/peds.103.3.686]

3 **Frisch M**, Aigrain Y, Barauskas V, Bjarnason R, Boddy SA, Czauderna P, de Gier RP, de Jong TP, Fasching G, Fetter W, Gahr M, Graugaard C, Greisen G, Gunnarsdottir A, Hartmann W, Havranek P, Hitchcock R, Huddart S, Janson S, Jaszczak P, Kupferschmid C, Lahdes-Vasama T, Lindahl H, MacDonald N, Markestad T, Märtson M, Nordhov SM, Pälve H, Petersons A, Quinn F, Qvist N, Rosmundsson T, Saxen H, Söder O, Stehr M, von Loewenich VC, Wallander J, Wijnen R. Cultural bias in the AAP's 2012 Technical Report and Policy Statement on male circumcision. *Pediatrics* 2013; **131**: 796-800 [PMID: 23509170]

4 **Svoboda JS**, Van Howe RS. Out of step: fatal flaws in the latest AAP policy report on neonatal circumcision. *J Med Ethics* 2013; **39**: 434-441 [PMID: 23508208 DOI: 10.1136/medethics-2013-101346]

5 **Task Force on Circumcision.** Cultural bias and circumcision: the AAP Task Force on circumcision responds. *Pediatrics* 2013; **131**: 801-804 [PMID: 23509171 DOI: 10.1542/peds.2013-0081]

6 **Morris BJ**, Tobian AA, Hankins CA, Klausner JD, Banerjee J, Bailis SA, Moses S, Wiswell TE. Veracity and rhetoric in paediatric medicine: a critique of Svoboda and Van Howe's response to the AAP policy on infant male circumcision. *J Med Ethics* 2014; **40**: 463-470 [PMID: 23955288 DOI: 10.1136/medethics-2013-101614]

7 **Royal Australasian College of Physicians**. Paediatrics & Child Health Division. Circumcision of infant males. [accessed 2015 May 5]. Available from: URL: http//www.racp.edu.au/index.cfm?objectid=65118B16-F145-8B74-236C86100E4E3E8E

8 **Morris BJ**, Wodak AD, Mindel A, Schrieber L, Duggan KA, Dilley A, Willcourt RJ, Lowy M, Cooper DA. The 2010 Royal Australasian College of Physicians' policy statement 'Circumcision of infant males' is not evidence based. *Intern Med J* 2012; **42**: 822-828 [PMID: 22805686 DOI: 10.1111/j.1445-5994.2012.02823.x]

9 **Centers for Disease Control and Prevention**. Recommendations for Providers Counseling Male Patients and Parents Regarding Male Circumcision and the Prevention of HIV Infection, STIs, and Other Health Outcomes. [accessed 2015 May 5]. Available from: URL: http//www.regulations.gov/ - !documentDetail;D=CDC-2014-0012-0002

10 **Morris BJ**, Wodak AD, Mindel A, Schrieber L, Duggan KA, Dilly A, Willcourt RJ, Cooper DA, Lumbers ER, Russell CT, Leeder SR. Infant male circumcision: An evidence-based policy statement. *Open J Prevent Med* 2012; **2**: 79-82 [DOI: 10.4236/ojpm.2012.21012]

11 **Williamson ML**, Williamson PS. Women's preferences for penile circumcision in sexual partners. *J Sex Educ Ther* 1988; **14**: 8-12 [DOI: 10.1080/01614576.1988.11074930]

12 **Morris BJ**, Bailis SA, Wiswell TE. Circumcision rates in the United States: rising or falling? What effect might the new affirmative pediatric policy statement have? *Mayo Clin Proc* 2014; **89**: 677-686 [PMID: 24702735 DOI: 10.1016/j.mayocp.2014.01.001]

13 **Bhat GH**, Bhat MA, Kour K, Shah BA. Density and structural variations of Meissner's corpuscles at different sites in human glaborous skin. *J Anat Soc India* 2008; **57**: 30-33

14 **Fleiss PM**, Hodges FM. What Your Doctor May Not Tell You about Circumcision. New York: Grand Central Publishing, 2002

15 **Sorrells ML**, Snyder JL, Reiss MD, Eden C, Milos MF, Wilcox N, Van Howe RS. Fine-touch pressure thresholds in the adult penis. *BJU Int* 2007; **99**: 864-869 [PMID: 17378847 DOI: 10.1111/j.1464-410X.2006.06685.x]

16 **Kim D**, Pang MG. The effect of male circumcision on sexuality. *BJU Int* 2007; **99**: 619-622 [PMID: 17155977 DOI: 10.1111/j.1464-410X.2006.06646.x]

17 **Waskett JH**, Morris BJ. Fine-touch pressure thresholds in the adult penis. *BJU Int* 2007; **99**: 1551-1552 [PMID: 17537227 DOI: 10.1111/j.1464-410X.2007.06970_6.x]

18 **Willcourt R**. The effect of male circumcision on sexuality. *BJU Int* 2007; **99**: 1169-1170 [PMID: 17437447 DOI: 10.1111/j.1464-410X.2007.06895_3.x]

19 **Dias J**, Freitas R, Amorim R, Espiridião P, Xambre L, Ferraz L. Adult circumcision and male sexual health: a retrospective analysis. *Andrologia* 2014; **46**: 459-464 [PMID: 23600924 DOI: 10.1111/and.12101]

20 **Cox G**, Krieger JN, Morris BJ. Histological correlates of penile sexual sensation: Does circumcision make a difference? *Sex Med*

2015; **3**: 76-85 [PMID: 26185672 DOI: 10.1002/sm2.67]
21 **Morris BJ**, Krieger JN. Does male circumcision affect sexual function, sensitivity, or satisfaction?--a systematic review. *J Sex Med* 2013; **10**: 2644-2657 [PMID: 23937309 DOI: 10.1111/jsm.12293]
22 **Tian Y**, Liu W, Wang JZ, Wazir R, Yue X, Wang KJ. Effects of circumcision on male sexual functions: a systematic review and meta-analysis. *Asian J Androl* 2013; **15**: 662-666 [PMID: 23749001 DOI: 10.1038/aja.2013.47]
23 **Kigozi G**, Watya S, Polis CB, Buwembo D, Kiggundu V, Wawer MJ, Serwadda D, Nalugoda F, Kiwanuka N, Bacon MC, Ssempijja V, Makumbi F, Gray RH. The effect of male circumcision on sexual satisfaction and function, results from a randomized trial of male circumcision for human immunodeficiency virus prevention, Rakai, Uganda. *BJU Int* 2008; **101**: 65-70 [PMID: 18086100 DOI: 10.1111/j.1464-410X.2007.07369.x]
24 **Krieger JN**, Mehta SD, Bailey RC, Agot K, Ndinya-Achola JO, Parker C, Moses S. Adult male circumcision: effects on sexual function and sexual satisfaction in Kisumu, Kenya. *J Sex Med* 2008; **5**: 2610-2622 [PMID: 18761593 DOI: 10.1111/j.1743-6109.2008.00979.x]
25 **Homfray V**, Tanton C, Mitchell KR, Miller RF, Field N, Macdowall W, Wellings K, Sonnenberg P, Johnson AM, Mercer CH. Examining the association between male circumcision and sexual function: evidence from a British probability survey. *AIDS* 2015; **29**: 1411-1416 [PMID: 26091302 DOI: 10.1097/QAD.0000000000000745]
26 **Bossio JA**, Pukall CF, Steele SS. Examining penile sensitivity in neonatally circumcised and intact men using quantitative sensory testing. *J Urol* 2016; **195**: 1848-1853 [PMID: 26724395 DOI: 10.1016/j.juro.2015.12.080]
27 **Bailis SA**, Halperin D. Review of book 'A Surgical Temptation: The Demonisation of the Foreskin and the Rise of Circumcision in Britain' by Robert Darby. *BMJ* 2006; **332**: 183
28 **Darby R**. A Surgical Temptation: The Demonization of the Foreskin and the Rise in Circumcision in Britain. Chicago: University of Chicago Press, 2005
29 **Morris BJ**, Wamai RG, Henebeng EB, Tobian AA, Klausner JD, Banerjee J, Hankins CA. Estimation of country-specific and global prevalence of male circumcision. *Popul Health Metr* 2016; **4**: 1-13 [PMID: 26933388 DOI: 10.1186/s12963-016-0073-5]
30 **Morris BJ**, Waskett JH, Banerjee J, Wamai RG, Tobian AA, Gray RH, Bailis SA, Bailey RC, Klausner JD, Willcourt RJ, Halperin DT, Wiswell TE, Mindel A. A 'snip' in time: what is the best age to circumcise? *BMC Pediatr* 2012; **12**: 20 [PMID: 22373281 DOI: 10.1186/1471-2431-12-20]
31 **El Bcheraoui C**, Zhang X, Cooper CS, Rose CE, Kilmarx PH, Chen RT. Rates of adverse events associated with male circumcision in U.S. medical settings, 2001 to 2010. *JAMA Pediatr* 2014; **168**: 625-634 [PMID: 24820907 DOI: 10.1001/jamapediatrics.2013.5414]
32 **Chambers M**. Circumcision ban overturned in Germany. [accessed 2015 Dec 12]. Available from: URL: http//www.theglobeandmail.com/news/world/circumcision-ban-overturned-in-germany/article6288050/
33 **Stafford N**. German ethics council backs religious circumcision if specific conditions met. *BMJ* 2012; **345**: e5789 [PMID: 22930712 DOI: 10.1136/bmj.e5789]
34 **Bates MJ**, Ziegler JB, Kennedy SE, Mindel A, Wodak AD, Zoloth LS, Tobian AA, Morris BJ. Recommendation by a law body to ban infant male circumcision has serious worldwide implications for pediatric practice and human rights. *BMC Pediatr* 2013; **13**: 136 [PMID: 24010685 DOI: 10.1186/1471-2431-13-136]
35 **Lewis EN**, Griffin MR, Szilagyi PG, Zhu Y, Edwards KM, Poehling KA. Childhood influenza: number needed to vaccinate to prevent 1 hospitalization or outpatient visit. *Pediatrics* 2007; **120**: 467-472 [PMID: 17766517 DOI: 10.1542/peds.2007-0167]
36 **Weller S**, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database Syst Rev* 2002; **(1)**: CD003255 [PMID: 11869658]
37 **Lopez LM**, Otterness C, Chen M, Steiner M, Gallo MF. Behavioral interventions for improving condom use for dual protection. *Cochrane Database Syst Rev* 2013; **(10)**: CD010662 [PMID: 24163112 DOI: 10.1002/14651858.CD010662.pub2]
38 **Morris BJ**, Hankins CA, Tobian AA, Krieger JN, Klausner JD. Does male circumcision protect against sexually transmitted infections? Arguments and meta-analyses to the contrary fail to withstand scrutiny. *ISRN Urol* 2014; **2014**: 684706 [PMID: 24944836 DOI: 10.1155/2014/684706]
39 **Tobian AA**, Gray RH. The medical benefits of male circumcision. *JAMA* 2011; **306**: 1479-1480 [PMID: 21972310 DOI: 10.1001/jama.2011.1431]
40 **Morris BJ**, Wiswell TE. Circumcision and lifetime risk of urinary tract infection: a systematic review and meta-analysis. *J Urol* 2013; **189**: 2118-2124 [PMID: 23201382 DOI: 10.1016/j.juro.2012.11.114]
41 **Badger J**. Circumcision, what you think. *Australian Forum* 1989; **2 (11)**: 10-29
42 **Badger J**. The great circumcision report part 2. *Australian Forum* 1989; **2 (11)**: 4-13
43 **Bailey RC**, Muga R, Poulussen R, Abicht H. The acceptability of male circumcision to reduce HIV infections in Nyanza Province, Kenya. *AIDS Care* 2002; **14**: 27-40 [PMID: 11798403 DOI: 10.1080/09540120220097919]
44 **Cortés-González JR**, Arratia-Maqueo JA, Gómez-Guerra LS. Does circumcision has an effect on female's perception of sexual satisfaction? *Rev Invest Clin* 2008; **60**: 227-230 [PMID: 18807735]
45 **Schultheiss D**, Truss MC, Stief CG, Jonas U. Uncircumcision: a historical review of preputial restoration. *Plast Reconstr Surg* 1998; **101**: 1990-1998 [PMID: 9623850]
46 **Kigozi G**, Lukabwe I, Kagaayi J, Wawer MJ, Nantume B, Kigozi G, Nalugoda F, Kiwanuka N, Wabwire-Mangen F, Serwadda D, Ridzon R, Buwembo D, Nabukenya D, Watya S, Lutalo T, Nkale J, Gray RH. Sexual satisfaction of women partners of circumcised men in a randomized trial of male circumcision in Rakai, Uganda. *BJU Int* 2009; **104**: 1698-1701 [PMID: 19522862 DOI: 10.1111/j.1464-410X.2009.08683.x]
47 **Anonymous**. AdamAndEve.com asks women: Do you prefer a circumcised or uncircumcised penis? [accessed 2014 Feb 20]. Available from: URL: http//www.prnewswire.com/news-releases/adamandevecom-asks-women-do-you-prefer-a-circumcised-or-uncircumcised-penis-246386151.html
48 **Laumann EO**, Masi CM, Zuckerman EW. Circumcision in the United States. Prevalence, prophylactic effects, and sexual practice. *JAMA* 1997; **277**: 1052-1057 [PMID: 9091693 DOI: 10.1001/jama.1997.03540370042034]
49 **Frisch M**, Lindholm M, Grønbæk M. Male circumcision and sexual function in men and women: a survey-based, cross-sectional study in Denmark. *Int J Epidemiol* 2011; **40**: 1367-1381 [PMID: 21672947 DOI: 10.1093/ije/dyr104]
50 **Morris BJ**, Waskett JH, Gray RH. Does sexual function survey in Denmark offer any support for male circumcision having an adverse effect? *Int J Epidemiol* 2012; **41**: 310-312; author reply 312-314 [PMID: 22422464 DOI: 10.1093/ije/dyr180]
51 **O'Hara K**, O'Hara J. The effect of male circumcision on the sexual enjoyment of the female partner. *BJU Int* 1999; **83** Suppl 1: 79-84 [PMID: 10349418]
52 **Morris BJ**, Gray RH, Castellsague X, Bosch FX, Halperin DT, Waskett JH, Hankins CA. The strong protective effect of circumcision against cancer of the penis. *Adv Urol* 2011; **2011**: 812368 [PMID: 21687572 DOI: 10.1155/2011/812368]
53 **Elder JS**. Urinary tract infections. In: Kligeman RM, Behrman re, jenson hb, stanton bf. textbook of pediatrics. 18th ed. Philadelphia: Saunders Elsevier, 2007: 2223-2228
54 **Morris BJ**, Bailey RC, Klausner JD, Leibowitz A, Wamai RG, Waskett JH, Banerjee J, Halperin DT, Zoloth L, Weiss HA, Hankins CA. Review: a critical evaluation of arguments opposing male circumcision for HIV prevention in developed countries. *AIDS Care*

2012; **24**: 1565-1575 [PMID: 22452415 DOI: 10.1080/09540121.2012.661836]
55 **Benatar M**, Benatar D. Between prophylaxis and child abuse: the ethics of neonatal male circumcision. *Am J Bioeth* 2003; **3**: 35-48 [PMID: 12859815]
56 **Benatar D**, Benatar M. How not to argue about circumcision. *Am J Bioeth* 2003; **3**: W1 [PMID: 14635630]
57 **Benatar D**. Evaluations of circumcision should be circumscribed by the evidence. *J Med Ethics* 2013; **39**: 431-432 [PMID: 23728421 DOI: 10.1136/medethics-2013-101519]
58 **Jacobs AJ**. The ethics of circumcision of male infants. *Isr Med Assoc J* 2013; **15**: 60-65 [PMID: 23484246]
59 **Jacobs AJ**, Arora KS. Ritual male infant circumcision and human rights. *Am J Bioeth* 2015; **15**: 30-39 [PMID: 25674955 DOI: 10.1080/15265161.2014.990162]
60 **Bester JC**. Ritual male infant circumcision: the consequences and the principles say yes. *Am J Bioeth* 2015; **15**: 56-58 [PMID: 25674963 DOI: 10.1080/15265161.2014.990164]
61 **American Urological Association**. Circumcision. [accessed 2015 Dec 10]. Available from: URL: http//www.auanet.org/about/policy-statements/circumcision.cfm
62 **Merkel R**, Putzke H. After Cologne: male circumcision and the law. Parental right, religious liberty or criminal assault? *J Med Ethics* 2013; **39**: 444-449 [PMID: 23698890 DOI: 10.1136/medethics-2012-101284]
63 **Svoboda JS**. Circumcision of male infants as a human rights violation. *J Med Ethics* 2013; **39**: 469-474 [PMID: 23698885 DOI: 10.1136/medethics-2012-101229]
64 **Van Howe RS**. Infant circumcision: the last stand for the dead dogma of parental (sovereignal) rights. *J Med Ethics* 2013; **39**: 475-481 [PMID: 23698886 DOI: 10.1136/medethics-2012-101209]
65 **Clark PA**, Eisenman J, Szapor S. Mandatory neonatal male circumcision in Sub-Saharan Africa: medical and ethical analysis. *Med Sci Monit* 2007; **13**: RA205-RA213 [PMID: 18049444]
66 **Mazor J**. The child's interests and the case for the permissibility of male infant circumcision. *J Med Ethics* 2013; **39**: 421-428 [PMID: 23698892 DOI: 10.1136/medethics-2013-101318]
67 **Brusa M**, Barilan YM. Cultural circumcision in EU public hospitals--an ethical discussion. *Bioethics* 2009; **23**: 470-482 [PMID: 19076127 DOI: 10.1111/j.1467-8519.2008.00683.x]
68 **Koyle MA**, Barqawi A, Wild J, Passamaneck M, Furness PD. Pediatric urinary tract infections: the role of fluoroquinolones. *Pediatr Infect Dis J* 2003; **22**: 1133-1137 [PMID: 14688587 DOI: 10.1097/01.inf.0000101849.11912.8e]
69 **Rushton HG**, Majd M. Pyelonephritis in male infants: how important is the foreskin? *J Urol* 1992; **148**: 733-736; discussion 736-738 [PMID: 1640557]
70 **Rushton HG**, Majd M. Dimercaptosuccinic acid renal scintigraphy for the evaluation of pyelonephritis and scarring: a review of experimental and clinical studies. *J Urol* 1992; **148**: 1726-1732 [PMID: 1331545]
71 **Rushton HG**. Urinary tract infections in children. Epidemiology, evaluation, and management. *Pediatr Clin North Am* 1997; **44**: 1133-1169 [PMID: 9326956]
72 **Hoberman A**, Wald ER, Hickey RW, Baskin M, Charron M, Majd M, Kearney DH, Reynolds EA, Ruley J, Janosky JE. Oral versus initial intravenous therapy for urinary tract infections in young febrile children. *Pediatrics* 1999; **104**: 79-86 [PMID: 10390264]
73 **Zorc JJ**, Kiddoo DA, Shaw KN. Diagnosis and management of pediatric urinary tract infections. *Clin Microbiol Rev* 2005; **18**: 417-422 [PMID: 15831830 DOI: 10.1128/CMR.18.2.417-422.2005]
74 **Morris BJ**. Why circumcision is a biomedical imperative for the 21st century. *Bioessays* 2007; **29**: 1147-1158 [PMID: 17935209 DOI: 10.1002/bies.20654]
75 **Clifford ID**, Craig SS, Nataraja RM, Panabokke G. Paediatric paraphimosis. *Emerg Med Australas* 2016; **28**: 96-99 [PMID: 26781045 DOI: 10.1111/1742-6723.12532]
76 **O'Farrell N**, Quigley M, Fox P. Association between the intact foreskin and inferior standards of male genital hygiene behaviour: a cross-sectional study. *Int J STD AIDS* 2005; **16**: 556-559 [PMID: 16105191 DOI: 10.1258/0956462054679151]
77 **Liu CM**, Hungate BA, Tobian AA, Serwadda D, Ravel J, Lester R, Kigozi G, Aziz M, Galiwango RM, Nalugoda F, Contente-Cuomo TL, Wawer MJ, Keim P, Gray RH, Price LB. Male circumcision significantly reduces prevalence and load of genital anaerobic bacteria. *MBio* 2013; **4**: e00076 [PMID: 23592260 DOI: 10.1128/mBio.00076-13]
78 **Liu CM**, Hungate BA, Tobian AA, Ravel J, Prodger JL, Serwadda D, Kigozi G, Galiwango RM, Nalugoda F, Keim P, Wawer MJ, Price LB, Gray RH. Penile microbiota and female partner bacterial vaginosis in Rakai, Uganda. *MBio* 2015; **6**: e00589 [PMID: 26081632 DOI: 10.1128/mBio.00589-15]
79 **Nelson DE**, Dong Q, Van der Pol B, Toh E, Fan B, Katz BP, Mi D, Rong R, Weinstock GM, Sodergren E, Fortenberry JD. Bacterial communities of the coronal sulcus and distal urethra of adolescent males. *PLoS One* 2012; **7**: e36298 [PMID: 22606251 DOI: 10.1371/journal.pone.0036298]
80 **Balci M**, Tuncel A, Baran I, Guzel O, Keten T, Aksu N, Atan A. High-risk oncogenic human papilloma virus infection of the foreskin and microbiology of smegma in prepubertal boys. *Urology* 2015; **86**: 368-372 [PMID: 26199167 DOI: 10.1016/j.urology.2015.04.034]
81 **Nakagawa T**, Toguri AG. Penile zipper injury. *Med Princ Pract* 2006; **15**: 303-304 [PMID: 16763399 DOI: 10.1159/000092995]
82 **Vanbuskirk K**, Winer RL, Hughes JP, Feng Q, Arima Y, Lee SK, Stern ME, O'Reilly SF, Koutsky LA. Circumcision and acquisition of human papillomavirus infection in young men. *Sex Transm Dis* 2011; **38**: 1074-1081 [PMID: 21992987 DOI: 10.1097/OLQ.0b013e31822e60cb]
83 **Vardas E**, Giuliano AR, Goldstone S, Palefsky JM, Moreira ED, Penny ME, Aranda C, Jessen H, Moi H, Ferris DG, Liaw KL, Marshall JB, Vuocolo S, Barr E, Haupt RM, Garner EI, Guris D. External genital human papillomavirus prevalence and associated factors among heterosexual men on 5 continents. *J Infect Dis* 2011; **203**: 58-65 [PMID: 21148497 DOI: 10.1093/infdis/jiq015]
84 **Backes DM**, Bleeker MC, Meijer CJ, Hudgens MG, Agot K, Bailey RC, Ndinya-Achola JO, Hayombe J, Hogewoning CJ, Moses S, Snijders PJ, Smith JS. Male circumcision is associated with a lower prevalence of human papillomavirus-associated penile lesions among Kenyan men. *Int J Cancer* 2012; **130**: 1888-1897 [PMID: 21618520 DOI: 10.1002/ijc.26196]
85 **Gray RH**, Serwadda D, Kong X, Makumbi F, Kigozi G, Gravitt PE, Watya S, Nalugoda F, Ssempijja V, Tobian AA, Kiwanuka N, Moulton LH, Sewankambo NK, Reynolds SJ, Quinn TC, Iga B, Laeyendecker O, Oliver AE, Wawer MJ. Male circumcision decreases acquisition and increases clearance of high-risk human papillomavirus in HIV-negative men: a randomized trial in Rakai, Uganda. *J Infect Dis* 2010; **201**: 1455-1462 [PMID: 20370483 DOI: 10.1086/652184]
86 **Senkomago V**, Backes DM, Hudgens MG, Poole C, Agot K, Moses S, Snijders PJ, Meijer CJ, Hesselink AT, Schlecht NF, Bailey RC, Smith JS. Acquisition and persistence of human papillomavirus 16 (HPV-16) and HPV-18 among men with high-HPV viral load infections in a circumcision trial in Kisumu, Kenya. *J Infect Dis* 2015; **211**: 811-820 [PMID: 25261492]
87 **Tobian AA**, Serwadda D, Quinn TC, Kigozi G, Gravitt PE, Laeyendecker O, Charvat B, Ssempijja V, Riedesel M, Oliver AE, Nowak RG, Moulton LH, Chen MZ, Reynolds SJ, Wawer MJ, Gray RH. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *N Engl J Med* 2009; **360**: 1298-1309 [PMID: 19321868 DOI: 10.1056/NEJMoa0802556]
88 **Wilson LE**, Gravitt P, Tobian AA, Kigozi G, Serwadda D, Nalugoda F, Watya S, Wawer MJ, Gray RH. Male circumcision reduces penile high-risk human papillomavirus viral load in a randomised clinical trial in Rakai, Uganda. *Sex Transm Infect* 2013; **89**: 262-266 [PMID:

23112341 DOI: 10.1136/sextrans-2012-050633]
89 **Auvert B**, Sobngwi-Tambekou J, Cutler E, Nieuwoudt M, Lissouba P, Puren A, Taljaard D. Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in Orange Farm, South Africa. *J Infect Dis* 2009; **199**: 14-19 [PMID: 19086814 DOI: 10.1086/595566]
90 **Tarnaud C**, Lissouba P, Cutler E, Puren A, Taljaard D, Auvert B. Association of low-risk human papillomavirus infection with male circumcision in young men: results from a longitudinal study conducted in Orange Farm (South Africa). *Infect Dis Obstet Gynecol* 2011; **2011**: 567408 [PMID: 21584275 DOI: 10.1155/2011/567408]
91 **Morris BJ**, Mindel A, Tobian AA, Hankins CA, Gray RH, Bailey RC, Bosch X, Wodak AD. Should male circumcision be advocated for genital cancer prevention? *Asian Pac J Cancer Prev* 2012; **13**: 4839-4842 [PMID: 23167429 DOI: 10.7314/APJCP.2012.13.9.4839]
92 **Castellsagué X**, Bosch FX, Muñoz N, Meijer CJ, Shah KV, de Sanjose S, Eluf-Neto J, Ngelangel CA, Chichareon S, Smith JS, Herrero R, Moreno V, Franceschi S. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med* 2002; **346**: 1105-1112 [PMID: 11948269 DOI: 10.1056/NEJMoa011688]
93 **Barbaro B**, Brotherton JM. Measuring HPV vaccination coverage in Australia: comparing two alternative population-based denominators. *Aust N Z J Public Health* 2015; **39**: 326-330 [PMID: 26094817 DOI: 10.1111/1753-6405.12372]
94 **Holman DM**, Benard V, Roland KB, Watson M, Liddon N, Stokley S. Barriers to human papillomavirus vaccination among US adolescents: a systematic review of the literature. *JAMA Pediatr* 2014; **168**: 76-82 [PMID: 24276343 DOI: 10.1001/jamapediatrics.2013.2752]
95 **Auvert B**, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med* 2005; **2**: e298 [PMID: 16231970 DOI: 10.1371/journal.pmed.0020298]
96 **Bailey RC**, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, Williams CF, Campbell RT, Ndinya-Achola JO. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007; **369**: 643-656 [PMID: 17321310 DOI: 10.1016/S0140-6736(07)60312-2]
97 **Gray RH**, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, Kiwanuka N, Moulton LH, Chaudhary MA, Chen MZ, Sewankambo NK, Wabwire-Mangen F, Bacon MC, Williams CF, Opendi P, Reynolds SJ, Laeyendecker O, Quinn TC, Wawer MJ. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007; **369**: 657-666 [PMID: 17321311 DOI: 10.1016/S0140-6736(07)60313-4]
98 **Sobngwi-Tambekou J**, Taljaard D, Lissouba P, Zarca K, Puren A, Lagarde E, Auvert B. Effect of HSV-2 serostatus on acquisition of HIV by young men: results of a longitudinal study in Orange Farm, South Africa. *J Infect Dis* 2009; **199**: 958-964 [PMID: 19220143 DOI: 10.1086/597208]
99 **Mehta SD**, Moses S, Agot K, Maclean I, Odoyo-June E, Li H, Bailey RC. Medical male circumcision and herpes simplex virus 2 acquisition: posttrial surveillance in Kisumu, Kenya. *J Infect Dis* 2013; **208**: 1869-1876 [PMID: 23901089 DOI: 10.1093/infdis/jit371]
100 **Tobian AA**, Charvat B, Ssempijja V, Kigozi G, Serwadda D, Makumbi F, Iga B, Laeyendecker O, Riedesel M, Oliver A, Chen MZ, Reynolds SJ, Wawer MJ, Gray RH, Quinn TC. Factors associated with the prevalence and incidence of herpes simplex virus type 2 infection among men in Rakai, Uganda. *J Infect Dis* 2009; **199**: 945-949 [PMID: 19220138 DOI: 10.1086/597074]
101 **Sobngwi-Tambekou J**, Taljaard D, Nieuwoudt M, Lissouba P, Puren A, Auvert B. Male circumcision and Neisseria gonorrhoeae, Chlamydia trachomatis and Trichomonas vaginalis: observations after a randomised controlled trial for HIV prevention. *Sex Transm Infect* 2009; **85**: 116-120 [PMID: 19074928 DOI: 10.1136/sti.2008.032334]
102 **Mehta SD**, Gaydos C, Maclean I, Odoyo-June E, Moses S, Agunda L, Quinn N, Bailey RC. The effect of medical male circumcision on urogenital Mycoplasma genitalium among men in Kisumu, Kenya. *Sex Transm Dis* 2012; **39**: 276-280 [PMID: 22421693 DOI: 10.1097/OLQ.0b013e318240189c]
103 **Wawer MJ**, Tobian AA, Kigozi G, Kong X, Gravitt PE, Serwadda D, Nalugoda F, Makumbi F, Ssempijja V, Sewankambo N, Watya S, Eaton KP, Oliver AE, Chen MZ, Reynolds SJ, Quinn TC, Gray RH. Effect of circumcision of HIV-negative men on transmission of human papillomavirus to HIV-negative women: a randomised trial in Rakai, Uganda. *Lancet* 2011; **377**: 209-218 [PMID: 21216000 DOI: 10.1016/S0140-6736(10)61967-8]
104 **Davis MA**, Gray RH, Grabowski MK, Serwadda D, Kigozi G, Gravitt PE, Nalugoda F, Watya S, Wawer MJ, Quinn TC, Tobian AA. Male circumcision decreases high-risk human papillomavirus viral load in female partners: a randomized trial in Rakai, Uganda. *Int J Cancer* 2013; **133**: 1247-1252 [PMID: 23400966 DOI: 10.1002/ijc.28100]
105 **Tobian AA**, Kong X, Wawer MJ, Kigozi G, Gravitt PE, Serwadda D, Eaton KP, Nalugoda F, Quinn TC, Gray RH. Circumcision of HIV-infected men and transmission of human papillomavirus to female partners: analyses of data from a randomised trial in Rakai, Uganda. *Lancet Infect Dis* 2011; **11**: 604-612 [PMID: 21489882]
106 **Tobian AA**, Kigozi G, Redd AD, Serwadda D, Kong X, Oliver A, Nalugoda F, Quinn TC, Gray RH, Wawer MJ. Male circumcision and herpes simplex virus type 2 infection in female partners: a randomized trial in Rakai, Uganda. *J Infect Dis* 2012; **205**: 486-490 [PMID: 22147796 DOI: 10.1093/infdis/jir767]
107 **Gray RH**, Kigozi G, Serwadda D, Makumbi F, Nalugoda F, Watya S, Moulton L, Chen MZ, Sewankambo NK, Kiwanuka N, Sempijja V, Lutalo T, Kagayii J, Wabwire-Mangen F, Ridzon R, Bacon M, Wawer MJ. The effects of male circumcision on female partners' genital tract symptoms and vaginal infections in a randomized trial in Rakai, Uganda. *Am J Obstet Gynecol* 2009; **200**: 42.e1-42.e7 [PMID: 18976733 DOI: 10.1016/j.ajog.2008.07.069]
108 **Tobian AA**, Gaydos C, Gray RH, Kigozi G, Serwadda D, Quinn N, Grabowski MK, Musoke R, Ndyanabo A, Nalugoda F, Wawer MJ, Quinn TC. Male circumcision and Mycoplasma genitalium infection in female partners: a randomised trial in Rakai, Uganda. *Sex Transm Infect* 2014; **90**: 150-154 [PMID: 24259189 DOI: 10.1136/sextrans-2013-051293]
109 **Van Howe RS**. Sexually transmitted infections and male circumcision: a systematic review and meta-analysis. *ISRN Urol* 2013; **2013**: 109846 [PMID: 23710368 DOI: 10.1155/2013/109846]
110 **Peterson S**. Assaulted and mutilated: a personal account of circumcision trauma. In: Denniston G, Hodges FM, Milos M, editors. Understanding Circumcision: A Multi-disciplinary Approach to a Multi-dimensional Problem. London and New York: Kluwer Academic and Plenum Press, 2001: 271-290
111 **Walter G**, Streimer J. Genital self-mutilation: attempted foreskin reconstruction. *Br J Psychiatry* 1990; **156**: 125-127 [PMID: 2404537]
112 **Collins S**, Upshaw J, Rutchik S, Ohannessian C, Ortenberg J, Albertsen P. Effects of circumcision on male sexual function: debunking a myth? *J Urol* 2002; **167**: 2111-2112 [PMID: 11956452]
113 **American Psychiatric Association**. Diagnostic & Statistical Manual 5th Revision (DSM-5). 2013. Available from: URL: http//www.dsm5.org/Pages/Default.aspx
114 **Kafka MP**. The DSM diagnostic criteria for paraphilia not otherwise specified. *Arch Sex Behav* 2010; **39**: 373-376 [PMID: 19779971 DOI: 10.1007/s10508-009-9552-0]
115 **Mohl PC**, Adams R, Greer DM, Sheley KA. Prepuce restoration seekers: psychiatric aspects. *Arch Sex Behav* 1981; **10**: 383-393 [PMID: 7295020]
116 **Schultheiss D**, Truss MC, Stief CG, Jonas U. Uncircumcision: a historical review of preputial restoration. *Plast Reconst Surg* 1998; **101**: 1990-1998 [PMID: 9623850]
117 **Kelishadi R**. To the readers. *Int J Prev Med* 2010; **1**: i [PMID:

21677759]
118 **Johns Hopkins University**. Hippocratic Oath, Modern version. [accessed 2015 Dec 21]. Available from: URL: http//guides.library.jhu.edu/c.php?g=202502&p=1335759

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REVIEW

Spectrum of intracranial incidental findings on pediatric brain magnetic resonance imaging: What clinician should know?

Surya N Gupta, Vikash S Gupta, Andrew C White

Surya N Gupta, Section of Child Neurology, Children's Hospital of Illinois, University of Illinois College of Medicine, Peoria, IL 61603, United States

Vikash S Gupta, Texila American University, Georgetown 30062, Guyana

Andrew C White, Department of General Surgery, University of Colorado Hospital, Aurora, CO 80045, United States

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Correspondence to: Surya N Gupta, MD, Professor (Pediatrics and Pediatric Neurology), Section of Child Neurology, Children's Hospital of Illinois, University of Illinois College of Medicine, 420 NE Glen Oak Ave, Suite 401, Peoria, IL 61603, United States. suryangupta@rediffmail.com
Telephone: +1-309-6554242
Fax: +1-309-6552565

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Abstract

Intracranial incidental findings on magnetic resonance imaging (MRI) of the brain continue to generate interest in healthy control, research, and clinical subjects. However, in clinical practice, the discovery of incidental findings acts as a "distractor". This review is based on existing heterogeneous reports, their clinical implications, and how the results of incidental findings influence clinical management. This draws attention to the followings: (1) the prevalence of clinically significant incidental findings is low; (2) there is a lack of a systematic approach to classification; and discusses (3) how to deal with the detected incidental findings based a proposed common clinical profile. Individualized neurological care requires an active discussion regarding the need for neuroimaging. Clinical significance of incidental findings should be decided based on lesion's neuroradiologic characteristics in the given clinical context. Available evidence suggests that the outcome of an incidentally found "serious lesion in children" is excellent. Future studies of intracranial incidental findings on pediatric brain MRI should be focused on a homogeneous population. The study should address this clinical knowledge based review powered by the statistical analyses.

Key words: Intracranial incidental finding; Magnetic resonance imaging; Children; Common clinical profile; Seizure; Headache; Developmental delay

Core tip: The magnetic resonance imaging of the brain in children frequently reveals incidental findings. There is paucity in the literature, how to deal with such findings in clinical practice. This review based on existing heterogeneous reports reveals that the prevalence of clinically significant incidental findings is low and discusses options in the management of incidental findings in children.

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INTRODUCTION

Magnetic resonance imaging (MRI) of the brain is the most commonly performed investigation in the practice of pediatric neurology. During a clinical evaluation, an unexpected finding on brain MRI is a common occurrence. This heightens parental anxiety and generates explanatory discrepancies amongst physicians. Discovery of such findings on neuroimaging is not unique or limited to pediatric brain MRI. Rather, it has been reported in several other conditions such as abdominal and pelvic computerized tomography (CT) and MRI[1] or in asymptomatic ankles[2]. Additionally, these findings have been described in asymptomatic healthy volunteer adults[3], young adults in the community, and in clinic-based subjects[4].

In clinical practice, MRI of the brain is performed for a variety of indications. Infrequently, findings like pituitary adenoma, lesions of the pineal gland, or central nervous system malignancy are discovered, which have serious implications.

Authors present the evidence-based reports of the current body of knowledge regarding such findings, their clinical implications, and how these findings translate to neurologic management, and discuss a common profile to aid in the clinical management of incidental finding.

METHODOLOGY: LITERATURE SEARCH AND THE RESULTS

In November 2014, we searched Ovid MEDLINE and PubMed databases for reports on the use of brain MRI in children aged 18 years and under. We supplemented the electronic searches with surveillance of electronic tables of contents in neurological journals and by hand searching the bibliographies of pertinent articles. Two authors (Gupta SN and White AC) read the title and abstract of every study identified by the electronic searches. We critically appraised the full text of potentially eligible studies. Two authors extracted data on study design, population characteristics, and MRI parameters from each study.

Several prospective and retrospective studies have reported incidental findings in pediatric patients. The MRIs of the brain were carried out as an investigatory step in children presenting within various disciplines of pediatric medicine. The summary of identified studies is provided in the Table 1[5-22].

TERMINOLOGY

The word "incidental or unexpected" generally applies when an identified brain lesion on neuroimaging would have not been predicated by clinicians. This definition can be questioned by some in specific clinical situation. Because the discovery of such lesions in the majority of children does not alter the management, some authors have described them as "benign findings", Schwedt *et al*[8], 2006.

Multiple terminology have been used to indicate white matter lesions such as periventricular malacia, periventricular white matter changes, white-matter hyperintensity, non-specific white matter abnormalities, white matter signal abnormality, and focal white matter lesion. In the exception to periventricular malacia, the question is if the rest of these terms are the same or of different pathologies. Clinicians have been charged with the task of determining whether or not these definitions are synonymous.

CLASSIFICATION

Intracranial incidental findings are inconsistently classified. The most findings being classified based upon their clinical significance, the type of lesion, normal variant *vs* abnormal finding, and the urgency for the referral.

Jordan *et al*[21], 2010, based on the need for referral, classified incidental finding into four categories: No referral, routine referral, urgent referral, or immediate referral. Graf *et al*[7], 2010 categorized neuroimaging results as normal, remarkable without clinical action, remarkable with clinical follow-up action, and abnormal. Bryan *et al*[23], 1994 used a very different classification, but a similar method which is used to classify the Cardiovascular Health Study in adults.

Yilmaz *et al*[5], 2014 classified incidental findings in five categories as follows: (1) cerebral abnormalities relevant to headache such as a growing tumor or hydrocephalus; (2) incidental cerebral abnormalities with potential clinical significance such as Chiari type I malformations, arachnoid cysts, cysts of pineal gland, and inflammatory lesions; (3) incidental cerebral abnormalities without clinical significance such as white matter hyperintensity, periventricular leukomalacia,

Table 1 Summarizes the reports of intracranial incidental findings in children on brain magnetic resonance imaging[5-22]

Ref.	Country	Study objective /conclusion
Yilmaz *et al*[5]	Turkey	To evaluate clinical significance of MRI abnormality in children with headache/ Despite the high rate of IFs, the yield is non-contributory to diagnosis and therapy
Bayram *et al*[6]	Turkey	To describe the prevalence of WML detected on MRI in children with headaches/ Non-specific WML may be seen in children with headache. In the absence of benefit, repeated MRI studies are unwarranted. It should be tailored according to clinical course
Graf *et al*[7]	United States	Studied the frequency and consequences of IFs on non-acute pediatric headache/ The frequency and types of all IFs were generally comparable to previous studies
Schwedt *et al*[8]	United States	To study the frequency of "benign" abnormalities in children with headache, compare it with the frequency of MRI findings that dictate a change in patient management/ About 20% children with headache have benign findings that do not result in a change in management which rarely occurred in 1.2% of children in this study
Koirala[9]	Nepal	To evaluate the yield of MRI findings in patients with seizure/ The majority of abnormalities on MRI included hippocampal sclerosis and T2 hyperintensity
Kalnin *et al*[10]	United States	To characterize IFs association with seizure onset and to standardize a classification system/ The MRI and a standardized scoring system demonstrated a higher rate of IFs than previously reported. MRI parameters need to expand the definition of significant IFs
Gupta *et al*[11]	United States	To test the hypothesis that children with developmental delay are more likely to have incidental findings than are the children with normal development status/ Authors reported a higher prevalence of IFs in children with developmental delay as compared with those with normal development status
Seki *et al*[12]	Japan	To report prevalence of IFs in healthy children and to suggest an ethical and practical management protocol/ The prevalence of IFs was high but those requiring further MRI was low. Evaluating equivocal findings was the most difficult part of IFs management
Gupta *et al*[13]	United States	To elucidate the prevalence of incidental findings in a general pediatric neurology practice/ Authors reported a high prevalence of and a low rate of referrals in comparison to previous studies. This study may help guide management decisions and discussions
Potchen *et al*[14]	Malawi	To collect normative magnetic resonance imaging data for clinical and research applications/ Incidental brain magnetic resonance abnormalities are common in Malawian children
Kim *et al*[15]	United States	To elucidate the prevalence of incidental findings in a healthy pediatric population/ Frequency of important IFs was not high. But, awareness of neurologic status, the presence and variety of IFs are of vital importance for research and welfare of the child
Oh *et al*[16]	South Korea	Incidental findings in pediatric specialty clinic other than neurology To investigated the clinical characteristics of children in whom Rathke's cleft cysts were incidentally discovered and the treatment response with endocrinopathy/ Rathke's cleft cysts less than 20 mm expressing cystic intensity can be treated medically
Rachmiel *et al*[17]	Canada	To assess IFs in children with congenital hypothyroidism compared to 38 healthy controls/ Both groups had a similar incidence of structural abnormalities. There was no association between those findings and neurocognitive function
Whitehead *et al*[18]	United States	The prevalence of pineal cysts in children who have had high-resolution 3T brain MRI/ Characteristic-appearing pineal cysts are benign findings. In lack of no referable comprehensive symptoms, no follow-up is required
Mogensen *et al*[19]	Denmark	To evaluate the outcome of brain MRI in girls referred with early signs of puberty/ Girls with central precocious puberty should have a brain MRI
Perret *et al*[20]	Switzerland	The prevalence and management options of incidentally found mass lesions at pediatric clinic/ A subgroup of lesions such as tectal glioma and dysembryoplastic neuroepithelial tumor can be monitored conservatively
Jordan *et al*[21]	United States	The prevalence of incidental findings on brain MRI in children with sickle cell disease/ IFs were present in 6.6% patients and a potentially serious or urgent finding was 0.6%

All except four studies: Potchen *et al*[14], 2013, Rachmiel *et al*[17], 2013, Koirala[9], 2011, and Seki *et al*[12], 2010, were retrospective. The retrospective study by Jordan *et al*[21], 2010 was carried out as a clinical trial for sickle cell disease. Itoh *et al*[22], 1994, investigated the evolution of high-signal–intensity abnormality on T2-weighted MR images[22] which are the expected findings thus it was excluded from this review. WML: White matter lesions; IFs: Incidental findings; MRI: Magnetic resonance imaging.

subtle gliosis, silent brain infarcts or lacune, and brain microbleeds; (4) extra-cerebral abnormalities relevant to headache such as sinusitis, which was considered as the cause of headache if an otolaryngologist made the diagnosis of sinusitis; and (5) incidental extra-cerebral abnormalities such as mucosal thickening or fluid retention in sinuses or mastoid cells.

The inclusion of "normal-variants" is confusing. For example, commonly occurring pineal cysts are an asymptomatic finding. Thus, this could be considered a normal finding[24]. But in a symptomatic patient with the same pineal cyst, there may be a true clinical implication[25,26]. In some patients, a particular finding in the context of clinical presentation after all may not be incidental. Occasionally, certain findings such as arachnoid cyst may be predicted in specific clinical situations[27,28].

Some of these findings are classified arbitrarily.

Table 2 Clinical demography of intracranial incidental findings on pediatric brain magnetic resonance imaging evaluated at general neurology clinic and at research center[5-15]

Ref.	Clinical demographics					Girls *n* (%) with MRI
	Study- setting	Reason for MRI	No. of subject	No. of MRI (%)	Mean age (range) year	
Yilmaz *et al*[5]	Pediatric neurology	Head pain	449	288 (64)[1]	11.2 (NA)	189 (58)
Bayram *et al*[6]			941	527 (61)[2]	12.1 (4-16)	NA
Graf *et al*[7]			400	91 (23)[2]	10.8 (3-18)	NA
Schwedt *et al*[8]			681	218 (32)[2]	12.1 (2-18)[3]	126 (52)
Koirala[9]	Pediatric and adult neurology	Seizure	36[c]	36 (100)[3]	NA (1-16)	NA
Kalnin *et al*[10]	Radiology		349	281 (81)	9.7 (6-14)	143 (51)
Gupta *et al*[11]	Pediatric neurology	Developmental delay	2185	771 (35)	7.6 (NA)	433 (56)
Gupta *et al*[13]		General	1618	666 (41)	9.8 (0-21)	280 (42)
Seki *et al*[12]	Research Institute	Healthy children	395	89 (25)[1]	NA (5-8)	53 (44)
Kim *et al*[15]	Radiology Research		225	198 (88)[1]	11.2 (1 mo-18)	126 (56)
Potchen *et al*[14]		Community-based	102	68 (71)[1]	12.1 (9-14)	54 (55)

[1]The MRI revealing extracranial incidental findings were excluded; [2]Children with computerized tomography of the brain were excluded; [3]Only pediatric patients are presented in Table. MRI: Magnetic resonance imaging; NA: Not available.

This practice has resulted in a variety of classification systems which lack clarity. There is an obvious need for a uniform classification system.

NEUROIMAGING

MRI acquisition modalities and the parameters utilized in these studies are variable.

Conventional brain MRI

The conventional MRI was usually performed by using 1.5 Tesla magnetic field strengths scanner. MRI parameters varied but conventional short-TR and short-TE, T1-weighted, long-TR and long-TE, T2-weighted, and fast fluid-attenuated inversion recovery-weighted images were performed in majority of patients. Diffusion and perfusion diffusions images were routinely available in North American Practice of Pediatric Neurology/ Neuroradiology.

Advance MRI

Diffusion tensor imaging is an application of diffusion weighted imaging which quantifies water diffusion by measuring molecular motion of water within the brain parenchyma. Lately, this modality has been increasingly used in studying the neuroanatomy of the brain[29]. This technique is useful particularly in the investigation of white matter abnormalities.

Reporting

Official interpretations are provided by different levels of trained and Board Certified Radiologists. A very limited number of MRI studies were reviewed by Board Certified Pediatric Neuroradiologists. The reporting procedure remains subjective.

The reports should distinguish cerebellar ectopia (downward displacement of cerebellar tonsil/s less than 1 cm through foramen magnum) from Chiari type I malformation. In the face of recent genetic and phenotypic correlation, there has been a retreat from the Dandy Walker "variant", thus it may be useful to just describe the posterior fossa abnormality. Most importantly, in case of serious lesions, the radiologic characteristics particularly the integrity of the blood-brain barrier should be described in detail.

Future studies may reveal the association between a patient's clinical status and the type of finding, while advances in neuroimaging may reveal their significance. Radiologists should report all such findings within the body of the text, in addition to their subjective interpretation.

The clinical demography of intracranial incidental findings is shown in Tables 2 and 3.

PREVALENCE

The prevalence of intracranial incidental findings is shown in Figure 1.

Variability in prevalence, lowest in healthy children (8%) and the highest in a specific neurologic condition can be explained by an increasing burden of a disorder on the brain. This is probably highest in an elderly brain secondary to ischemic injury particularly to white matter. Arguably, some of the white matter changes are expected findings in neurofibromatosis type I.

Despite suggestions that prevalence rate of incidental findings have increased with frequent use of neuroimaging, during the past decade, it has remained stable in children referred for non-acute headache, Graf *et al*[30], 2008. Of note, an increasing proportion of neuroimaging studies are being ordered by primary care providers.

TYPE AND DISTRIBUTION

Three most common incidental findings

The three most commonly reported intracranial incidental findings on brain MRI in various pediatric settings

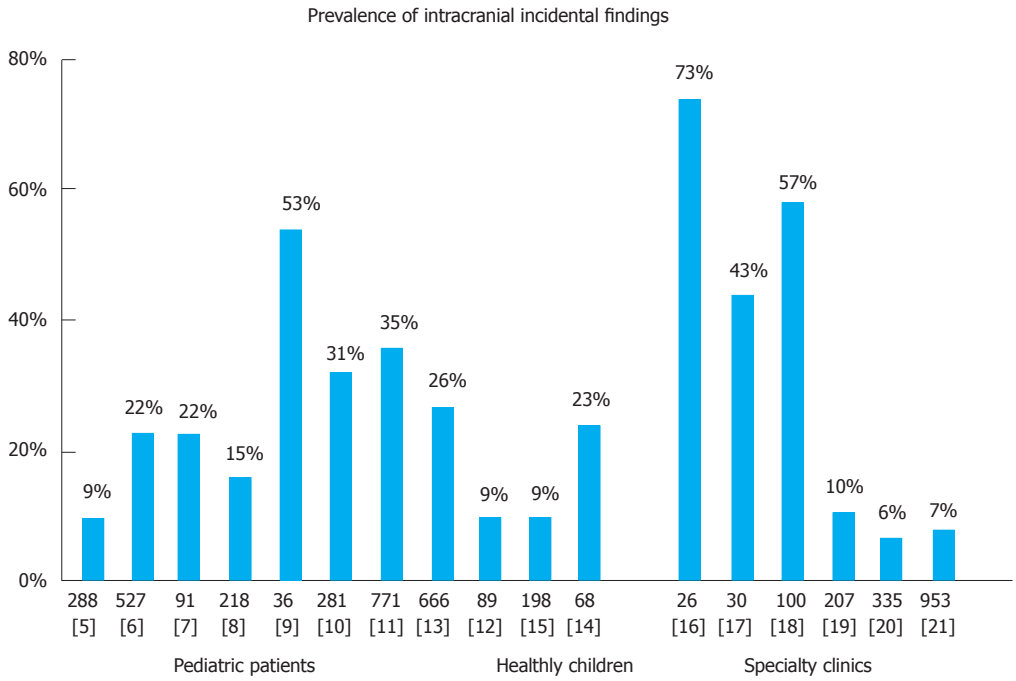

Figure 1 A comparative prevalence of incidental findings on pediatric magnetic resonance imaging of the studies. The numbers above bracket represents number of children in the study; Number in the brackets represents the reference for the study. The subjects in the studies' reference[5-13] except[12] on the left were from General Neurology Clinic. The studies'[16-21] on the right were from Specialty Clinics other than neurology. Three studies in middle; ref.[12,15] were from research in healthy children and the study[14] was community-based in healthy population.

Table 3 Clinical demography of children with intracranial incidental findings on pediatric brain magnetic resonance imaging studies at pediatric specialty clinic other than neurology[16-21]

Ref.	Study-setting	Reason for MRI	No. of subject	No. of MRI (%)	Clinical demographics	
					Mean age (range) year	Girls *n* (%) with MRI
Oh *et al*[16]	Endocrinology	Rathke's cleft cysts	34[1]	26 (76)	NA (4-18)	17 (65)
Rachmiel *et al*[17]	Endocrinology	Congenital hypothyroidism	68[2]	30 (100)	12.5 (10-15)	16 (55)
Whitehead *et al*[18]	Radiology	Pineal cyst	100	100 (100)	6.8 (1 mo-17)	52 (52)
Mogensen *et al*[19]	Endocrinology	Early puberty	229	207 (100)[3]	NA (6-9)	207 (100)
Perret *et al*[20]	Oncology	Primary brain tumor[4]	335	335 (100)	7.6 (0-18)	132 (39)
Jordan *et al*[21]	Neurology research	Sickle cell disease	953	953 (100)	9.2 (5-15)	460 (48)

[1]76% of patient with Rathke's cleft cysts were discovered during evaluations for endocrine disorders; [2]This includes 38 healthy boys 11.7 ± 1.7 years; [3]22 (11%) patients who had computerized tomography of the brain due to contraindication of MRI are not included in this table; [4]Central nervous system tumors were identified incidentally. MRI: Magnetic resonance imaging; NA: Not available.

are shown in Table 4. The types of incidental findings on MRI outside of a neurology-setting were generally comparable in these studies.

Incidental "serious brain lesion"

It should be noted that community or general pediatric neurology based studies in healthy subjects have not reported serious or progressively worsening incidentally identified lesions. Nonetheless, serious lesions have been reported by a few studies which are shown in the Table 5[31].

Morris *et al*[32] published a meta-analysis, which reviewed 16 studies of subjects within the age range of 1 to 97 years, all of whom had no neurological symptoms. All subjects had brain MRI performed for the purpose of research and for occupational or commercial screening. The authors reported 135 (0.70%) of 19559 subjects with a neoplastic incidental finding. No age specific prevalence of neoplastic lesion was available for children aged 1 to 9 years. After omitting 34 adults aged 90 to 99, only four 20 year age bands were left for analysis[32].

Serious lesions can be divided into two groups: (1) ones that are known to get worse, such as a tumor; and (2) those that have the potential for worsening over time, such as pituitary lesions, pineal cysts, or vascular malformations. Such lesions typically manifest with compressive symptoms localized to the adjacent neuroanatomical structure.

Incidental vascular malformations, although uncommon, are frequently asymptomatic, which can greatly complicate the clinical management. It should be noted

Table 4 Lists three most commonly reported intracranial incidental findings on brain magnetic resonance in various pediatric-settings[5-19]

Ref.	Three most common intracranial IFs, *n* (%)	Comment or serious finding
Yilmaz *et al*[5]	White-matter hyperintensity 14 (4.3) Old infarcts 4 (1.2), and CM I 3 (0.9)	2 (0.6%) malignant tumor and 1 hydrocephalus, 0.3% IFs were relevant to headache
Bayram *et al*[6]	Supratentorial non-specific WMC 23 (4.4)	All patients with IFs had normal development and no seizures or head trauma
Graf *et al*[7]	CM I 6 (15), arachnid cysts 6 (15), brain stem parenchymal abnormality, 4 (10)	Brain stem IFs included Dandy-Walker variant, cerebellar calcification, and tectal plate hyperintensity
Schwedt *et al*[8]	CM I 11 (4.6), nonspecific white matter abnormalities 7 (2.9), venous angiomas and arachnoid cyst each 5 (2.5)	Discovery of 4 tumors, 4 old infarcts, 3 CM I, and 2 moyamoya required a change in management
Koirala[9]	Hippocampal sclerosis, T2 hyperintense foci in various distributions, both 4 (21) each, cortical atrophy 3 (16)	Study focus was IFs in patient with seizure. The lesions were better detected by MRI than computerized tomography
Kalnin *et al*[10]	Ventricular enlargement 143 (51), leukomalacia/gliosis 64 (23), heterotopias and cortical dysplasia 33 (12)	Temporal lobe lesions were detected 15%, a higher frequency than in previous studies
Gupta *et al*[11]	Variant signal intensity 30 (18), WMC changes 23 (13), and PVL, 10 (6)	IFs were reported in children with developmental delay as to those with normal development status
Seki *et al*[12]	Cavum septi pellucid 6 (15) and Pineal cyst 2 (5), Enlarged perivascular spaces 1 (2.5)	Focus of the study was reporting of extracranial IFs in healthy children
Gupta *et al*[13]	CM I and cerebellar ectopia, 16 (3.5), Arachnoid cysts, 12 (1.8)	White matter changes were the most common IFs classified under normal-variants
Potchen *et al*[14]	PVW matter changes/gliosis 6 (6), mild diffuse atrophy 4 (4), and Empty sella 3 (3)	Incidental findings were unassociated with age, sex, antenatal problems, or febrile seizures
Kim *et al*[15]	Focal white matter lesion 3 (1.3), arachnoid cyst, frontal venous angioma, and mega cisterna magna, all three 2 (0.9) each	IFs were detected on 225 conventional research in a cohort of neurologically healthy children
IFs in pediatric specialty clinics other than neurology		
Oh *et al*[16]	Low signal intensities on T1-WI and high signal intensities on T2-WI 26 (73)	Incidence of hypointensity on T1-WI was higher in patients with Rathke's cleft cysts
Rachmiel *et al*[17]	Prominent VR perivascular spaces, cerebellar ectopia, and abnormalities in sella region all 3 (7.9) each	The comparative study found no IFs association with clinical and cognitive abnormalities
Mogensen *et al*[19]	Arachnoid cysts 5 (9.2), of which one patient had hydrocephalus	Incidental findings were unrelated to early puberty

The study by Whitehead *et al*[18], 2013, which is not listed in table, because this study was limited to prevalence of pineal cysts in children, who have undergone high-resolution 3-T MRI. CM I: Chiari malformation I; WMC: White matter changes; VR: Virchow-Robin; PVL: Periventricular malacia; PVW: Periventricular white matter changes; IFs: Incidental findings; MRI: Magnetic resonance imaging.

that none of the prospective studies reported any malignant findings as incidental. Potchen *et al*[14], 2013 prospectively reported granulomas with gliosis as a serious lesion.

Not surprisingly, a significant number of brain tumors were reported from pediatric oncologic-setting, Perret *et al*[20], 2011. The incidental serious findings in this study included low-grade glioma, craniopharyngioma, ependymoma, choroid plexus papilloma, medulloblastoma, and dysembryoplastic neuroepithelial tumor.

CLINICAL IMPLICATION

Common clinical profile

The common clinical profile of intracranial incidental findings on pediatric brain MRI is shown in the Table 6.

Multiple incidental findings

A 16-year-old girl presented with right facial nerve palsy. She had an unremarkable past medical history. A CT scan of the brain performed due to tingling feeling on the right side of her tongue revealed a partially calcified pineal cyst (Figure 2A). An MRI revealed an enhancing pituitary lesion measuring 13 mm × 10 mm × 10 mm, cerebellar ectopia (Figure 2B), and left maxillary sinusitis, which is not shown. She had no headaches, visual field defect, hearing difficulty or upper respiratory infection. The question is if her facial nerve palsy is related in any way to neuroimaging findings. The significance of more than one incidental finding is largely unknown.

More than one incidental finding is not uncommon. In the lack of any known implication some of these findings go unreported.

Four out of 18 (22%) studies listed in Table 1 reported more than one incidental finding. An average prevalence of more than one incidental finding in three studies (11, 13, and 17) was 3.8%. The forth study by Bayram *et al*[6], 2013 reported a very high prevalence (52%) of more than one white matter lesion in children with migraine. In fact the number of patients with more than one lesion exceeded the total number of the patients in this study. Authors' indicated that these were migraine associated changes in the brain[33].

Managing the MRI results

Incidentally discovered findings should always be considered in the context of the overall clinical impression. One should bear in mind the reason for performing the MRI of the brain. The answer to this

Table 5 Summarizes incidentally found "serious lesions" on pediatric brain magnetic resonance imaging

Ref.	The context in which brain MRI was ordered	Worsening course		Outcome/comment
		Known	Potential	
Yilmaz *et al*[5]	Children mean age 11.2 yr presented for headache evaluation	Malignant brain tumor and hydrocephalus	Chiari I malformation I; Relevant to headache	Tissue type of tumor in study was unspecified
Schwedt *et al*[8]	Children mean age 12.1 yr presented for headache evaluation	Tumors, moyamoya disease, and demyelinating disease	Arteriovenous malformation and intracerebral hemorrhage	Study focus was "benign" imaging abnormalities, no further information for serious lesion other than pineal tumor was available
Kalnin *et al*[10]	Children mean age 9.7 yr presented for the first onset seizure	None	Temporal lobe lesions	Various Epileptic abnormalities[1] have been associated with pediatric brain MRI
Potchen *et al*[14]	Community-based children mean age 12.1 yr	Granulomas with gliosis	Empty sella and vermian atrophy	Calcified granulomas caused by neurocysticercosis or tuberculosis occurs in the endemic part of the world
Mogensen *et al*[19]	All girls, mean age unavailable, presented for early puberty evaluation to endocrine clinic	Pontine and pineal tumor, and hypothalamic pilocytic astrocytoma	Hydrocephalus, cortical dysplasia, and chiari II malformation	A high frequency a pathological brain findings occurred in 6-8 yr old girls with precocious puberty
[2]Perret *et al*[20]	Incidentally found mass lesions management in children mean age 7.6 yr in oncology	Low-grade glioma, craniopharyngioma, ependymoma, and CPP	Medulloblastoma and fibrillary astrocytoma	Dysembryoplastic neuroepithelial tumor and tectal glioma can be monitored conservatively
Jordan, *et al*[21]	Children mean age 9.2 yr with sickle cell disease in neurology research	Chiari I malformation with large spinal cord syrinx[3]	Possible tectal glioma, Possible tumor *vs* dysplasia	Amongst 6.6% incidental findings identified, 0.6% children with sickle cell disease had potentially serious or urgent finding

[1]Various epileptic abnormalities includes leukomalacia/gliosis, encephalomalacia, any gray matter lesion, mass lesion, hemorrhage, vascular lesion, hippocampal abnormality, ventricular enlargement > 1.5 cm, or prominence of extra-axial fluid spaces > 1.0 cm[31]; [2]Of 335 newly diagnosed central nervous system tumors (CNS), 19 (5.7%) children's CNS tumors were identified incidentally; [3]Of note: Chiari I malformation with a small cervical spinal cord syrinx in asymptomatic patients is not uncommon on pediatric brain MRI. CPP: Choroid plexus papilloma; MRI: Magnetic resonance imaging.

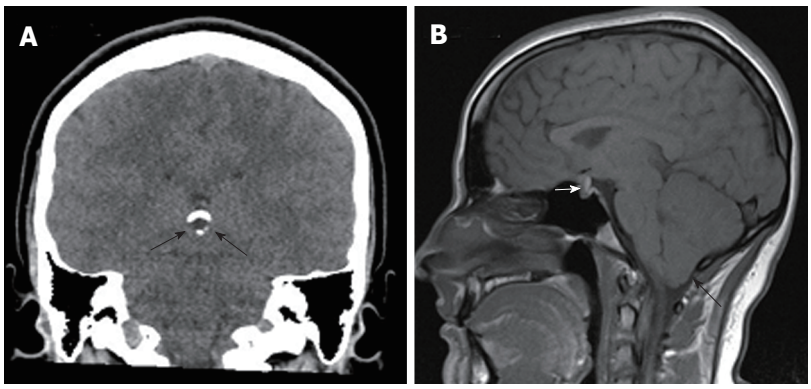

Figure 2 Three out of four incidental findings in a single 16-year-old girl who presented with right facial nerve palsy. The left maxillary sinusitis is not shown. A: Coronal non-contrasted computerized tomography of the brain shows a partially calcified cystic pineal lesion (black arrows); B: A true midline sagittal magnetic resonance image contrast enhancing pituitary mass measuring 13 mm × 10 mm × 10 mm (white arrow) and cerebellar ectopia, 7 mm (black arrow). There was no enhancement of facial nerve in vicinity of the right internal carotid canal.

question can often provide the direction for the next step of clinical management.

The MRI results are best managed at the time of planning for neuroimaging by considering the possibility of an incidental finding. Such preemptive action serves to alleviate parental concern, reduce additional medical care cost, and save physicians' time[34]. After all, incidental findings are the most common insignificant abnormal findings revealed on pediatric brain MRI.

The parental perceived importance for MRI procedure is significantly higher than those of physicians. This disassociation of perception may lead to confrontation. This could be avoided by considering the parental concern. The physician's explanation should be based upon the clinical context and what is known about the particular finding. It is only rarely that these findings perpetuate more concerns than the relief[35].

How did we manage the results of our case? The patient's right facial nerve palsy has no neuroanatomical relation with pituitary lesion, cerebellar ectopia, pineal

Table 6 A proposal for a common clinical profile of intracranial incidental findings on pediatric brain magnetic resonance imaging

	Clinical implication
Discovery of the unexpected incidental findings	Revealing during investigation enhances the patients or parents anxiety. The evidence-based knowledge will provide an additional confidence for the practicing physicians
Type of the incidental findings	Varieties of white matter changes are reported. However, these usually do not initiate a neurologic consultation. Chiari type I malformation, arachnoid cyst, and pineal cyst, all continued to be a common source of concern for some physicians
Distribution of incidental findings	Attention to the distribution of findings is a useful tool in deciding the clinical importance of such findings. A midline lesion particularly in the posterior fossa and hippocampal location is likely to have a serious clinical implication
The clinical context in which MRI was performed	This is probably the single most important step in understating the clinical implication of incidental findings (Table 6). This is particularly important when the child was referred to neurology after revealing the incidental finding on brain MRI

MRI: Magnetic resonance imaging.

cyst, and the left maxillary sinusitis. Of note; sinusitis is the most common extracranial incidental finding on brain MRI. Our patient with facial nerve palsy was treated with a 5 d course of oral steroid. She was referred to an endocrinologist for further evaluation of the pituitary lesion.

How to deal with a "serious incidental finding"?

An MRI revealing serious incidental findings requires close attention. These findings in a pediatric neurology practice remain low (0.3%-3.4%). Presently, there is no consensus regarding the optimal strategy on how to deal with these findings in practice or research[36].

In general, a midline located lesion with or without surrounding edema or contrast - enhancement needs to be further investigated. Depending upon the nature of the lesion or clinical impression, endocrinological, oncological, or neurosurgical evaluation should be considered.

Author (Gupta SN) preference is to first discuss with the interpreting radiologist and have a plan before delivery of the results to the parents. The necessity and results of such a discussion may vary depending upon the expertise of the clinician or radiologist. To characterize such a lesion systemically, the neuroradiologic differential diagnosis based on the MRI characteristics should be discussed. The presence or absence of perfusion- and diffusion-weighted MRI revealing changes in the diffusion coefficient should be documented[37]. With the use of intravenous contrast, the status of a blood-brain barrier should be evaluated. In case of non-enhancing lesions such as benign tumors, magnetic resonance spectroscopy[38] or diffuse tensor imaging may be additional use.

At times an equivocal finding may be perplexing in regards of the management strategy. In such a situation the patient should be followed clinically. Unless neurosurgical intervention is thought to be a realistic probability, the patient with incidental findings of this nature should not receive neurosurgical referral. This will prevent escalating parental anxiety.

Referral and ramification

The majority of children with intracranial incidental findings do not require clinical or neuroimaging follow-up. Scheduling further appointments merely for incidentally found findings or neuroimaging is likely to increase parental anxiety. Some parents may seek another neurologic consultation. Pituitary lesions, vascular malformations, or tumors have a true future clinical[39,40] or medico-legal implications. Fortunately, serious lesions in children remain extremely low as compared with adults or the elderly[41]. Occasionally, they require emergent medical attention and/or subsequent neurosurgical intervention.

Requiring surgical intervention

A very limited number of incidentally found serious lesions include various tumors, which neurosurgical intervention. Non-tumor serious lesions includes Chiari I malformations, syrinx of the cervical spinal cord, and Rathke's cleft cysts. Incidentally discovered lesions requiring neurosurgical interventions and their outcomes are shown in Table 7.

Perret *et al*[20], 2011, studied 335 children age < 18 years in an oncologic-setting. They reported 19 patients (5.67%) with an incidentally discovered primary brain tumor. Seven patients (2%) underwent immediate surgery; four patients had a low-grade glioma. Craniopharyngioma, ependymoma, and choroid plexus papilloma occurred one in each individual patient. The rest of the 12 (3.5%) children were treated conservatively. Of these 12 conservatively followed, 10 patients (83%) remained stable. The other 2 (17%) underwent surgery because of medulloblastoma and fibrillary astrocytoma progression. The authors of the study concluded that a subgroup of lesions such as tectal glioma and dysembryoplastic neuroepithelial tumor can be monitored conservatively.

Bredlau *et al*[42] reviewed the clinical course of 244 children over a 10 year period. The study reported 21 (8.6%) incidental brain lesions on MRI. Twelve (4.9%) patients underwent surgical resection of their lesions. Nine out of 10 patients (90%) had a posterior fossa lesion, and three out of 11 (27%) had supratentorial lesions. Authors of the study concluded that incidentally detected serious CNS lesions are small. The outcome for children with such lesions is excellent. They recommended close monitoring with serial MRIs as a safe alternative to immediate biopsy and/or resection

Table 7 Summarizes the neurosurgical intervention and their outcome in children with incidentally discovered serious lesions

Ref.	Incidentally found serious findings	No. of patients	Surgical procedure performed	Outcome
Schwedt *et al*[8]	Chiari type I malformation	3	Surgical decompression	Headache relieved in 2 patients after surgery
Jordan *et al*[21]	Chiari I malformation with spinal cord syrinx	2	Surgical decompression	Neurologic stable
Perret *et al*[20]	Pilocystic astrocytoma	2	Primary subtotal resection	Stable disease
	Craniopharyngioma	1	Primary total resection	Complete remission
	Anaplastic ependymoma	1	Primary total resection, radio-chemotherapy	Complete remission
	Choroid plexus papilloma	1	Primary total resection	Complete remission
	Medulloblastoma	1	Delayed subtotal resection, radio-chemotherapy	Neurologic stable
	Fibrillary astrocytoma	1	Delayed total resection	Complete remission
	Mature teratoma	1	Delayed subtotal resection	Neurologic stable
	Desmoplastic ganglioglioma	1	Primary total resection	Complete remission
Mogensen *et al*[19]	Pilocytic astrocytoma	1	Hypophysectomy	Patients developed pan hypopituitarism after surgery
Yilmaz *et al*[5]	Medulloblastoma	1	Urgent surgery for space occupying lesion	Headache relieved after surgery

Incidental findings; Chiari I malformation studied by Seki *et al*[12], 2010 and temporal arachnoid cyst with mass effect and cerebellar venous malformation studied by Gupta *et al*[13], 2008 all three were referred to neurosurgery, but no information regarding outcomes were available.

for select patients[42]. Of note; the data from adult patients demonstrate that most Rathke's cleft cysts the response to surgery tends to vary based on the endocrinopathology[43].

MEDICOLEGAL IMPLICATION

Dissatisfaction is an inciting event of litigation in the medical setting. Unlike research or healthy volunteer subjects, no consensus exists on how to handle incidental findings in clinical practice[44,45].

Claims of inappropriate management, ignorance, or discovery of a serious incidental finding on a later date, all have the potential to result in litigation. The discovery of incidental findings on brain MRI have led to its familiarity and a burden to clinical practice. Clinicians have an obligation of addressing the incidental finding revealed on MRI during the course of clinical evaluation. It is best prevented by pursuing before the availability of actual reports of MRI.

Based on the individual radiologist's perception, the reports of incidental findings on MRI are variable. Hence, many incidental findings might, therefore, remain unreported. Rarely, inconsistencies in reporting may be a cause for litigation.

FUTURE

Neuroimaging with diffuse tensor imaging is likely to unfold the nature of the incidental findings particularly white matter changes. In the future, they are likely to be identified with the use of a high resolution MRI sequences. Use of a standardized scoring system by radiologists will eliminate the individual variability in reporting. This will also be useful in expanding our understating of the incidental findings.

Future review should address the reason for variable prevalence and answer the question if the pattern of incidental finding relates to a specific condition such as headache, seizure, development delay, or any other neurologic condition. Most importantly, this investigation should be addressed by an adequately powered statistical analysis of retrospective or prospective studies in homogeneous populations.

CONCLUSION

The detection of intracranial incidental findings on pediatric brain MRI is of immense importance to daily radiological or clinical practice. The Radiologist should report each and every incidentally discovered finding. Individual variability in reporting of brain MRI findings can be minimized by using unified terminology, describing radiologic characteristics, and by developing a standard radiologic classification system. Because significance of these findings remains unclear, it is important to report them as they are observed, rather than a subjective description.

Intracranial incidental findings are common in both healthy children and children presenting for neurologic evaluation. Prevalence increases with disorders affecting the brain.

Whether or not a reported "incidental finding" should be assigned as clinically significant, is the clinician's prerogative. In uncertainty, the clinical context and course of the problem in question should take precedence. The spectrum of intracranial incidental findings on pediatric brain MRI presented in this review should be the basis for an evidence-based discussion. In addition, the proposed common profile will aid the clinical management of incidentally discovered findings. Most importantly, the management of an incidentally found

serious lesion demands constant surveillance in clinical practice.

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REFERENCES

1 **Sebastian S**, Araujo C, Neitlich JD, Berland LL. Managing incidental findings on abdominal and pelvic CT and MRI, Part 4: white paper of the ACR Incidental Findings Committee II on gallbladder and biliary findings. *J Am Coll Radiol* 2013; **10**: 953-956 [PMID: 24295947 DOI: 10.1016/j.jacr.2013.05.022]

2 **Saxena A**, Luhadiya A, Ewen B, Goumas C. Magnetic resonance imaging and incidental findings of lateral ankle pathologic features with asymptomatic ankles. *J Foot Ankle Surg* 2011; **50**: 413-415 [PMID: 21570324 DOI: 10.1053/j.jfas.2011.03.011]

3 **Katzman GL**, Dagher AP, Patronas NJ. Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. *JAMA* 1999; **282**: 36-39 [PMID: 10404909 DOI: 10.1001/jama.282.1.36]

4 **Weber F**, Knopf H. Incidental findings in magnetic resonance imaging of the brains of healthy young men. *J Neurol Sci* 2006; **240**: 81-84 [PMID: 16256141 DOI: 10.1016/j.jns.2005.09.008]

5 **Yılmaz Ü**, Çeleğen M, Yılmaz TS, Gürçınar M, Ünalp A. Childhood headaches and brain magnetic resonance imaging findings. *Eur J Paediatr Neurol* 2014; **18**: 163-170 [PMID: 24268890 DOI: 10.1016/j.ejpn.2013.11.003]

6 **Bayram E**, Topcu Y, Karaoglu P, Yis U, Cakmakci Guleryuz H, Kurul SH. Incidental white matter lesions in children presentıng with headache. *Headache* 2013; **53**: 970-976 [PMID: 23551192 DOI: 10.1111/head.12089]

7 **Graf WD**, Kayyali HR, Abdelmoity AT, Womelduff GL, Williams AR, Morriss MC. Incidental neuroimaging findings in nonacute headache. *J Child Neurol* 2010; **25**: 1182-1187 [PMID: 20724750 DOI: 10.1177/0883073809353149]

8 **Schwedt TJ**, Guo Y, Rothner AD. "Benign" imaging abnormalities in children and adolescents with headache. *Headache* 2006; **46**: 387-398 [PMID: 16618255 DOI: 10.1111/j.1526-4610.2006.00371.x]

9 **Koirala K**. Magnetic resonance neuroimaging in patient with complain of seizure. *J Nepal Health Res Counc* 2011; **9**: 56-60 [PMID: 22929715]

10 **Kalnin AJ**, Fastenau PS, deGrauw TJ, Musick BS, Perkins SM, Johnson CS, Mathews VP, Egelhoff JC, Dunn DW, Austin JK. Magnetic resonance imaging findings in children with a first recognized seizure. *Pediatr Neurol* 2008; **39**: 404-414 [PMID: 19027586 DOI: 10.1016/j.pediatrneurol.2008.08.008]

11 **Gupta S**, Kanamalla U, Gupta V. Are incidental findings on brain magnetic resonance images in children merely incidental? *J Child Neurol* 2010; **25**: 1511-1516 [PMID: 20558674 DOI: 10.1177/0883073810370622]

12 **Seki A**, Uchiyama H, Fukushi T, Sakura O, Tatsuya K. Incidental findings of brain magnetic resonance imaging study in a pediatric cohort in Japan and recommendation for a model management protocol. *J Epidemiol* 2010; **20** Suppl 2: S498-S504 [PMID: 20179362 DOI: 10.2188/jea.JE20090196]

13 **Gupta SN**, Belay B. Intracranial incidental findings on brain MR images in a pediatric neurology practice: a retrospective study. *J Neurol Sci* 2008; **264**: 34-37 [PMID: 17698082 DOI: 10.1016/j.jns.2007.06.055]

14 **Potchen MJ**, Kampondeni SD, Mallewa M, Taylor TE, Birbeck GL. Brain imaging in normal kids: a community-based MRI study in Malawian children. *Trop Med Int Health* 2013; **18**: 398-402 [PMID: 23331928 DOI: 10.1111/tmi.12064]

15 **Kim BS**, Illes J, Kaplan RT, Reiss A, Atlas SW. Incidental findings on pediatric MR images of the brain. *AJNR Am J Neuroradiol* 2002; **23**: 1674-1677 [PMID: 12427622]

16 **Oh YJ**, Park HK, Yang S, Song JH, Hwang IT. Clinical and radiological findings of incidental Rathke's cleft cysts in children and adolescents. *Ann Pediatr Endocrinol Metab* 2014; **19**: 20-26 [PMID: 24926459 DOI: 10.6065/apem.2014.19.1.20]

17 **Rachmiel M**, Blaser S, Widjaja E, Rovet J. Children with congenital hypothyroidism have similar neuroradiological abnormal findings as healthy ones. *ScientificWorldJournal* 2013; **2013**: 194918 [PMID: 24222727 DOI: 10.1155/2013/194918]

18 **Whitehead MT**, Oh CC, Choudhri AF. Incidental pineal cysts in children who undergo 3-T MRI. *Pediatr Radiol* 2013; **43**: 1577-1583 [PMID: 23852563 DOI: 10.1007/s00247-013-2742-x]

19 **Mogensen SS**, Aksglaede L, Mouritsen A, Sørensen K, Main KM, Gideon P, Juul A. Pathological and incidental findings on brain MRI in a single-center study of 229 consecutive girls with early or precocious puberty. *PLoS One* 2012; **7**: e29829 [PMID: 22253792 DOI: 10.1371/journal.pone.0029829]

20 **Perret C**, Boltshauser E, Scheer I, Kellenberger CJ, Grotzer MA. Incidental findings of mass lesions on neuroimages in children. *Neurosurg Focus* 2011; **31**: E20 [PMID: 22133179 DOI: 10.3171/2011.9.FOCUS]

21 **Jordan LC**, McKinstry RC, Kraut MA, Ball WS, Vendt BA, Casella JF, DeBaun MR, Strouse JJ. Incidental findings on brain magnetic resonance imaging of children with sickle cell disease. *Pediatrics* 2010; **126**: 53-61 [PMID: 20547639 DOI: 10.1542/peds.2009-2800]

22 **Itoh T**, Magnaldi S, White RM, Denckla MB, Hofman K, Naidu S, Bryan RN. Neurofibromatosis type 1: the evolution of deep gray and white matter MR abnormalities. *AJNR Am J Neuroradiol* 1994; **15**: 1513-1519 [PMID: 7985572]

23 **Bryan RN**, Manolio TA, Schertz LD, Jungreis C, Poirier VC, Elster AD, Kronmal RA. A method for using MR to evaluate the effects of cardiovascular disease on the brain: the cardiovascular health study. *AJNR Am J Neuroradiol* 1994; **15**: 1625-1633 [PMID: 7847205]

24 **Sawamura Y**, Ikeda J, Ozawa M, Minoshima Y, Saito H, Abe H. Magnetic resonance images reveal a high incidence of asymptomatic pineal cysts in young women. *Neurosurgery* 1995; **37**: 11-15; discussion 15-16 [PMID: 8587669 DOI: 10.1227/00006123-199507000-00002]

25 **Peres MF**, Zukerman E, Porto PP, Brandt RA. Headaches and pineal cyst: a (more than) coincidental relationship? *Headache* 2004; **44**: 929-930 [PMID: 15447706 DOI: 10.1111/j.1526-4610.2004.04178_2.x]

26 **Mandera M**, Marcol W, Bierzyńska-Macyszyn G, Kluczewska E. Pineal cysts in childhood. *Childs Nerv Syst* 2003; **19**: 750-755 [PMID: 12920545 DOI: 10.1007/s00381-003-0813-2]

27 **Zuketto C**, van Gijn J. [Severe reversible dysphagia caused by herniation of the cerebellar ectopia]. *Ned Tijdschr Geneeskd* 2002; **146**: 771-773 [PMID: 11998356]

28 **Gosalakkal JA**. Intracranial arachnoid cysts in children: a review of pathogenesis, clinical features, and management. *Pediatr Neurol* 2002; **26**: 93-98 [PMID: 11897472 DOI: 10.1016/S0887-8994(01)00329-0]

29 **Chokshi FH**, Poretti A, Meoded A, Huisman TA. Normal and abnormal development of the cerebellum and brainstem as depicted by diffusion tensor imaging. *Semin Ultrasound CT MR* 2011; **32**: 539-554 [PMID: 22108217 DOI: 10.1053/j.sult.2011.06.005]

30 **Graf WD**, Kayyali HR, Alexander JJ, Simon SD, Morriss MC. Neuroimaging-use trends in nonacute pediatric headache before and after clinical practice parameters. *Pediatrics* 2008; **122**: e1001-e1005 [PMID: 18838461 DOI: 10.1542/peds.2008-1159]

31 **Chuang NA**, Otsubo H, Chuang SH. Magnetic resonance imaging in pediatric epilepsy. *Top Magn Reson Imaging* 2002; **13**: 39-60 [PMID: 11847500 DOI: 10.1097/00002142-200202000-00004]

32 **Morris Z**, Whiteley WN, Longstreth WT, Weber F, Lee YC, Tsushima Y, Alphs H, Ladd SC, Warlow C, Wardlaw JM, Al-Shahi Salman R. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ* 2009; **339**: b3016 [PMID: 19687093 DOI: 10.1136/bmj.b3016]

33 **De Benedittis G**, Lorenzetti A, Sina C, Bernasconi V. Magnetic resonance imaging in migraine and tension-type headache. *Headache* 1995; **35**: 264-268 [PMID: 7775189 DOI: 10.1111/

j.1526-4610.1995.hed3505264.x]
34 **Grossman RI**, Bernat JL. Incidental research imaging findings: Pandora's costly box. *Neurology* 2004; **62**: 849-850 [PMID: 15037680 DOI: 10.1212/01.WNL.0000118214.02495.41]
35 **Mold JW**, Stein HF. The cascade effect in the clinical care of patients. *N Engl J Med* 1986; **314**: 512-514 [PMID: 3945278 DOI: 10.1056/NEJM198602203140809]
36 **Borra RJ**, Sorensen AG. Incidental findings in brain MRI research: what do we owe our subjects? *J Am Coll Radiol* 2011; **8**: 848-852 [PMID: 22137002 DOI: 10.1016/j.jacr.2011.08.009]
37 **Gajewicz W**, Papierz W, Szymczak W, Goraj B. The use of proton MRS in the differential diagnosis of brain tumors and tumor-like processes. *Med Sci Monit* 2003; **9**: MT97-M105 [PMID: 12960934]
38 **Ambrosetto P**, Bacci A. In re: Basilar artery migraine and reversible imaging abnormalities. *AJNR Am J Neuroradiol* 2000; **21**: 234-235 [PMID: 10669258]
39 **Arnett BC**. Tonsillar ectopia and headaches. *Neurol Clin* 2004; **22**: 229-236 [PMID: 15062536 DOI: 10.1016/S0733-8619(03)00101-4]
40 **Bertrand RA**, Martinez SN, Robert F. Vestibular manifestations of cerebellar ectopia. (Sub-group of Chiari I). *Adv Otorhinolaryngol* 1973; **19**: 355-366 [PMID: 4541599 DOI: 10.1159/000394008]
41 **Yue NC**, Longstreth WT, Elster AD, Jungreis CA, O'Leary DH, Poirier VC. Clinically serious abnormalities found incidentally at MR imaging of the brain: data from the Cardiovascular Health Study. *Radiology* 1997; **202**: 41-46 [PMID: 8988190 DOI: 10.1148/radiology.202.1.8988189]
42 **Bredlau AL**, Constine LS, Silberstein HJ, Milano MT, Korones DN. Incidental brain lesions in children: to treat or not to treat? *J Neurooncol* 2012; **106**: 589-594 [PMID: 21853423 DOI: 10.1007/s11060-011-0695-1]
43 **Kim JE**, Kim JH, Kim OL, Paek SH, Kim DG, Chi JG, Jung HW. Surgical treatment of symptomatic Rathke cleft cysts: clinical features and results with special attention to recurrence. *J Neurosurg* 2004; **100**: 33-40 [PMID: 14743909 DOI: 10.3171/jns.2004.100.1.0033]
44 **Wolf SM**, Lawrenz FP, Nelson CA, Kahn JP, Cho MK, Clayton EW, Fletcher JG, Georgieff MK, Hammerschmidt D, Hudson K, Illes J, Kapur V, Keane MA, Koenig BA, Leroy BS, McFarland EG, Paradise J, Parker LS, Terry SF, Van Ness B, Wilfond BS. Managing incidental findings in human subjects research: analysis and recommendations. *J Law Med Ethics* 2008; **36**: 219-248, 211 [PMID: 18547191 DOI: 10.1111/j.1748-720X.2008.00266.x]
45 **Booth TC**, Jackson A, Wardlaw JM, Taylor SA, Waldman AD. Incidental findings found in "healthy" volunteers during imaging performed for research: current legal and ethical implications. *Br J Radiol* 2010; **83**: 456-465 [PMID: 20335427 DOI: 10.1259/bjr/15877332]

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History of the infantile hepatic hemangioma: From imaging to generating a differential diagnosis

Maria Gnarra, Gerald Behr, Alison Kitajewski, June K Wu, Sudha A Anupindi, Carrie J Shawber, Nick Zavras, Dimitrios Schizas, Chris Salakos, Konstantinos P Economopoulos

Maria Gnarra, Vascular Biology Program, Department of Surgery, Boston Children's Hospital and Harvard Medical School, Boston, MA 02115, United States

Gerald Behr, Department of Radiology, Columbia University Medical Center, New York, NY 10020, United States

Alison Kitajewski, June K Wu, Carrie J Shawber, Department of Surgery, Columbia University Medical Center, New York, NY 10020, United States

Sudha A Anupindi, Department of Radiology, the Children's Hospital of Philadelphia, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19082, United States

Carrie J Shawber, Department of OB/GYN, Columbia University Medical Center, New York, NY 10020, United States

Nick Zavras, Dimitrios Schizas, Chris Salakos, Department of Pediatric Surgical, "ATTIKO" General University Hospital, 12462 Haidari, Greece

Dimitrios Schizas, Chris Salakos, Konstantinos P Economopoulos, Society of Junior Doctors, Surgery Working Group, 15123 Maroussi, Greece

Konstantinos P Economopoulos, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, United States

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Correspondence to: Konstantinos P Economopoulos, MD, PhD, Postdoctoral Research Fellow, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, 101 Merrimac street, Boston, MA 02114, United States. keconomopoulos@mgh.harvard.edu
Telephone: +1-617-5104641

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Abstract

We aim to provide an up-to-date summary of infantile hepatic hemangioma (IHH) and its misnomers and to dialectically present the differential diagnosis of these rare entities of the liver. Eligible peer-reviewed articles on hepatic infantile hemangiomas, published between 2000 and 2015, were reviewed for this study. IHH is the most common hepatic vascular tumor in children. Once a liver mass is identified in an infant, the differential diagnosis ranges from vascular malformations to benign and malignant tumors including mesenchymal hamartoma, hepatoblastoma, metastatic neuroblastoma, so careful physical examination, imaging studies, and, if indicated, tumor markers and biopsy, are of pivotal importance to ascertain the correct diagnosis. Despite the benign nature of IHHs, some of these lesions may demand medical and/or surgical intervention, especially for multiple and diffuse IHH. Complications can include hepatomegaly, hypothyroidism and cardiac failure. Therefore, a close follow-up is required until complete

involution of the lesions. We propose an algorithm to guide the physicians towards the proper management of hepatic lesions.

Key words: Hepatic hemangiomas; Infant; Children; Vascular tumors

Core tip: Differential diagnosis of pediatric liver lesions ranges from vascular malformations to benign and malignant tumors. Infantile hepatic hemangioma (IHH) is the most common, benign, hepatic vascular tumor in infants. They are sub-classified in focal, multiple and diffuse lesions, based on degree of unaffected liver parenchyma. Despite the benign nature of IHHs, multiple and diffuse lesions can present with life-threatening complications including severe hypothyroidism and cardiac failure, requiring prompt medical intervention. Therefore, a proper diagnosis is of pivotal importance. Including severe hypothyroidism and cardiac failure, requiring prompt medical intervention, therefore, a proper diagnosis is of pivotal importance.

Gnarra M, Behr G, Kitajewski A, Wu JK, Anupindi SA, Shawber CJ, Zavras N, Schizas D, Salakos C, Economopoulos KP. History of the infantile hepatic hemangioma: From imaging to generating a differential diagnosis. *World J Clin Pediatr* 2016; 5(3): 273-280 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i3/273.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i3.273

INTRODUCTION

Infantile hemangiomas (IHs) are the most common benign tumor of infancy, affecting up to 10% of the pediatric population with a higher incidence in female (3:1), preterm infants, and Caucasian population. Most IHs are not present at birth but become apparent a few days to a few weeks after birth. IHs are characterized by a rapid proliferative phase in the first 6-10 mo, followed by a slow involution, which can last up to 10 years[1].

Despite their benign nature, IHs can cause severe morbidities and therefore sometimes require medical intervention[2]. IHs can range from asymptomatic to life threatening. Vital functions such as breathing, vision, and feeding can be impaired, depending on the location of the lesion.

IHs are be confirmed by positive immunostaining for glucose transporter-1 (GLUT-1), which is pathognomonic for the diagnosis of IHs, and therefore helps to distinguish IHs from other vascular anomalies[3]. While most IHs are present in the skin, IHs can occur in the viscera, with or without cutaneous manifestations. The liver is the most common site of visceral IHs, followed by the gastrointestinal system[4].

Screening for liver IHs (IHH) by ultrasonography (USG) is recommended when 5 or more cutaneous IHs are noted. However, the majority of IHHs are discovered as incidental findings during routine imaging.

IHHs are classified in three different subtypes, focal, multifocal and diffuse IHH, based on the remaining unaffected liver parenchyma.

Singular or focal lesions will often involute rapidly after birth without any complications. Multifocal lesions tend to involute in a similar pattern to cutaneous IHs, over a 6-10 year period. Diffuse lesions tend to replace almost the entire liver parenchyma, with severe complications.

These can include cardiac failure[5], high volume arteriovenous shunting[6], hypothyroidism secondary to overproduction of type III iodothyronine deiodinase[7], bleeding and abdominal compartment syndrome[8].

Therefore, once diagnosed, patients with IHHs usually require close monitoring until complete involution of the lesions.

Before the modern classification system developed by Mulliken in 1982[9], and the more recent subtyping of liver IHs by Christison-Lagay *et al*[10] in 2007, there was widespread confusion. Terminology for IHHs has been varied, a fact which can propagate the confusion and delay in the correct diagnosis and proper treatment of the affected patients. Moreover, there are several other hepatic lesions that may mimic different types of IHHs. Solitary hepatic lesions in an infant can also include, hepatoblastoma, mesenchymal hamartoma, congenital cysts (such as ciliated foregut duplication cysts) or kaposiform hemangioendotheliomas (KHEs). IHHs have also been historically called "hemangiomaendothelioma", regardless of the type of lesion.

It is therefore imperative to distinguish all 3 subtypes of true IHHs from other benign and malignant liver lesions, as this can deeply impact the management of these conditions. For this reason, we systematically review the literature in order to provide an up-to-date understanding of IHHs and their misnomers and to dialectical present the differential diagnosis of these rare entities of the liver.

RESEARCH AND LITERATURE

Eligible articles were identified thorough search of the PubMed bibliographical database extending from January 2000 to 2015. Two investigators working independently executed the search using the following keywords in all the possible combinations: Hepatic hemangioma, infantile hepatic hemangioma, liver hemangioma and visceral hemangioma. In addition, we checked all the references of relevant reviews and eligible articles that our search retrieved. Search of the literature was restricted to those articles published in English, based on the following criteria: (1) original clinical series and case reports describe infants with hepatic hemangiomas; and (2) reviews of the literature on infantile hepatic hemangiomas. The selection-process excluded at the same time: (1) studies that

Table 1 Description of the clinical, radiological, histological findings of the different subtypes of infantile hepatic hemangiomas and recommended treatment for the three different subgroups of infantile hepatic hemangiomas

IHH	Focal	Multifocal	Diffuse
Onset	Prenatal development	Postnatal (few weeks after birth)	Postnatal (few weeks after birth)
Association with cutaneous IH	Rarely	Frequently	Frequently
MRI	Solitary tumor; robust enhancement; often with Ca^{2+} and central cystic change	Hypointense to liver on T1, hyperintense on T2. Rapid enhancement. May have central flow voids on T2 spin echo sequence	Near-total replacement of the hepatic parenchyma with many lesions
CT	Rapid enhancement. Often with Ca^{2+} and central cystic changes	Homogenously; uniform or centripetal	Innumerable centripetally but rapidly enhancing lesions
Glut-1 staining	Negative	Positive	Positive
Comorbidities	Possible anemia and relatively mild thrombocytopenia; AV shunting; High-output cardiac state	High-flow shunting resulting in high-output; Cardiac failure	High-output cardiac failure; Abdominal compartment syndrome; Severe hypothyroidism
Treatment	Observation; embolization for problematic shunting	Observation; propranolol/ embolization for problematic shunting, possibly propranolol; hypothyroidism	Propranolol, thyroid hormone replacement, embolization in the cases of severe arteriovenous shunting (rare in diffuse IHHs), transplantation evaluation for the most extreme cases

IHH: Infantile hepatic hemangioma; CT: Computed tomography; MRI: Magnetic resonance imaging.

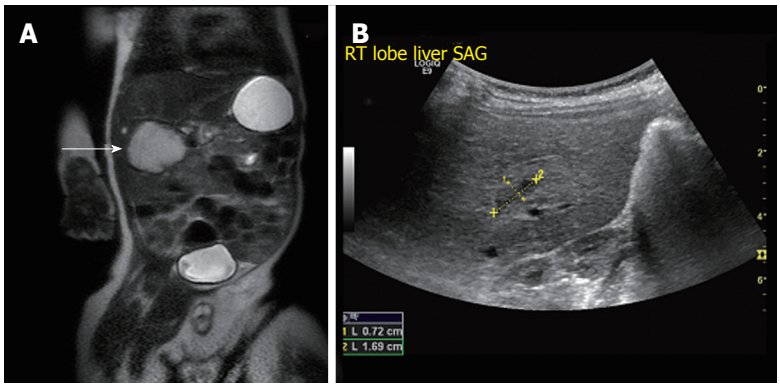

Figure 1 Focal infantile hepatic hemangiomas. A: Coronal T2 weighted MRI image through the abdomen of an 8-wk-old boy revealing a large hyperintense mass arising from the liver (arrow); B: Abdominal USG of the same patient at 17-mo-old shows a minimal residual scar (demarcated by calipers). USG: Ultrasonography; MRI: Magnetic resonance imaging.

describe malignant lesions alone; (2) lesions that are mistakenly categorized under the definition of infantile hepatic hemangiomas; (3) studies that do not contain the main outcomes of interest as described below.

In addition, historical evaluations of the failings of certain clinical treatments from beyond that timeline have been considered and included in order to present the story of IHHs as it has evolved.

CLINICAL PRESENTATION

A complete description of the clinical, radiological, histological findings of the different subtypes of IHH, and recommended treatment, can be found in Table 1. IHH lesions typically present and evolve in three different categorized patterns: Focal lesions, multifocal lesions, and diffuse lesions[11].

Focal lesions

Focal lesions are completely formed at birth and are mainly detected prenatally during routine USG. They fully involute soon after birth, sharing a similar evolution of their cutaneous counterpart, rapidly involuting congenital hemangiomas (RICHs)[10]. Similar to RICHs, focal hepatic hemangiomas stain negative for GLUT-1. Magnetic resonance imaging (MRI) shows these lesions as single hypointense areas relative to the surrounding liver parenchyma on T1-weighted sequences, and hyperintense on T2-weighted sequences (Figure 1)[12]. They often demonstrate central cystic areas that may be interpreted as central necrosis. In over 15% of cases, focal liver lesions are associated with cutaneous IHs[13]. Despite being usually asymptomatic, focal lesions can be accompanied by mild thrombocytopenia and arteriovenous shunting, which may require medical intervention if present after involution of the IHH. The presence of mild thrombocytopenia has to be distinguished from Kasabach Merritt Phenomenon (KMP) in which the symptoms of severe thrombocytopenia and coagulopathy are seen in combination with a rapidly growing vascular lesion. KMP is associated with KHE and Tufted Angiomas, rare and locally aggressive vascular infantile tumors which are part of the same neoplastic spectrum[14]. Mild coagulopathy can also occur in venous malformations and can be defined as Localized Intravascular Coagulopathy.

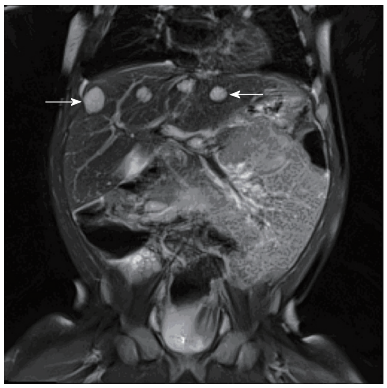

Figure 2 Multiple infantile hepatic hemangiomas. Coronal T2 weighted MRI image through the upper abdomen in a 5-mo-old girl depicts multiple well-defined, T2 hyperintense masses in the liver (arrows). This was consistent with multifocal infantile hepatic hemangiomas. MRI: Magnetic resonance imaging.

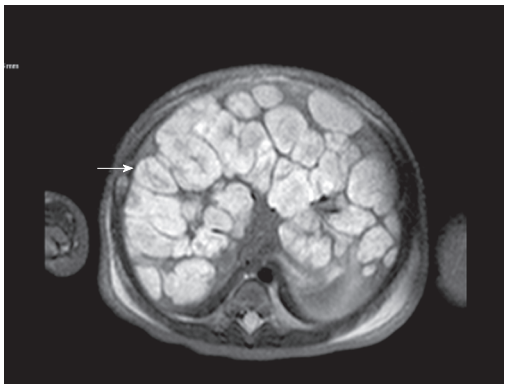

Figure 3 Diffuse infantile hepatic hemangiomas. T2 weighted axial MRI image of a 7-d-old with diffuse hemangiomas. Note the innumerable T2 hyperintense masses throughout the liver with central hypo-intense central regions (arrow). MRI: Magnetic resonance imaging.

Multifocal lesions

Multifocal lesions share a similar clinical course with cutaneous IHs. As for the cutaneous counterpart, multiple IHHs develop postnatally and exhibit a proliferating phase of around 9-12 mo in length, followed by a slow involution phase. They are more prevalent in females and Caucasians, and stain positive for GLUT-1. Multifocal IHHs can be detected on MRI as intensely enhancing spherical masses that are hypointense relative to the liver on T1-weighted sequences and hyperintense on T2-weighted sequences. They often present with a stellate (star shaped) central flow void on T2 spin echo sequences (Figure 2). Unlike focal lesions, multifocal IHHs can lead, in some cases, to moderate cardiomegaly and high-output heart failure due to arteriovenous and portovenous shunting. In over 60% of the cases, multifocal lesions are accompanied by cutaneous counterparts[5].

Diffuse lesions

Diffuse lesions are characterized by massive replacement of the hepatic parenchyma with various proliferating lesions with hyper enhancement on MRI (Figure 3). They have similar demographics with multifocal lesions, and also stain positive for GLUT-1. Association of cutaneous IH, may be present. Aortovenos, aortoportal, and venoportal shunting lead to high output cardiac failure[15]. Severe hepatomegaly may lead to compression of the systemic veins and thoracic cavity, leading to respiratory distress, abdominal compartment syndrome and multi-organ system failure. Diffuse lesions may also lead to severe hypothyroidism due to massive overproduction of type Ⅲ iodothyronine deiodinase[7] (an enzyme involved in converting thyroxine into an inactive form) and leads to acquired hypothyroidism. Therefore, it is mandatory that when diffuse lesions are suspected, thyroid hormone levels be closely monitored, as undetected hypothyroidism can cause permanent neurologic damage, impaired hemostasis, and low-flow cardiac depression[16].

DIFFERENTIAL DIAGNOSIS

Since IHHs are benign lesions, more aggressive liver malignancies need to be excluded at the time of diagnosis that at times may be challenging. Radiological imaging should be the first-line diagnostic analysis for physicians. A schematic algorithm to guide physicians through correct diagnosis and management of hepatic lesion can be seen in Figure 4.

Single lesions

Focal hepatic hemangiomas have been shown to be biologically identical to RICH. They may present with central calcifications, a finding amenable to detection by ultrasound or CT scan. Posterior acoustic shadowing and high density are the hallmarks of calcification on ultrasound and CT scan, respectively. The primary differential diagnoses include metastatic neuroblastoma, hepatoblastoma (Figure 5) and mesenchymal hamartoma (Figure 6). Primary sites of neuroblastoma (adrenal glands, organ of Zuckerkandel and paraspinal chain) should be evaluated and the urine samples should be screened for the presence of catecholamines. If the above results are unremarkable, the lesion demonstrates hyper enhancement (either on multiphase CT with iodinated contrast or MRI with gadolinium based contrast material) and there is no invasion of other structures, then a presumptive focal IHHs may be diagnosed but should still be monitored to ensure there is no further growth.

Unlike IHHs, hepatoblastomas typically demonstrate a more heterogenic signal on T2 weighted MRI. The enhancement pattern is variable after the administration of contrast. Hepatoblastomas often enhance less than the surrounding hepatic parenchyma, as opposed to the typical hyper enhancement of IHHs. When hepatoblastoma is considered in the differential diagnosis of IHH, α-fetoprotein (AFP) levels should be monitored over time. AFP is a major plasma protein produced by the yolk sac and later on from the liver during fetal

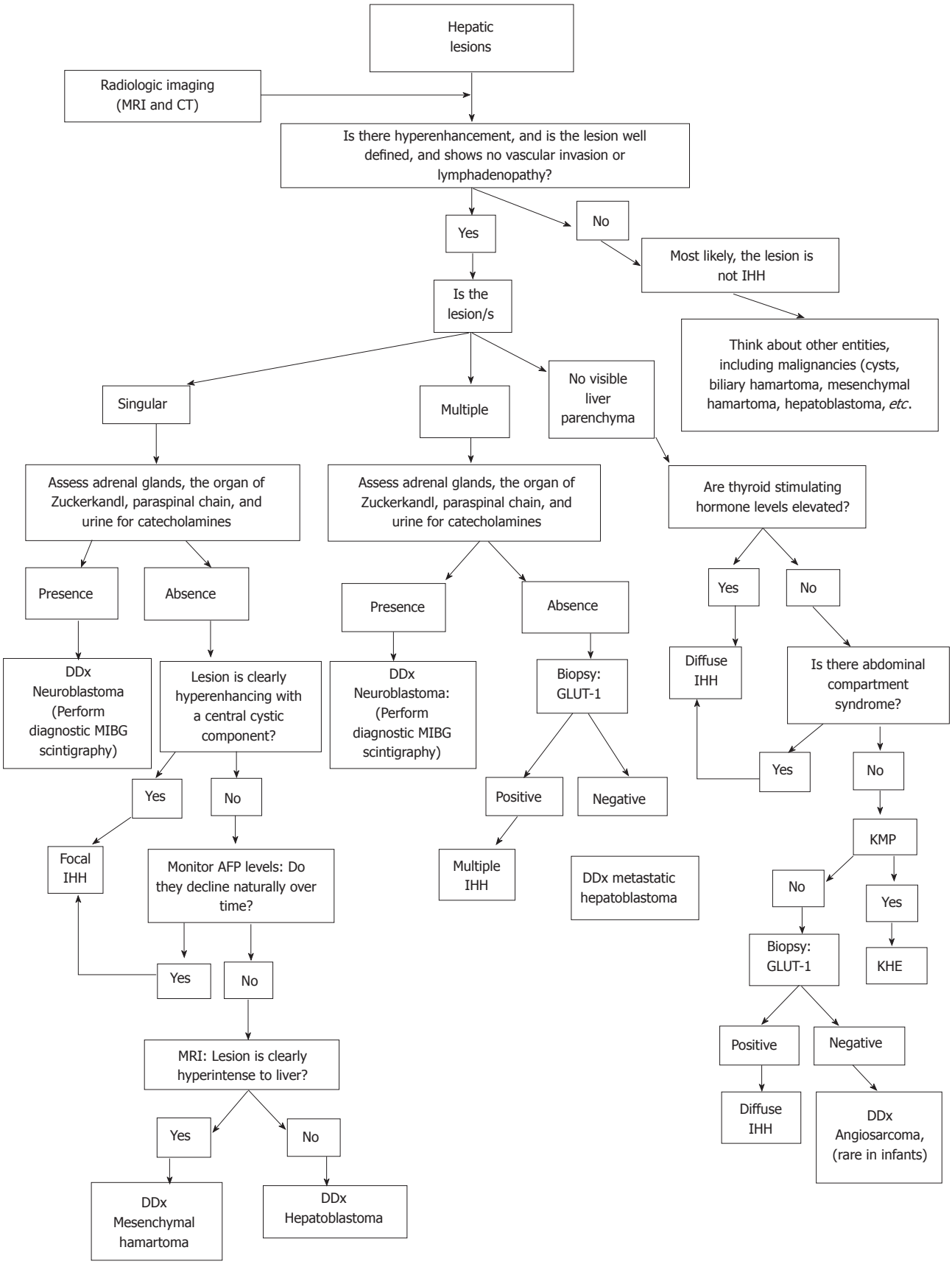

Figure 4 A schematic algorithm to guide physicians through correct diagnosis and management of hepatic lesions. IHH: Infantile hepatic hemangioma; CT: Computed tomography; MRI: Magnetic resonance imaging; DDx: Differential diagnosis; GLUT-1: Glucose transporter-1; AFP: α-fetoprotein; KHE: Kaposiform Hemangioendothelioma.

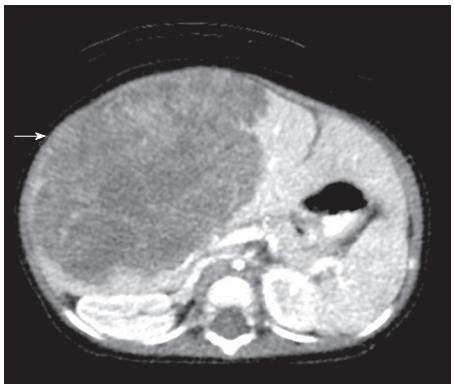

Figure 5 Hepatoblastoma. Axial computed tomography scan after the injection of IV contrast material in a 7-mo-old girl demonstrates a poorly enhancing large mass within the liver (arrow).

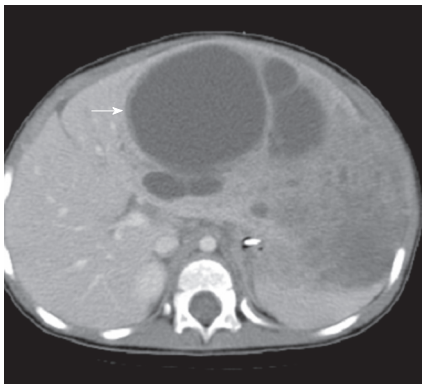

Figure 6 Mesenchymal hamartoma. 15-mo-old with abdominal distention: Axial computed tomography scan after the administration of IV contrast material demonstrates a large multi-cystic mass arising from the liver (arrow). Additional mixed solid and cystic elements are present laterally in the expanded left hepatic lobe.

development. At birth, normal infants have high AFP levels that decreases to a normal range over the first year of life. A baseline measurement in an infant with a focal hepatic lesion can be useful to be certain AFP is appropriately trending down towards the normal range, especially in a patient for whom the diagnosis of focal IHHs is later questioned. In case of hepatoblastomas, AFP levels do not decline over time.

Persistent mild elevation of AFP can also be observed in mesenchymal hamartoma. Mesenchymal hamartoma lesions typically appear distinct from IHHs, as they have predominant cystic components. However, the more mass-like variants can have some imaging overlap with IHHs. Both IHHs and mesenchymal hamartomas are benign lesions. In the literature evidence of association between these two entities has been reported[17].

Multiple and diffuse lesions

When multiple well-demarked hepatic lesions are present - particularly if they demonstrate avid enhancement at MRI, and all appear similar on each sequence - a multifocal IH is the most likely diagnosis, although an atypical presentation of neuroblastoma is still possible. When the hepatic parenchyma appears entirely or nearly entirely replaced with similar appearing lesions as previously described without other abdominal masses, diffuse IHH is likely. The diagnosis can be more confidently made in the context of supporting evidence such as profoundly suppressed thyroid function (or can say elevated TSH), bleeding or compartment syndrome. For a presumptive diagnosis of IHHs, regardless of the subtype, the enhancement pattern must be hyperacute (*i.e.,* arterial), the lesion(s) must be well defined and there must not be any vascular invasion or lymphadenopathy. If any of these criteria are not met, an alternative diagnosis should be considered. The lesion may warrant tissue sampling or resection.

Other rare tumors that can potentially mimic IHHs include the KHE. This tumor is more infiltrative appearing (less well-defined) and Kasabach-Merrit phenomenon often accompanies it. Undifferentiated embryonal sarcoma is a primary hepatic tumor, which can be included in the differential diagnosis (DDx), however it typically presents later in childhood. Though it is typically rare in infants, angiosarcoma can mimic IHH on CT and MRI. In this case of suspected malignancy, a biopsy staining for GLUT-1 positivity can rule out or confirm the diagnosis of IHHs.

Radiological imaging can prove extremely helpful to further characterize the lesion(s) and define the anatomic extent of liver involvement. For instance, radiologically IHHs can be differentiated from hepatoblastomas. Hepatoblastomas tend to appear heterogeneous on a T2 weighted MRI sequence and enhance heterogeneosly as opposed to the homogeneous and rapid enhancement of IHHs. If there are atypical features, percutaneous biopsy and staining for GLUT-1 positivity is indicated, despite the high risk of bleeding[4]. DDx includes also other benign lesions such as cysts, biliary hamartomas and arteriovenous malformations. These entities, however, present imaging characteristics in the neonates that do not overlap with IHH.

MANAGEMENT OF COMPLICATIONS

Despite the benign nature of IHs, a careful follow-up should be planned in case of hepatic lesions. Unlike focal IHHs, multifocal and diffuse IHHs may lead to severe complications and possibly death[18].

Multifocal and diffuse lesions are often associated with arteriovenus shunting. In this case, frequent echocardiograms and close cardiologic follow-ups should be recommended until complete regression of the lesion, due to increased risk of congestive heart failure secondary to high-cardiac output. Congestive heart failure represents the main cause of mortality in these patients.

In case of severe high-flow arteriovenous shunting, embolization should be considered. Shunt embolization should be attempted however only in refractory lesions and those with a worsening clinical course. Poten-

tial complications of this procedure include hepatic infarction, necrosis, cirrhosis, and sepsis. Therefore, embolization has to be performed only when expert interventional radiologists, skilled in performing intrahepatic infant embolization, are available.

As previously mentioned, another possible complication of multifocal and diffuse IHHs is severe consumptive hypothyroidism. For this reason, TSH, T3, and T4 levels should be closely monitored by specialized pediatric endocrinologists. Thyroid hormone replacement should be considered if thyroid hormone levels are low. These patients, however, require much higher doses of thyroxin to achieve a stabilizing euthyroid status than required in patients with congenital hypothyroidism due to continuous catabolism of the exogenous thyroid hormone by the deiodinase 3. As IHHs undergo involution, the hypothyroidism resolves[19]. Therefore, thyroid hormone levels represent excellent biomarkers of tumor response to IHHs treatment.

When the lesions occupy a significant portion of the liver parenchyma, hepatic transaminases, bilirubin and coagulation factors should also be included in the laboratory follow-up to monitor liver and coagulation function.

TREATMENT

Following the validated treatment algorithm developed by the Fishman's group at Boston Children's Hospital[10], focal hemangioma mostly do not require medical intervention, since they mostly involute before or soon after birth. In the rare cases associated with arteriovenous shunting, embolization should be considered. Multifocal and diffuse IHHs may require medical intervention and/or therapy. A recent study confirmed that the mortality rate is greater in patients with diffuse IHHs than in those with multifocal lesions[10]. In 2008 there was a serendipitous discovery of the effectiveness of treatment of cutaneous IH with propranolol, a non-selective ß-blocker, revolutionizing the treatment of hemangiomas by accelerating IH involution compared to other therapies[20].

IHHs have been shown to successfully respond to the propranolol, as well as the cutaneous counterpart[21-23]. Despite this, many studies published after 2008 still indicated interferon-α (INF-α) and corticosteroids for the treatment of IHHs. It is estimated that 2.5% of children who received INF-α for the treatment of vascular anomalies developed spastic diplegia (SD), while an additional 4.1% were diagnosed with a motor developmental disturbance other than SD[24].

Before propranolol was established as the mainstay therapy, corticosteroids were considered the gold-standard treatment for problematic multifocal or diffuse IHHs[25]. However failure rate was as high as 20%-30% and in 40% of cases there was only a stabilization of the lesion growth more than acceleration in the involution[26]. Moreover corticosteroids lead to significant side effects. These include growth retardation, hyperglycemia, Cushinoid syndrome, hypertension and immunosuppression[27]. It has to be mentioned, however, that even propranolol is not free from side effects and include hypotension, hypoglycemia and bradycardia and exacerbation of bronchospasm, that are much less severe than the above medications[22].

Before pharmacotherapy proved successful for the treatment of IHH lesions, and when the benign nature of IHHs had not been clearly established, surgical resection and embolization was considered the mainstay treatment[28]. Surgery for hepatic hemangiomas is rarely performed, mainly only in cases that are refractory to medical management cases. Surgery complications include internal bleeding and hepatic necrosis[29]. In rare case, patients may presents with acute IHH complications such as compartment syndrome. This represents a negative prognostic factor and if medical treatment is not effective decompressed laparotomy up to hepatic transplant should be considered.

CONCLUSION

The literature of infantile hepatic hemangiomas has been greatly confusing in the past. Recent acceptance of IHH classification and subsequent treatment algorithms have proven an advancement in the diagnosis and management of these vascular lesions. Treatment of IHHs has evolved rapidly in the past decade, especially in the studies on the efficacy of propranolol as opposed to the efficacy and problems with long-term corticosteroid treatment. The understanding of IHHs is likely nearing the tipping point into a new revolution of clinical knowledge and treatment. Based on the new classification of IHHs, we propose an algorithm to guide the physicians towards the proper management of hepatic lesions.

REFERENCES

1 **Itinteang T**, Withers AH, Davis PF, Tan ST. Biology of infantile hemangioma. *Front Surg* 2014; **1**: 38 [PMID: 25593962 DOI: 10.3389/fsurg.2014.00038]

2 **Drolet BA**, Swanson EA, Frieden IJ. Infantile hemangiomas: an emerging health issue linked to an increased rate of low birth weight infants. *J Pediatr* 2008; **153**: 712-715, 715.e1 [PMID: 18940356 DOI: 10.1016/j.jpeds.2008.05.043]

3 **Patiño-Seijas B**, Lorenzo-Franco F, Rey-Sanjurjo JL, González-Cuesta M, López-Cedrún Cembranos JL. Vascular Lesions: GLUT-1 expression as a diagnostic tool to discriminate tumors from malformations. *J Oral Maxillofac Surg* 2012; **70**: 2333-2342 [PMID: 22330334 DOI: 10.1016/j.joms.2011.11.013]

4 **Dickie B**, Dasgupta R, Nair R, Alonso MH, Ryckman FC, Tiao GM, Adams DM, Azizkhan RG. Spectrum of hepatic hemangiomas: management and outcome. *J Pediatr Surg* 2009; **44**: 125-133 [PMID: 19159729 DOI: 10.1016/j.jpedsurg.2008.10.021]

5 **Lu CC**, Ko SF, Liang CD, Kuo HW, Tiao MM. Infantile hepatic hemangioendothelioma presenting as early heart failure: report of two cases. *Chang Gung Med J* 2002; **25**: 405-410 [PMID: 12173671 DOI: 10.2298/AOO1302072D]

6 **Gallego C**, Miralles M, Marín C, Muyor P, González G, García-Hidalgo E. Congenital hepatic shunts. *Radiographics* 2004; **24**: 755-772 [PMID: 15143226 DOI: 10.1148/rg.243035046]

7 **Huang SA**, Tu HM, Harney JW, Venihaki M, Butte AJ, Kozakewich HP, Fishman SJ, Larsen PR. Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. *N Engl J Med* 2000; **343**: 185-189 [PMID: 10900278 DOI: 10.1056/NEJM200007203430305]

8 **Zenzen W**, Perez-Atayde AR, Elisofon SA, Kim HB, Alomari AI. Hepatic failure in a rapidly involuting congenital hemangioma of the liver: failure of embolotherapy. *Pediatr Radiol* 2009; **39**: 1118-1123 [PMID: 19588131 DOI: 10.1007/s00247-009-1346-y]

9 **Mulliken JB**, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg* 1982; **69**: 412-422 [PMID: 7063565 DOI: 10.1097/00006534-198203000-00003]

10 **Christison-Lagay ER**, Burrows PE, Alomari A, Dubois J, Kozakewich HP, Lane TS, Paltiel HJ, Klement G, Mulliken JB, Fishman SJ. Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry. *J Pediatr Surg* 2007; **42**: 62-67; discussion 67-68 [PMID: 17208542 DOI: 10.1016/j.jpedsurg.2006.09.041]

11 **Meyers RL**. Tumors of the liver in children. *Surg Oncol* 2007; **16**: 195-203 [PMID: 17714939 DOI: 10.1016/j.suronc.2007.07.002]

12 **Kassarjian A**, Zurakowski D, Dubois J, Paltiel HJ, Fishman SJ, Burrows PE. Infantile hepatic hemangiomas: clinical and imaging findings and their correlation with therapy. *AJR Am J Roentgenol* 2004; **182**: 785-795 [PMID: 14975986 DOI: 10.2214/ajr.182.3.1820785]

13 **Kulungowski AM**, Alomari AI, Chawla A, Christison-Lagay ER, Fishman SJ. Lessons from a liver hemangioma registry: subtype classification. *J Pediatr Surg* 2012; **47**: 165-170 [PMID: 22244411 DOI: 10.1016/j.jpedsurg.2011.10.037]

14 **Arai E**, Kuramochi A, Tsuchida T, Tsuneyoshi M, Kage M, Fukunaga M, Ito T, Tada T, Izumi M, Shimizu K, Hirose T, Shimizu M. Usefulness of D2-40 immunohistochemistry for differentiation between kaposiform hemangioendothelioma and tufted angioma. *J Cutan Pathol* 2006; **33**: 492-497 [PMID: 16872472 DOI: 10.1111/j.1600-0560.2006.00461.x]

15 **Smith AA**, Nelson M. High-Output Heart Failure from a Hepatic Hemangioma With Exertion-Induced Hypoxia. *Am J Cardiol* 2016; **117**: 157-158 [PMID: 26525213 DOI: 10.1016/j.amjcard.2015.10.019]

16 **Fisher DA**. Clinical review 19: Management of congenital hypothyroidism. *J Clin Endocrinol Metab* 1991; **72**: 523-529 [PMID: 1997508 DOI: 10.1210/jcem-72-3-523]

17 **Behr GG**, Fishman SJ, Caty MG, Kulungowski AM, Paltiel HJ, Alomari AI. Hepatic mesenchymal hamartoma and infantile hemangioma: a rare association. *J Pediatr Surg* 2012; **47**: 448-452 [PMID: 22424336 DOI: 10.1016/j.jpedsurg.2011.10.049]

18 **Rialon KL**, Murillo R, Fevurly RD, Kulungowski AM, Christison-Lagay ER, Zurakowski D, Kozakewich HP, Alomari AI, Fishman SJ. Risk factors for mortality in patients with multifocal and diffuse hepatic hemangiomas. *J Pediatr Surg* 2015; **50**: 837-841 [PMID: 25783331 DOI: 10.1016/j.jpedsurg.2014.09.056]

19 **Konrad D**, Ellis G, Perlman K. Spontaneous regression of severe acquired infantile hypothyroidism associated with multiple liver hemangiomas. *Pediatrics* 2003; **112**: 1424-1426 [PMID: 14654623 DOI: 10.1542/peds.112.6.1424]

20 **Léauté-Labrèze C**, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taïeb A. Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008; **358**: 2649-2651 [PMID: 18550886 DOI: 10.1056/NEJMc0708819]

21 **Marsciani A**, Pericoli R, Alaggio R, Brisigotti M, Vergine G. Massive response of severe infantile hepatic hemangioma to propanolol. *Pediatr Blood Cancer* 2010; **54**: 176 [PMID: 19743301 DOI: 10.1002/pbc.22262]

22 **Mazereeuw-Hautier J**, Hoeger PH, Benlahrech S, Ammour A, Broue P, Vial J, Ohanessian G, Léauté-Labrèze C, Labenne M, Vabres P, Rössler J, Bodemer C. Efficacy of propranolol in hepatic infantile hemangiomas with diffuse neonatal hemangiomatosis. *J Pediatr* 2010; **157**: 340-342 [PMID: 20488455 DOI: 10.1016/j.jpeds.2010.04.003]

23 **Sarialioglu F**, Erbay A, Demir S. Response of infantile hepatic hemangioma to propranolol resistant to high-dose methylprednisolone and interferon-α therapy. *Pediatr Blood Cancer* 2010; **55**: 1433-1434 [PMID: 20981697 DOI: 10.1002/pbc.22691]

24 **Barlow CF**, Priebe CJ, Mulliken JB, Barnes PD, Mac Donald D, Folkman J, Ezekowitz RA. Spastic diplegia as a complication of interferon Alfa-2a treatment of hemangiomas of infancy. *J Pediatr* 1998; **132**: 527-530 [PMID: 9544915 DOI: 10.1097/00001577-199801040-00009]

25 **Bertrand J**, McCuaig C, Dubois J, Hatami A, Ondrejchak S, Powell J. Propranolol versus prednisone in the treatment of infantile hemangiomas: a retrospective comparative study. *Pediatr Dermatol* 2011; **28**: 649-654 [PMID: 21995756 DOI: 10.1111/j.1525-1470.2011.01551.x]

26 **Enjolras O**, Riche MC, Merland JJ, Escande JP. Management of alarming hemangiomas in infancy: a review of 25 cases. *Pediatrics* 1990; **85**: 491-498 [PMID: 2097998 DOI: 10.1016/0022-3468(91)90449-4]

27 **Boon LM**, MacDonald DM, Mulliken JB. Complications of systemic corticosteroid therapy for problematic hemangioma. *Plast Reconstr Surg* 1999; **104**: 1616-1623 [PMID: 10541160 DOI: 10.1097/00006534-199911000-00002]

28 **Markiewicz-Kijewska M**, Kasprzyk W, Broniszczak D, Bacewicz L, Ostoja-Chyzynska A, Ismail H, Kosciesza A, Dembowska-Baginska B, Teisseyre J, Kluge P, Brzezinska-Rajszys G, Jankowska I, Kalicinski P. Hemodynamic failure as an indication to urgent liver transplantation in infants with giant hepatic hemangiomas or vascular malformations--report of four cases. *Pediatr Transplant* 2009; **13**: 906-912 [PMID: 18992048 DOI: 10.1111/j.1399-3046.2008.01050.x]

29 **Draper H**, Diamond IR, Temple M, John P, Ng V, Fecteau A. Multimodal management of endangering hepatic hemangioma: impact on transplant avoidance: a descriptive case series. *J Pediatr Surg* 2008; **43**: 120-125; discussion 126 [PMID: 18206468 DOI: 10.1016/j.jpedsurg.2007.09.030]

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MINIREVIEWS

Drug delivery interfaces: A way to optimize inhalation therapy in spontaneously breathing children

Arzu Ari

Arzu Ari, Department of Respiratory Therapy, Georgia State University, Atlanta, GA 30303-3083, United States

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Correspondence to: Arzu Ari, FAARC, PhD, PT, RRT, Department of Respiratory Therapy, Georgia State University, 140 Decatur Street Suite 1228, Atlanta, GA 30303-3083, United States. arzuari@hotmail.com
Telephone: +1-404-4131269
Fax: +1-404-4131230

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Abstract

There are several different types of drug delivery interfaces available on the market. Using the right interface for aerosol drug delivery to children is essential for effective inhalation therapy. However, clinicians usually focus on selecting the right drug-device combination and often overlook the importance of interface selection that lead to suboptimal drug delivery and therapeutic response in neonates and pediatrics. Therefore, it is necessary to critically assess each interface and understand its advantage and disadvantages in aerosol drug delivery to this patient population. The purpose of this paper is to provide a critical assessment of drug delivery interfaces used for the treatment of children with pulmonary diseases by emphasizing advantages and problems associated with their use during inhalation therapy.

Key words: Aerosols; Inhalation therapy; Children; Masks; Mouthpiece; High flow nasal cannula; Blow-by; Hood; Spacer/valved holding chamber

Core tip: Many interfaces exist for aerosol drug delivery to spontaneously breathing children and inhalation therapy with different interfaces has become an important topic of interest among clinicians. However, clinicians usually focus on selecting the right drug-device combination and often overlook the importance of interface selection that lead to suboptimal drug delivery and therapeutic response in neonates and pediatrics. This paper provides a critical assessment of drug delivery interfaces used for the treatment of children with pulmonary diseases by emphasizing advantages and problems associated with their use during inhalation therapy.

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INTRODUCTION

There are several different types of drug delivery interfaces available on the market. Using the right interface for aerosol drug delivery to children is essential for effective inhalation therapy. However, clinicians usually focused on selecting the right drug-device combination and often overlooked the importance of interface selection that lead to suboptimal drug delivery and therapeutic response in neonates and pediatrics[1-6]. Therefore, it is necessary to critically assess each interface and understand its advantage and disadvantages in aerosol drug delivery to neonates and pediatrics. The purpose of this paper is to provide a critical assessment of drug delivery interfaces used for the treatment of children with pulmonary diseases by emphasizing advantages and problems associated with their use during inhalation therapy.

BLOW-BY

Blow-by is a technique that is used with a jet nebulizer placed within a distance from the child and directs aerosol plume towards the patient's face. Historically, aerosolized medications were delivered to neonates and pediatrics using blow-by because it was considered to be an effective technique especially for crying, fussing and uncooperative children. Also, many parents preferred to use blow-by, a mask-free aerosol delivery technique, to avoid struggling with their children during inhalation therapy.

However, there are several disadvantages of this technique. For instance, it cannot be used with pressurized metered-dose inhalers (pMDIs) with valved holding chambers (VHCs) and breath-actuated nebulizers due to poor mask seal that will inhibit valve opening[7]. Also, blow-by cannot be used with mesh nebulizers due to lack of supplemental gas flow[7]. Previous research reported that blow-by is not efficient in aerosol drug delivery to children because it results in 50%-85% lower dose than the facemask[8-11]. Therefore, using blow-by for aerosol therapy is not recommended[7,11-13].

Problems associated with blow-by highlight not only the importance of interface selection in inhalation therapy, but also finding a better alternative for delivering aerosolized medications to neonates and pediatrics. Mouthpiece, facemask, nasal mask, pasifier mask, hood, high flow nasal cannula and VHCs may be viable choices of interface in children and the following sections will describe each interface more in detail.

MOUTHPIECE

Previous *in vitro* studies showed that aerosol delivery *via* a mouthpiece may provide twice as much drug compared with a facemask and is the most effective interface in spontaneously breathing older pediatrics[14,15]. Since children less than 3 years of age cannot keep the mouthpiece in their mouth with an adequate seal during inhalation therapy, the mouthpiece is not the right interface for them[16-19]. Therefore, when a mouthpiece cannot be used by a child, choosing another interface such as facemask, high flow nasal cannula or hood is important to improve the efficiency and efficacy of aerosol drug delivery to neonates and pediatrics.

FACEMASK

Facemasks are commonly used for aerosol drug delivery to children until they develop sufficient understanding to inhale through the mouthpiece during inhalation therapy. In children who cannot use a mouthpiece until 3 years of age, clinicians should consider using a well-fitting facemask. Therefore, it is essential to select a lightweight and flexible facemask with anatomic contours and small dead space in order to increase tolerability of facemask by children during inhalation therapy[20,21]. Using smaller masks with less dead space in neonates will lead to a greater inhaled dose especially with use of aerosol devices such as mesh nebulizers or pMDIs that do not add gas to the system during treatment.

Facemasks designs can be divided into two categories: (1) front-loaded facemasks and (2) bottom-loaded facemasks. Front-loaded facemasks have small entrainment ports on the side of the mask and direct aerosol toward the oronasal area of the patient as opposed to bottom-loaded masks that direct aerosol toward the upper part of the mask. Previous research reported that aerosol deposition with the front-loaded facemask (Bubbles Fish Ⅱ Mask, PARI, Midlothian, Virginia) was greater than bottom-loaded facemask[8,22-24]. They also have lower deposition in the eye and face compared with bottom-loaded facemask designs[22,23,25].

When a facemask is used for aerosol drug delivery to neonates or pediatrics, clinicians should have a good face-mask seal to maximize the efficiency of treatment and prevent the drug from getting to the eyes and the face of children. However, keeping a good face-mask seal during inhalation therapy is frequently associated with crying and rejection of the facemask. Previous research showed that aerosol drug delivery to children will decrease significantly without an optimum face-mask seal because of leaks, crying or children intolerance of the facemask[2-4,22,25-29]. Janssens *et al*[30] suggested that administration of inhaled medications while children are asleep may be a viable option for inhalation therapy because children have more regular breathing patterns during sleep that may lead to greater lung deposition and better patient outcomes. However, Esposito-Festen *et al*[31] reported that 69% of the young children woke up and 75% of them distressed during inhalation therapy with the pMDI and VHC combination.

In the past, clinicians believed that crying improves aerosol drug delivery to children because of the large breath at the end of the cry. However, crying results in a

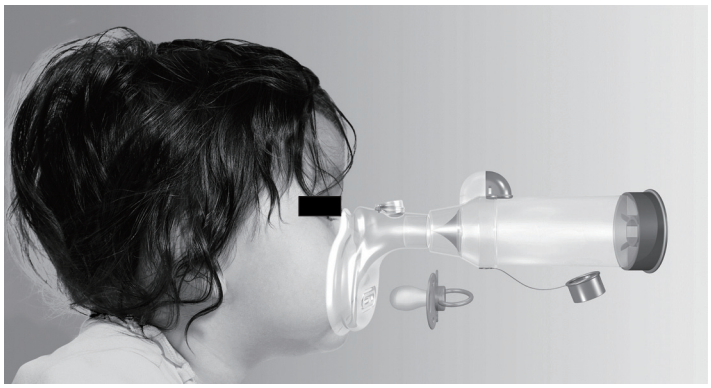

Figure 1 Soother mask (Reproduced with permission from the InspiRx, Somerset, New Jersey).

very long exhalation followed by fast and short inhalation that leads to deposition of aerosolized medications in the upper respiratory track than in the lower respiratory therapy track. Also, it is difficult to have a good seal with the facemask when a baby cries. Using a facemask with the pMDI - VHC, Tal *et al*[32] found that lung deposition of babies crying was 0.35% as opposed to 2% when they have quite breating. Similarly, Murakami *et al*[33] showed that aerosol deposition in a crying infant using a facemask with a nebulizer was negligible and Iles *et al*[34] reported a 4-fold decrease in lung deposition when infants were crying. According to the findings of the study conducted by Wildhaber *et al*[35] the gastrointestinal deposition in crying children was 50% higher than their non-crying peers.

PACIFIER MASK

As a new and innovative development of chidren-oriented drug delivery interface, the pacifier mask (Soother Mask, InspiRx, Somerset, New Jersey) was designed to achieve therapeutic lung deposition in children by eliminating their discomfort, fear and cry with the conventional facemask and keeping them calm through a pacifier. It includes the infant's own pacifier that is attached to the anterior wall of the mask (Figure 1). The infant keeps the Soother mask sealed to his face by sucking the pacifier during treatment while nasally inhaling aerosolized medications generated by pMDIs/VHCs or nebulizers during inhalation therapy[36,37]. Amirav *et al*[38] compared the Soother mask with a conventional bottom-loaded face mask on bronchodilator delivery in 12 infants less than 1 year of age. Using scintigraphic measurements of aerosol deposition in infants, they reported that lung deposition with the Soother Mask was similar to that with the conventional face mask without a pacifier[38]. Since sucking calms children, the Shooter Mask can be used for prolonged periods of time without rejection by infants and improves compliance to aerosol treatments in infants[18,36-38].

HIGH FLOW NASAL CANNULA

Infants and young children are nose breathers. Since previous research showed that nasal delivery of aerosolized medications to the lungs of infants and pediatrics is superior or more effective than oral delivery[39,40], aerosol delivery through high flow nasal cannula (HFNC) has become a popular procedure in the treatment of children with pulmonary diseases. Several *in vitro* studies evaluated aerosol drug delivery through HFNC in infants and pediatrics[41-44]. Using dose quantification with the laser diffraction technique, Bhashyam *et al*[43] determined the efficiency of inhalation therapy through adult and pediatric HFNC with a mesh nebulizer placed downstream of a heated humidifier. They reported that aerosolized medications could be efficiently delivered to pediatrics through HFNC. Ari *et al*[44] compared aerosol drug delivery with helium-oxygen mixture (heliox) and oxygen at 3 L/min and 6 L/min, using a pediatric HFNC with a mesh nebulizer placed on the inspiratory inlet of a heated humidification system. They reported that bronchodilator delivery with heliox at 3 L/min was similar to that with oxygen whereas heliox delivered 2 fold greater aerosol than oxygen at 6 L/min. Sunbul *et al*[42] evaluated bronchodilator delivery using HFNC, bubble continuous positive airway pressure (CPAP) and sigh intermittent mandatory ventilation (SiPAP) with a mesh nebulizer placed proximal to the patient interface and prior to the humidifier. Using spontaneously breathing lung model attached to a low-birth-weight anatomic nasal airway cast, they showed that aerosol delivery with SiPAP was lower than HFNC and the Bubble CPAP. Aerosol deposition through HFNC was less than 2% but higher than drug delivery with the Bubble CPAP. Also, nebulizer placement at the humidifier resulted in greater aerosol deposition in HFNC, SiPAP and Bubble CPAP[42]. According to Perry *et al*[41] HFNC should not be used for bronchodilator delivery to children because the amount of aerosol deposition obtained with different cannula sizes of flows used with HFNC was lower than the amount needed for a clinical response. Also, skin irritation and condensate accumulating in the cannula are potential issues with HFNC. Therefore, clinical studies evaluating the safety and efficacy of aerosol drug delivery with HFNC are warranted.

NASAL MASK

Nasal masks were developed in recent years to improve

Table 1 Descriptions, advantages and disadvantages of each interface used for aerosol drug delivery to spontaneously breathing neonates and pediatrics

Interface	Description	Advantages	Disadvantages	Suggestions for the best practice
Blow-by	A technique that directs aerosol plume towards the patient's face by placing a jet nebulizer within a distance from the child that ranges from 1 to 30 cm	Easy to use Comfortable and easy to tolerate by the patient A mask-free aerosol delivery technique Used with fussing, crying and uncooperative children	Inefficient aerosol drug delivery to children Drug delivery with blow-by is 50%-85% less than the facemask Cannot be used with pMDIs, breath- actuated nebulizers and mesh nebulizers	Inhalation therapy with blow-by is not efficient; therefore, it should not be used for aerosol drug delivery to neonates and pediatrics
Mouthpiece	A cylindrical tube that extends between the lips so that aerosol can pass through the oropharynx to reach lower respiratory tract	Efficient inhalation therapy in children Aerosol drug delivery with a mouthpiece is two-fold more than that with a face mask	Children less than 3 yr of age cannot use a mouthpiece An adequate consistent seal is needed during inhalation therapy	The mouthpiece should not be used for children who are less than 3 yr old When using a mouthpiece child should be encouraged to keep it in their mouth during therapy If a child cannot keep the mouthpiece in his mouth with an adequate seal during aerosol drug delivery, another interface should be used for inhalation therapy
Facemask	An interface that covers the nose and mouth. It is kept in place through an elastic band that extends beyond the back of the head or neck	Can be used in children all years of age Can be used with nebulizers and pMDIs to deliver aerosolized medications to neonates and pediatrics	A good facemask seal is needed for optimum aerosol drug delivery Is frequently associated with crying, intolerance and rejection of the mask Crying and leaks between face and mask decrease aerosol drug delivery to children	Select a lightweight and flexible facemask with anatomic contours to increase tolerability of face mask by children during therapy Choose a facemask with small dead space and have a good face-mask seal to increase delivery efficiency of inhalation therapy Use another interface if the patient starts to fuss, and cry during aerosol drug delivery with a facemask
Pacifier mask	A face mask with the attachment of the infant's own pacifier	A new and innovative facemask design that eliminates fear, discomfort and cry with the standard facemask A children-oriented drug delivery interface designed to achieve therapeutic lung deposition in children Improves compliance to inhalation therapy in infants		May be a good option for children who fuss, cry and does not tolerate other interfaces used for aerosol drug delivery in neonates and pediatrics
Nasal mask	An interface that covers the nose to allow aerosol to pass through the nasopharynx to reach the lower respiratory tract	Easy to use Better tolerance than the facemask	Aerosol delivery with the nasal mask is less than that with the standard facemask	
High flow nasal cannula	A tubing with two small prongs that are inserted into the nares to allow aerosol pass through the nasopharynx and reach the lower respiratory tract	Efficient delivery of aerosolized medications to neonates and pediatrics Children may tolerate HFNC better than the facemask	More information about the safety and efficacy of aerosol drug delivery though HFNC is needed Cannot be used with pMDIs	When using mesh nebulizers for aerosol drug delivery to neonates and pediatrics, place the nebulizer prior to the heated humidifier
Hood	An enclosure that covers the head and neck of a neonate or small children to deliver aerosol to the lungs while isolating it from ambient air	A good option for aerosol delivery to children who cannot use a mouthpiece and tolerate the facemask Likelihood of agitating infants and making them cry is low Aerosol delivery with the hood is the same as the facemask Parents prefer the hood over the mask	User may need additional training and practice to provide proper inhalation therapy with the hood More time and parts may be needed for the set-up	Use the hood for aerosol drug delivery to children who cannot use a mouthpiece and tolerate the facemask Put the infant in the face-side position when using the hood for inhalation therapy because it has less facial-ocular deposition than face-up position

Valved holding chamber	A chamber shaped interface with a one-way valve that allows aerosols to be contained in the chamber during aerosol therapy	Reduces oropharyngeal deposition Minimize hand-breath coordination during inhalation therapy Improves efficiency of aerosol therapy	Electrostatic charge and large volume VHCs result in a decrease in aerosol drug delivery to children	Wash the VHC with detergent and air dry before inhalation therapy in order to eliminate static charge and improve aerosol delivery to neonates and pediatrics Choose small volume VHCs for aerosol therapy Actuate one-dose at a time into VHC instead of multiple doses

VHC: Valved holding chambers; pMDIs: Pressurized metered-dose inhalers.

aerosol drug delivery to neonates and pediatrics. The nasal mask is a special type of mask that is placed over the nasal airway during inhalation therapy. A recent *in vitro* study showed that aerosol delivery with the nasal mask was less than that with the facemask in simulated spontaneously breathing infants and young children using a jet nebulizer[24].

HOOD

Hood is a good option for aerosol drug delivery to children who cannot use a mouthpiece and tolerate the facemask[18,45-48]. Since there is no attachment to the patient's face, the likelihood of agitating infants and making them cry with the use of hood for inhalation therapy may be less than facemasks. Aerosol drug delivery *via* hood is easy to operate and often provided when infants are asleep. Amirav *et al*[49] showed that bronchodilator delivery with the hood and facemask was similar (2.6% and 2.4%, respectively) in 14 wheezing children. Kugelman *et al*[47] reported that both treatment time and discomfort were lower in infants using the hood. In another study, Amirav *et al*[48] found that respiratory scores of infants with bronchiolitis received aerosol therapy with the hood and facemask were similar, but parents preferred the hood over the masks[48]. It is also important to ensure the optimal position of the child within the hood. Kim *et al*[50] found similar lung deposition in face-up and face down positions during hood nebulization; however, the face-side position has less facial-ocular deposition than face-up position.

VALVED-HOLDING CHAMBERS

VHCs are commonly used with pMDIs in order to decrease oropharyngeal deposition and minimize hand-breath coordination in children[12,51]. According to previous research, spacers and VHCs should be washed with detergent and air-dry to eliminate static charge and improve aerosol delivery to infants and pediatrics[52-55]. Thus, deposition of drug particles on the inner surface of the spacer or VHC will be eliminated. Another alternative would be to use anti-static spacers/VHCs during inhalation therapy in children[56].

Also, infants and toddlers may not empty aerosolized medication from a large volume spacer of 200-700 mL. Therefore, it is important to use small volume spacers or VHCs so that the concentration of aerosol in the VHC is kept higher and children can inhale all the medication in less time with fewer breaths. Parents need to be educated to actuate one dose at a time into VHC instead of multiple doses and let their children inhale from VHC right after the pMDI has been actuated[12,57].

EDUCATING PARENTS ABOUT INTERFACES USED IN INHALATION THERAPY

Typically, inhaled medications are prescribed without demonstrating parents how inhalation therapy should be undertaken with each device and interface. Therefore, parents don't know how to use each interface and how to solve problems that may arise during aerosol drug delivery to children. For instance, when their baby fights with the facemask, some parents may decide to use blow-by without knowing that it will reduce the efficiency of therapy and others force the baby to accept the facemask by holding it tightly on the baby' s face and believing that crying improves aerosol drug delivery to their children. As a result, parents report poor response to inhalation therapy to their physicians who usually decide to increase the dose or change the inhaled agent as they assume parents' technique in aerosol drug delivery is adequate[18]. Therefore, parental awareness and training on proper technique with each interface during inhalation therapy is essential. Table 1 includes descriptions, advantages and disadvantages of each interface used for aerosol drug delivery to spontaneously breathing neonates and pediatrics. After careful instructions on how to use and handle an aerosol device, clinicians should reinforce instructions on a regular basis and the choice of drug delivery interface should be re-assessed[58].

In conclusion, delivering aerosolized drugs through different interfaces to children poses a number of challenges. Clearly, there is a need to develop more acceptable and child-friendly interfaces in order to improve aerosol drug delivery to this patient population. New interfaces should take into account the special needs and respiratory characteristics of children. Meanwhile, educating parents and healthcare professionals about drug delivery interfaces used in inhalation therapy is

essential for the well-being of neonates and pediatrics.

REFERENCES

1 **Nikander K**, Berg E, Smaldone GC. Jet nebulizers versus pressurized metered dose inhalers with valved holding chambers: effects of the facemask on aerosol delivery. *J Aerosol Med* 2007; **20** Suppl 1: S46-55; discussion S55-8 [PMID: 17411405 DOI: 10.1089/jam.2007.0588]

2 **Janssens HM**, Tiddens HA. Facemasks and aerosol delivery by metered dose inhaler-valved holding chamber in young children: a tight seal makes the difference. *J Aerosol Med* 2007; **20** Suppl 1: S59-S63; discussion S63-65 [PMID: 17411407 DOI: 10.1089/jam.2007.0578]

3 **Esposito-Festen J**, Ates B, van Vliet F, Hop W, Tiddens H. Aerosol delivery to young children by pMDI-spacer: is facemask design important? *Pediatr Allergy Immunol* 2005; **16**: 348-353 [PMID: 15943599 DOI: 10.1111/j.1399-3038.2005.00285]

4 **Erzinger S**, Schueepp KG, Brooks-Wildhaber J, Devadason SG, Wildhaber JH. Facemasks and aerosol delivery in vivo. *J Aerosol Med* 2007; **20** Suppl 1: S78-83; discussion S83-S84 [PMID: 17411409 DOI: 10.1089/jam.2007.0572]

5 **Ari A**, Fink JB. Effective bronchodilator resuscitation of children in the emergency room: device or interface? *Respir Care* 2011; **56**: 882-885 [PMID: 21679497 DOI: 10.4187/respcare.01375]

6 **Ari A**, Hess D, Myers TR, Rau JL. A Guide to Aerosol Delivery Devices for Respiratory Therapists. Dallas, Texas: American Association for Respiratory Care, 2009

7 **DiBlasi RM**. Clinical Controversies in Aerosol Therapy for Infants and Children. *Respir Care* 2015; **60**: 894-914; discussion 914-916 [PMID: 26070582 DOI: 10.4187/respcare.04137]

8 **Lin HL**, Restrepo RD, Gardenhire DS, Rau JL. Effect of face mask design on inhaled mass of nebulized albuterol, using a pediatric breathing model. *Respir Care* 2007; **52**: 1021-1026 [PMID: 17650358]

9 **Restrepo RD**, Dickson SK, Rau JL, Gardenhire DS. An investigation of nebulized bronchodilator delivery using a pediatric lung model of spontaneous breathing. *Respir Care* 2006; **51**: 56-61 [PMID: 16381619]

10 **Rubin BK**. Bye-bye, blow-by. *Respir Care* 2007; **52**: 981 [PMID: 17650350]

11 **Ari A**, Restrepo RD. Aerosol delivery device selection for spontaneously breathing patients: 2012. *Respir Care* 2012; **57**: 613-626 [PMID: 22472501 DOI: 10.4187/respcare.01756]

12 **Ari A**, Fink JB. Aerosol therapy in children: challenges and solutions. *Expert Rev Respir Med* 2013; **7**: 665-672 [PMID: 24224509 DOI: 10.1586/17476348.2013.847369]

13 **Ari A**, Fink JB. Guidelines for aerosol devices in infants, children and adults: which to choose, why and how to achieve effective aerosol therapy. *Expert Rev Respir Med* 2011; **5**: 561-572 [PMID: 21859275 DOI: 10.1586/ers.11.49]

14 **Ari A**, de Andrade AD, Sheard M, AlHamad B, Fink JB. Performance Comparisons of Jet and Mesh Nebulizers Using Different Interfaces in Simulated Spontaneously Breathing Adults and Children. *J Aerosol Med Pulm Drug Deliv* 2015; **28**: 281-289 [PMID: 25493535 DOI: 10.1089/jamp.2014]

15 **Ditcham W**, Murdzoska J, Zhang G, Roller C, von Hollen D, Nikander K, Devadason SG. Lung deposition of 99mTc-radiolabeled albuterol delivered through a pressurized metered dose inhaler and spacer with facemask or mouthpiece in children with asthma. *J Aerosol Med Pulm Drug Deliv* 2014; **27** Suppl 1: S63-S75 [PMID: 25054483 DOI: 10.1089/jamp.2014.1139]

16 **Everard ML**. Aerosol delivery to children. *Pediatr Ann* 2006; **35**: 630-636 [PMID: 16999296 DOI: 10.3928/0090-4481-20060901-06]

17 **Everard ML**. Inhalation therapy for infants. *Adv Drug Deliv Rev* 2003; **55**: 869-878 [PMID: 12842605 DOI: 10.1016/S0169-409X(03)00082-6]

18 **Amirav I**, Newhouse MT. Aerosol therapy in infants and toddlers: past, present and future. *Expert Rev Respir Med* 2008; **2**: 597-605 [PMID: 20477295 DOI: 10.1586/17476348.2.5.597]

19 **Devadason SG**. Recent advances in aerosol therapy for children with asthma. *J Aerosol Med* 2006; **19**: 61-66 [PMID: 16551216 DOI: 10.1089/jam.2006.19.61]

20 **Amirav I**, Mandelberg A. Face masks for aerosols-there is more science... *Pediatr Pulmonol* 2010; **45**: 221-223 [PMID: 20146372 DOI: 10.1002/ppul.21163]

21 **Amirav I**, Newhouse MT. Review of optimal characteristics of face-masks for valved-holding chambers (VHCs). *Pediatr Pulmonol* 2008; **43**: 268-274 [PMID: 18219694 DOI: 10.1002/ppul.20767]

22 **Smaldone GC**, Berg E, Nikander K. Variation in pediatric aerosol delivery: importance of facemask. *J Aerosol Med* 2005; **18**: 354-363 [PMID: 16181009 DOI: 10.1089/jam.2005.18.354]

23 **Sangwan S**, Gurses BK, Smaldone GC. Facemasks and facial deposition of aerosols. *Pediatr Pulmonol* 2004; **37**: 447-452 [PMID: 15095329 DOI: 10.1002/ppul.10454]

24 **El Taoum KK**, Xi J, Kim J, Berlinski A. In Vitro Evaluation of Aerosols Delivered via the Nasal Route. *Respir Care* 2015; **60**: 1015-1025 [PMID: 25587167 DOI: 10.4187/respcare.03606]

25 **Smaldone GC**, Sangwan S, Shah A. Facemask design, facial deposition, and delivered dose of nebulized aerosols. *J Aerosol Med* 2007; **20** Suppl 1: S66-75; discussion S75-7 [PMID: 17411408 DOI: 10.1089/jam.2007.0579]

26 **Amirav I**, Newhouse MT. Aerosol therapy with valved holding chambers in young children: importance of the facemask seal. *Pediatrics* 2001; **108**: 389-394 [PMID: 11483804 DOI: 10.1542/peds.108.2.389]

27 **Esposito-Festen JE**, Ates B, van Vliet FJ, Verbraak AF, de Jongste JC, Tiddens HA. Effect of a facemask leak on aerosol delivery from a pMDI-spacer system. *J Aerosol Med* 2004; **17**: 1-6 [PMID: 15120007 DOI: 10.1089/089426804322994406]

28 **Smaldone GC**. Assessing new technologies: patient-device interactions and deposition. *Respir Care* 2005; **50**: 1151-1160 [PMID: 16122399]

29 **Hayden JT**, Smith N, Woolf DA, Barry PW, O'Callaghan C. A randomised crossover trial of facemask efficacy. *Arch Dis Child* 2004; **89**: 72-73 [PMID: 14709514]

30 **Janssens HM**, van der Wiel EC, Verbraak AF, de Jongste JC, Merkus PJ, Tiddens HA. Aerosol therapy and the fighting toddler: is administration during sleep an alternative? *J Aerosol Med* 2003; **16**: 395-400 [PMID: 14977430 DOI: 10.1089/089426803772455659]

31 **Esposito-Festen J**, Ijsselstijn H, Hop W, van Vliet F, de Jongste J, Tiddens H. Aerosol therapy by pressured metered-dose inhaler-spacer in sleeping young children: to do or not to do? *Chest* 2006; **130**: 487-492 [PMID: 16899849 DOI: 10.1378/chest.130.2.487]

32 **Tal A**, Golan H, Grauer N, Aviram M, Albin D, Quastel MR. Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. *J Pediatr* 1996; **128**: 479-484 [PMID: 8618180 DOI: 10.1016/S0022-3476(96)70357-8]

33 **Murakami G**, Igarashi T, Adachi Y, Matsuno M, Adachi Y, Sawai M, Yoshizumi A, Okada T. Measurement of bronchial hyperreactivity in infants and preschool children using a new method. *Ann Allergy* 1990; **64**: 383-387 [PMID: 2321816]

34 **Iles R**, Lister P, Edmunds AT. Crying significantly reduces absorption of aerosolised drug in infants. *Arch Dis Child* 1999; **81**: 163-165 [PMID: 10490528 DOI: 10.1136/adc.81.2.163]

35 **Wildhaber JH**, Dore ND, Wilson JM, Devadason SG, LeSouëf PN. Inhalation therapy in asthma: nebulizer or pressurized metered-dose inhaler with holding chamber? In vivo comparison of lung deposition in children. *J Pediatr* 1999; **135**: 28-33 [PMID: 10393600 DOI: 10.1016/S0022-3476(99)70323-9]

36 **Amirav I**, Newhouse MT, Luder A, Halamish A, Omar H, Gorenberg M. Feasibility of aerosol drug delivery to sleeping infants: a prospective observational study. *BMJ Open* 2014; **4**: e004124 [PMID: 24670428 DOI: 10.1136/bmjopen-2013-004124]

37 **Amirav I**, Luder AS, Halamish A, Raviv D, Kimmel R, Waisman D, Newhouse MT. Design of aerosol face masks for children using computerized 3D face analysis. *J Aerosol Med Pulm Drug Deliv* 2014; **27**: 272-278 [PMID: 24074142 DOI: 10.1089/

jamp.2013.1069]
38 **Amirav I**, Luder A, Chleechel A, Newhouse MT, Gorenberg M. Lung aerosol deposition in suckling infants. *Arch Dis Child* 2012; **97**: 497-501 [PMID: 22362720 DOI: 10.1136/archdischild-2011-301236]
39 **Chua HL**, Collis GG, Newbury AM, Chan K, Bower GD, Sly PD, Le Souef PN. The influence of age on aerosol deposition in children with cystic fibrosis. *Eur Respir J* 1994; **7**: 2185-2191 [PMID: 7713202 DOI: 10.1183/09031936.94.07122185]
40 **Amirav I**, Borojeni AA, Halamish A, Newhouse MT, Golshahi L. Nasal versus oral aerosol delivery to the "lungs" in infants and toddlers. *Pediatr Pulmonol* 2014 Jan 31; Epub ahead of print [PMID: 24482309 DOI: 10.1002/ppul.22999]
41 **Perry SA**, Kesser KC, Geller DE, Selhorst DM, Rendle JK, Hertzog JH. Influences of cannula size and flow rate on aerosol drug delivery through the Vapotherm humidified high-flow nasal cannula system. *Pediatr Crit Care Med* 2013; **14**: e250-e256 [PMID: 23628834 DOI: 10.1097/PCC.0b013e31828a7f79]
42 **Sunbul FS**, Fink JB, Harwood R, Sheard MM, Zimmerman RD, Ari A. Comparison of HFNC, bubble CPAP and SiPAP on aerosol delivery in neonates: An in-vitro study. *Pediatr Pulmonol* 2015; **50**: 1099-1106 [PMID: 25491434 DOI: 10.1002/ppul.23123]
43 **Bhashyam AR**, Wolf MT, Marcinkowski AL, Saville A, Thomas K, Carcillo JA, Corcoran TE. Aerosol delivery through nasal cannulas: an in vitro study. *J Aerosol Med Pulm Drug Deliv* 2008; **21**: 181-188 [PMID: 18518794 DOI: 10.1089/jamp.2007.0662]
44 **Ari A**, Harwood R, Sheard M, Dailey P, Fink JB. In vitro comparison of heliox and oxygen in aerosol delivery using pediatric high flow nasal cannula. *Pediatr Pulmonol* 2011; **46**: 795-801 [PMID: 21438178 DOI: 10.1002/ppul.21421]
45 **Amirav I**, Shakked T, Broday DM, Katoshevski D. Numerical investigation of aerosol deposition at the eyes when using a hood inhaler for infants--a 3D simulation. *J Aerosol Med Pulm Drug Deliv* 2008; **21**: 207-214 [PMID: 18518796 DOI: 10.1089/jamp.2007.0619]
46 **Shakked T**, Broday DM, Katoshevski D, Amirav I. Administration of aerosolized drugs to infants by a hood: a three-dimensional numerical study. *J Aerosol Med* 2006; **19**: 533-542 [PMID: 17196081 DOI: 10.1089/jam.2006.19.533]
47 **Kugelman A**, Amirav I, Mor F, Riskin A, Bader D. Hood versus mask nebulization in infants with evolving bronchopulmonary dysplasia in the neonatal intensive care unit. *J Perinatol* 2006; **26**: 31-36 [PMID: 16341026 DOI: 10.1038/sj.jp.7211434]
48 **Amirav I**, Oron A, Tal G, Cesar K, Ballin A, Houri S, Naugolny L, Mandelberg A. Aerosol delivery in respiratory syncytial virus bronchiolitis: hood or face mask? *J Pediatr* 2005; **147**: 627-631 [PMID: 16291353 DOI: 10.1016/j.jpeds.2005.05.035]
49 **Amirav I**, Balanov I, Gorenberg M, Groshar D, Luder AS. Nebuliser hood compared to mask in wheezy infants: aerosol therapy without tears! *Arch Dis Child* 2003; **88**: 719-723 [PMID: 12876173 DOI: 10.1136/adc.88.8.719]
50 **Kim J**, Xi J, Si X, Berlinski A, Su WC. Hood nebulization: effects of head direction and breathing mode on particle inhalability and deposition in a 7-month-old infant model. *J Aerosol Med Pulm Drug Deliv* 2014; **27**: 209-218 [PMID: 23808762 DOI: 10.1089/jamp.2013.1051]
51 **Muchão FP**, Perín SL, Rodrigues JC, Leone C, Silva Filho LV. Evaluation of the knowledge of health professionals at a pediatric hospital regarding the use of metered-dose inhalers. *J Bras Pneumol* 2008; **34**: 4-12 [PMID: 18278370]
52 **Wildhaber JH**, Janssens HM, Piérart F, Dore ND, Devadason SG, LeSouëf PN. High-percentage lung delivery in children from detergent-treated spacers. *Pediatr Pulmonol* 2000; **29**: 389-393 [PMID: 10790251 DOI: 10.1002/(SICI)1099-0496]
53 **Piérart F**, Wildhaber JH, Vrancken I, Devadason SG, Le Souëf PN. Washing plastic spacers in household detergent reduces electrostatic charge and greatly improves delivery. *Eur Respir J* 1999; **13**: 673-678 [PMID: 10232445 DOI: 10.1183/09031936.99.13367399]
54 **Dompeling E**, Oudesluys-Murphy AM, Janssens HM, Hop W, Brinkman JG, Sukhai RN, de Jongste JC. Randomised controlled study of clinical efficacy of spacer therapy in asthma with regard to electrostatic charge. *Arch Dis Child* 2001; **84**: 178-182 [PMID: 11159302 DOI: 10.1136/adc.84.2.178]
55 **Anhøj J**, Bisgaard H, Lipworth BJ. Effect of electrostatic charge in plastic spacers on the lung delivery of HFA-salbutamol in children. *Br J Clin Pharmacol* 1999; **47**: 333-336 [PMID: 10215759 DOI: 10.1046/j.1365-2125.1999.00893]
56 **Bisgaard H**, Anhøj J, Klug B, Berg E. A non-electrostatic spacer for aerosol delivery. *Arch Dis Child* 1995; **73**: 226-230 [PMID: 7492160 DOI: 10.1136/adc.73.3.226]
57 **Wildhaber JH**, Devadason SG, Eber E, Hayden MJ, Everard ML, Summers QA, LeSouëf PN. Effect of electrostatic charge, flow, delay and multiple actuations on the in vitro delivery of salbutamol from different small volume spacers for infants. *Thorax* 1996; **51**: 985-988 [PMID: 8977597 DOI: 10.1136/thx.51.10.985]
58 **Lannefors L**. Inhalation therapy: Practical considerations for nebulisation therapy. *Phy Ther Rev* 2006; **11**: 21-27 [DOI: 10.1179/108331906X98976]

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ORIGINAL ARTICLE

Case Control Study

Skin disease and thyroid autoimmunity in atopic South Italian children

Marcella Pedullà, Vincenzo Fierro, Pierluigi Marzuillo, Francesco Capuano, Emanuele Miraglia del Giudice, Eleonora Ruocco

Marcella Pedullà, Vincenzo Fierro, Pierluigi Marzuillo, Francesco Capuano, Emanuele Miraglia del Giudice, Department of Woman, Child and General and Specialized Surgery, Seconda Università degli Studi di Napoli, 80138 Napoli, Italy

Eleonora Ruocco, Department of Dermatology, Seconda Università degli Studi di Napoli, 80138 Napoli, Italy

Author contributions: Pedullà M drafted the manuscript; Pedullà M, Fierro V and Marzuillo P participated in the conception and the design of the study; Pedullà M and Capuano F examined the patients, collected anthropometric data; Miraglia del Giudice E and Ruocco E supervised the design and execution of the study.

Institutional review board statement: An informed consent was obtained from the parents and the children all enrolled after the nature of the investigation was explained and in accordance with the approved protocol from the Institutional Review Board at the Second University of Naples.

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Correspondence to: Pierluigi Marzuillo, MD, Department of Woman, Child and General and Specialized Surgery, Seconda Università degli Studi di Napoli, Via L. De Crecchio n° 2, 80138 Napoli, Italy. pierluigi.marzuillo@gmail.com
Telephone: +39-081-5665420

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Abstract

AIM: To verify the prevalence of thyroid autoimmunity (TA) and the possible association between atopy and TA in children affected by skin disease.

METHODS: Three hundred and twenty-four children consecutively referred due to skin disease symptoms to our Pediatric Department were enrolled. One hundred and eighty-seven were diagnosed with atopic dermatitis (AD), 95 with acute urticaria, 40 with chronic urticaria (CU), and 2 with alopecia areata (AA). According to the work-up for atopy, the children were divided into two groups: Atopics and non-atopics. TA was diagnosed by serum thyroid peroxidase autoantibodies and/or thyroglobulin autoantibodies levels more than twice normal values over a period of two months by immunoassay.

RESULTS: In all children with skin disease, a significant prevalence of TA in atopics compared with non-atopics (13.67% *vs* 2.67%, $P = 0.0016$) and a significant association between TA and atopy (OR = 5.76, 95%CI: 1.71-19.35) were observed. These findings were confirmed as significant in children with AD: TA in atopics was 11.5%, while TA in non-atopics was

2.7% (P = 0.03, OR = 4.68, 95%CI: 1.02-21.38). In addition, atopics with CU showed a significantly higher prevalence of TA (26.9%), but none of the non-atopics showed CU (P = 0.0326). On the other hand, atopics with AA showed a 100% (2 out of 2) prevalence of TA, compared with none of the non-atopics.

CONCLUSION: In children with skin disease, atopy seems to be associated with an increased risk of TA.

Key words: Skin disease; Thyroid autoimmunity; Atopic dermatitis; Children

Core tip: We observed a significant association between atopy and thyroid autoimmunity (TA) in atopic children with skin disease. This association was confirmed in atopic children affected by atopic dermatitis. The key message from our study for pediatricians is that clinicians should always evaluate thyroid peroxidase and thyroglobulin autoantibodies in atopic children with skin disease, as these children could also have TA.

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INTRODUCTION

Recent observations have challenged the validity of the Th1/Th2 paradigm[1] and considerable effort has been focused on understanding the relationship between atopic inflammation and developing autoimmunity both in experimental models and in human populations[2].

Thyroid autoimmunity (TA) has been regularly associated with chronic urticaria (CU) both in adults[3] and in children[4] and less frequently with several dermatological diseases such as vitiligo[5], alopecia areata (AA)[6], post-adolescent acne[7] and atopic dermatitis (AD)[8]. On the other hand, even if less frequent, atopy is considered a cause of both AD and acute urticaria (AU) or CU presenting with intermittent symptoms[9] and has been associated with increased risk and severity of AA[10].

The aim of the present study is to verify the prevalence of TA and the possible association between atopy and TA in South Italian children affected by skin disease.

MATERIALS AND METHODS

From January 2013 to July 2015, 324 children consecutively referred to the Pediatric Department of the Second University of Naples for evaluation of dermatological symptoms such as erythema, pruritus, eczematous rash, xerosis, hair loss, wheals and/or angioedema were enrolled. None of the children suffered from endocrine or systemic diseases and did not show signs of genetic syndromes.

The work-up for dermatological disease included complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum levels of complement C3, C4 and C1 inhibitor, serum immunoglobulins, antinuclear antibody and anti-DNA antibody (if needed), immunoglobulin A (IgA) and IgG anti-transglutaminase, FT3, FT4, TSH, thyroid peroxidase antibodies (TPO Ab) and thyroglobulin antibodies (TG Ab), urine analysis and culture, nasal and throat swabs, and microscopic investigation of stool for *Helicobacter pylori* antigens and parasite ova. No urticarial vasculitis, physical or other types of eliciting urticaria were diagnosed. In addition, cold provocation and threshold test (ice cube and cold water) were also performed in patients to exclude physical urticaria.

None of the patients had IgA deficiency, but two patients with urticaria were diagnosed with celiac disease and excluded. Therefore, 324 children were enrolled.

The same dermatologist from the Dermatology Department of the Second University of Naples defined the dermatological diseases. On the basis of the dermatologist's diagnosis, the cohort was then divided into 4 subgroups: 187 children were affected by AD, 95 by AU, 40 by CU, and 2 by AA.

TA was diagnosed by TPO Ab and /or TG Ab (immunoassay: High-specific solid-phase technique-chemiluminescence immune-assays PerkinElmer, Turku, Finland) serum levels more than twice normal values (TPO Ab n.v. < 30 UI/mL; TG Ab n.v. < 100 UI/mL) over a period of two months.

Atopy, defined as serum-specific IgE positivity against inhalant allergens was suspected on the basis of clinical history and diagnosed by skin prick tests (SPTs) and by a specific IgE assay (> 0.36 kUA/L - ImmunoCap 0-100 Phadia AB, Uppsala, Sweden). SPTs were performed using a standard battery of aeroallergens and food allergens: House dust mite (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*), *Parietaria officinalis*, grasses (*Dactylis glomerata*, *Lolium perenne*, *Phaleum pratense*), mold (Alternaria, Aspergillus, Cladosporium), dog fur, cat fur, egg, cow milk, casein, wheat, soyabean, codfish, peanut and tree-nuts (Epernox, Cedex, France). Allergens were applied to a stencil stamped on the forearm with ink and pricked with a lancet (Bayer DHS Diagnostic). Histamine chloride (10 mg/mL) was used as a positive control and the allergen diluent served as the negative control. The results were read after 15 and 30 min and the test was considered positive if the wheal was at least 3 mm in diameter compared with the negative control. Thus, on the basis of the work-up for atopy, the children affected by skin disease were divided into atopics (n = 212) and non-atopics (n = 112). None of the children received steroids or immuno-suppressive therapy for at least 3

Table 1 Differences between clinical characteristics in children with skin disease divided into atopics and non-atopics

	Atopics (n = 212)	Non-atopics (n = 112)	Statistical analysis
Age in years (mean ± SD)	6.3 ± 4.18	5.55 ± 3.67	P = 0.1
Sex (male %)	111/212 (52.8%)	48/112 (42.8%)	P = 0.26
Family history of atopy (%)	188/212 (88.67%)	93/112 (83.03%)	P = 0.91
Family history of thyroid diseases (%)	93/212 (43.86%)	43/112 (38.39%)	P = 0.6

Table 2 Thyroid autoimmunity in children with skin disease divided into atopics and non-atopics

	Thyroid autoimmunity (%)	Atopics (%)	Non-atopics (%)	Statistical analysis
All skin diseases	9.6	29/212 (13.67)	3/112 (2.67)	P = 0.0016 OR = 5.76 (1.71-19.35)
Atopic dermatitis	8.02	13/113 (11.5)	2/74 (2.7)	P = 0.03 OR = 4.68 (1.02-21.38)
Alopecia areata	100	2/2	0	NA
Chronic urticaria	17.5	7/26 (26.9)	0/14	P = 0.0326
Acute urticaria	8.42	7/71 (9.85)	1/24 (4.1)	P = 0.38

mo before the investigation. Antihistamine therapy was stopped at least 2 wk before the investigation.

An informed consent was obtained from the parents and the children all enrolled after the nature of the investigation was explained and in accordance with the approved protocol from the Institutional Review Board at the Second University of Naples.

Statistical analysis

In this observational study the t test was used to compare the difference between the mean values and a χ^2 test was used to analyze the differences between the frequencies among categorical variables assessed by Kurtosis. A P value < 0.05 was considered significant.

An odds ratio (OR) was calculated to evaluate the association between atopy and TA. This was considered significant when showing a 95%CI and excluding unity.

Statistical analyses were performed using StatGraph 3.0 for Windows.

RESULTS

Table 1 shows the differences between the characteristics of the 324 children with skin diseases divided into atopics and non-atopics.

Significant differences regarding age in years, sex, and family history of atopic and thyroidal disease were not observed between the two groups (Table 1).

It is worth noting that in all children with skin disease a significant prevalence of TA in atopics compared with non-atopics (13.67% *vs* 2.67%, P = 0.0016) and a significant association between TA and atopy (OR = 5.76, 95%CI: 1.71-19.35) were observed (Table 2). These findings were confirmed as significant in AD affected children: TA prevalence in atopics was 11.5%, while TA prevalence in non-atopics was 2.7% (P = 0.03, OR = 4.68, 95%CI: 1.02-21.38) (Table 2). In addition, atopics affected by CU showed a significantly higher prevalence of TA (26.9%) compared with non-atopics (P = 0.0326), but none of the non-atopics had CU (Table 2). On the other hand, AA atopics showed a 100% (2 out of 2) prevalence of TA compared with none of the non-atopics (Table 2).

AU atopics did not show a significant difference compared with non-atopics in terms of a significant risk for TA.

DISCUSSION

There is currently great interest in defining the link between atopy and autoimmunity.

T regulatory (T reg) cells seem to play a pivotal role in this relationship, as they are essential for the maintenance of immune homeostasis and prevention of autoimmunity[11]. There is also evidence that the number or function of T reg cells may be deficient in patients with atopy[12].

Furthermore, decoy receptor 3 (DcR3), a member of the tumor necrosis factor receptor superfamily, can promote M2 macrophage differentiation *via* epigenetic regulation, with a pleiotropic immunomodulatory effect[13]. Indeed, elevated levels of DcR3 have been found in the serum of atopic patients[14]. DcR3 can also promote tumorigenesis *via* the induction of tumor-associated macrophages[15]. It has also been proposed that atopy may have effects on the risk of cancer, but studies of thyroid cancer[16] and non-melanoma skin cancer[17] have shown no association or conflicting results related to atopy.

To date, few papers in the literature address the relationship between atopy and TA. In our study, TA prevalence in children with skin disease was 8.9% and atopics had a significant higher prevalence of TA compared with non-atopics. Moreover, they showed a significant risk for TA. We would underline a possible selection bias in our patient sample, which was selected

from children referred to a University Pediatric Center for the diagnosis and treatment of allergic disease. The prevalence of TA reported for age-matched healthy children in different geographic areas ranges from 0.3%[18] to 1.6%[19]. In a recent study conducted in a Mediterranean area similar to South Italy with regard to iodine status (Almeria, Spain), the prevalence of TA was higher and reached 3.7% in healthy children and adolescents[20].

In the four subgroups selected on the basis of different dermatological diagnoses, a significant association between TA and atopy was found only in children with AD, similar to the findings in our previously published paper[8].

We also identified 2 cases of AA, both atopics. In the literature, AA is regularly associated both with TA and atopy. This was not confirmed in our cohort as only two patients were diagnosed with AA. Barahmani *et al*[21] suggested that AA has features of both atopic and autoimmune-mediated skin disease.

Leznoff *et al*[22], for the first time, demonstrated a TA prevalence of 16% in a large population of adults with CU. Rumbyrt *et al*[23] described a TA prevalence ranging from 10% to 35% in adults with CU.

TA prevalence in our CU children was 17.5%, slightly higher than the reported prevalence in healthy children, which ranged from 4.3%[4] to 14.8%[24]. On the other hand, in our CU atopics we found a TA prevalence of 26.9%, significantly higher compared to our non-atopics (0%, $P = 0.0326$) and higher than that reported in healthy children in the literature. In addition, TA prevalence in our AU patients was 8.42% and no significant association between TA and atopy was found. It is possible that an acute atopic inflammation could contribute to the occurrence of TA in patients with AU. To date, only Gangemi *et al*[25] have identified TA positivity in 3 out of 6 adult patients affected by idiopathic acute urticaria.

To our knowledge, this is the first report to show a significant prevalence of TA in a population of atopic children affected by skin disease and a significant risk of TA in these atopics.

The key message from our study for pediatricians is that clinicians should always evaluate TPO and TG autoantibodies in atopic children affected by skin disease, as these children could have concomitant TA.

COMMENTS

Background

Thyroid autoimmunity (TA) is regularly associated with chronic urticaria both in adults and in children and less frequently with several dermatological diseases such as vitiligo, alopecia areata, post-adolescent acne and atopic dermatitis. The aim of the present study was to verify the prevalence of TA and the possible association between atopy and TA in children affected by skin disease.

Research frontiers

Important areas of research related to this study are represented by the field of pediatric dermatology and allergology. This study aimed to verify the association between TA and skin diseases in a population of atopic children.

Innovations and breakthroughs

To our knowledge, this is the first report to show a significant prevalence of TA in a population of atopic children affected by skin disease and a significant risk of TA in these atopics.

Applications

Future research is necessary to confirm the authors' findings and to understand the pathophysiological basis underlying the association between TA and skin diseases in atopic children.

Terminology

Atopy is defined as serum-specific IgE positivity against inhalant allergens suspected on the basis of clinical history and diagnosed by skin prick tests and by a specific IgE assay (> 0.36 kUA/L - ImmunoCap 0-100).

Peer-review

This is a very interesting manuscript with the aim to verify the prevalence of thyroid autoimmunity and the possible association with atopy in a restricted population showing skin disease.

REFERENCES

1 **Nowak EC**, Noelle RJ. Interleukin-9 as a T helper type 17 cytokine. *Immunology* 2010; **131**: 169-173 [PMID: 20673237 DOI: 10.1111/j.1365-2567.2010.03332.x]

2 **Shah A**. The pathologic and clinical intersection of atopic and autoimmune disease. *Curr Allergy Asthma Rep* 2012; **12**: 520-529 [PMID: 22898881 DOI: 10.1007/s11882-012-0293-0]

3 **Pan XF**, Gu JQ, Shan ZY. The prevalence of thyroid autoimmunity in patients with urticaria: a systematic review and meta-analysis. *Endocrine* 2015; **48**: 804-810 [PMID: 25064381 DOI: 10.1007/s12020-014-0367-y]

4 **Levy Y**, Segal N, Weintrob N, Danon YL. Chronic urticaria: association with thyroid autoimmunity. *Arch Dis Child* 2003; **88**: 517-519 [PMID: 12765919]

5 **Kroon MW**, Vrijman C, Chandeck C, Wind BS, Wolkerstorfer A, Luiten RM, Bos JD, Geskus RB, van Trotsenburg P, van der Veen JP. High prevalence of autoimmune thyroiditis in children and adolescents with vitiligo. *Horm Res Paediatr* 2013; **79**: 137-144 [PMID: 23548513 DOI: 10.1159/000348388]

6 **Huang KP**, Mullangi S, Guo Y, Qureshi AA. Autoimmune, atopic, and mental health comorbid conditions associated with alopecia areata in the United States. *JAMA Dermatol* 2013; **149**: 789-794 [PMID: 23700152 DOI: 10.1001/jamadermatol.2013.3049]

7 **Vergou T**, Mantzou E, Tseke P, Moustou AE, Katsambas A, Alevizaki M, Antoniou C. Association of thyroid autoimmunity with acne in adult women. *J Eur Acad Dermatol Venereol* 2012; **26**: 413-416 [PMID: 21521376 DOI: 10.1111/j.1468-3083.2011.04084.x]

8 **Pedullá M**, Fierro V, Papacciuolo V, Alfano R, Ruocco E. Atopy as a risk factor for thyroid autoimmunity in children affected with atopic dermatitis. *J Eur Acad Dermatol Venereol* 2014; **28**: 1057-1060 [PMID: 24118567 DOI: 10.1111/jdv.12281]

9 **Zuberbier T**, Asero R, Bindslev-Jensen C, Walter Canonica G, Church MK, Giménez-Arnau A, Grattan CE, Kapp A, Merk HF, Rogala B, Saini S, Sánchez-Borges M, Schmid-Grendelmeier P, Schünemann H, Staubach P, Vena GA, Wedi B, Maurer M. EAACI/GA(2)LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009; **64**: 1417-1426 [PMID: 19772512 DOI: 10.1111/j.1398-9995.2009.02179.x]

10 **Li SF**, Zhang XT, Qi SL, Ye YT, Cao H, Yang YQ, McElwee KJ, Zhang X. Allergy to dust mites may contribute to early onset and severity of alopecia areata. *Clin Exp Dermatol* 2015; **40**: 171-176 [PMID: 25252126 DOI: 10.1111/ced.12471]

11 **Wing JB**, Sakaguchi S. Foxp3$^+$ T(reg) cells in humoral immunity. *Int Immunol* 2014; **26**: 61-69 [PMID: 24324208 DOI: 10.1093/intimm/dxt060]

12 **Josefowicz SZ**, Niec RE, Kim HY, Treuting P, Chinen T, Zheng Y, Umetsu DT, Rudensky AY. Extrathymically generated regulatory

T cells control mucosal TH2 inflammation. *Nature* 2012; **482**: 395-399 [PMID: 22318520 DOI: 10.1038/nature10772]
13 **Lin WW**, Hsieh SL. Decoy receptor 3: a pleiotropic immunomodulator and biomarker for inflammatory diseases, autoimmune diseases and cancer. *Biochem Pharmacol* 2011; **81**: 838-847 [PMID: 21295012 DOI: 10.1016/j.bcp.2011.01.011]
14 **Chen CC**, Yang YH, Lin YT, Hsieh SL, Chiang BL. Soluble decoy receptor 3: increased levels in atopic patients. *J Allergy Clin Immunol* 2004; **114**: 195-197 [PMID: 15282937]
15 **Tai SK**, Chang HC, Lan KL, Lee CT, Yang CY, Chen NJ, Chou TY, Tarng DC, Hsieh SL. Decoy receptor 3 enhances tumor progression via induction of tumor-associated macrophages. *J Immunol* 2012; **188**: 2464-2471 [PMID: 22287720 DOI: 10.4049/jimmunol.1101101]
16 **Merrill RM**, Isakson RT, Beck RE. The association between allergies and cancer: what is currently known? *Ann Allergy Asthma Immunol* 2007; **99**: 102-116; quiz 117-119, 150 [PMID: 17718097]
17 **Skaaby T**, Nystrup Husemoen LL, Roswall N, Thuesen BH, Linneberg A. Atopy and development of cancer: a population-based prospective study. *J Allergy Clin Immunol Pract* 2014; **2**: 779-785 [PMID: 25439371 DOI: 10.1016/j.jaip.2014.06.010]
18 **Jaksić J**, Dumić M, Filipović B, Ille J, Cvijetić M, Gjurić G. Thyroid diseases in a school population with thyromegaly. *Arch Dis Child* 1994; **70**: 103-106 [PMID: 8129428]
19 **Marwaha RK**, Tandon N, Karak AK, Gupta N, Verma K, Kochupillai N. Hashimoto's thyroiditis: countrywide screening of goitrous healthy young girls in postiodization phase in India. *J Clin Endocrinol Metab* 2000; **85**: 3798-3802 [PMID: 11061541]
20 **García-García E**, Vázquez-López MÁ, García-Fuentes E, Rodríguez-Sánchez FI, Muñoz FJ, Bonillo-Perales A, Soriguer F. Iodine intake and prevalence of thyroid autoimmunity and autoimmune thyroiditis in children and adolescents aged between 1 and 16 years. *Eur J Endocrinol* 2012; **167**: 387-392 [PMID: 22728345 DOI: 10.1530/EJE-12-0267]
21 **Barahmani N**, Schabath MB, Duvic M. History of atopy or autoimmunity increases risk of alopecia areata. *J Am Acad Dermatol* 2009; **61**: 581-591 [PMID: 19608295 DOI: 10.1016/j.jaad.2009.04.031]
22 **Leznoff A**, Sussman GL. Syndrome of idiopathic chronic urticaria and angioedema with thyroid autoimmunity: a study of 90 patients. *J Allergy Clin Immunol* 1989; **84**: 66-71 [PMID: 2754146]
23 **Rumbyrt JS**, Schocket AL. Chronic urticaria and thyroid disease. *Immunol Allergy Clin North Am* 2004; **24**: 215-223, vi [PMID: 15120148]
24 **Kilic G**, Guler N, Suleyman A, Tamay Z. Chronic urticaria and autoimmunity in children. *Pediatr Allergy Immunol* 2010; **21**: 837-842 [PMID: 20609133 DOI: 10.1111/j.1399-3038.2010.00986.x]
25 **Gangemi S**, Saitta S, Lombardo G, Patafi M, Benvenga S. Serum thyroid autoantibodies in patients with idiopathic either acute or chronic urticaria. *J Endocrinol Invest* 2009; **32**: 107-110 [PMID: 19411805]

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ORIGINAL ARTICLE

Case Control Study

Effects of resistance training on cardiovascular health in non-obese active adolescents

Clare Chung-Wah Yu, Alison Mary McManus, Hung-Kwan So, Ping Chook, Chun-Ting Au, Albert Martin Li, Jack Tat-Chi Kam, Raymond Chi-Hung So, Christopher Wai-Kei Lam, Iris Hiu-Shuen Chan, Rita Yn-Tz Sung

Clare Chung-Wah Yu, Department of Health and Physical Education, the Education University of Hong Kong, Hong Kong, China

Clare Chung-Wah Yu, Alison Mary McManus, Jack Tat-Chi Kam, Institute of Human Performance, the University of Hong Kong, Hong Kong, China

Alison Mary McManus, Centre for Heart, Lung and Vascular Health, School of Health and Exercise Sciences, University of British Columbia, Kelowna, BC V1V 1V7, Canada

Hung-Kwan So, Ping Chook, Chun-Ting Au, Albert Martin Li, Rita Yn-Tz Sung, Department of Paediatrics, the Chinese University of Hong Kong, Hong Kong, China

Raymond Chi-Hung So, Hong Kong Sports Institute, Hong Kong, China

Christopher Wai-Kei Lam, Faculty of Health Sciences and University Hospital, Macau University of Science and Technology, 999078 Taipa, Macau, China

Iris Hiu-Shuen Chan, Department of Chemical Pathology, Prince of Wales Hospital, the Chinese University of Hong Kong, Hong Kong, China

Author contributions: Yu CCW designed and coordinated this study, interpreted the data, and draft the manuscript; McManus AM supervised statistical analyses, data interpretation and the preparation of the manuscript; So HK and Li AM assisted in the pubertal assessment for male participants and took part in the trial coordination; Chook P conducted all endothelial function measurements; Au CT contributed to data collection and statistical analyses; Kam JTC and So RCH designed and supervised the training program of this study; Lam CWK and Chan IHS are responsible for all laboratory assessments; Sung RYT supervised the whole program.

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Correspondence to: Dr. Clare Chung-Wah Yu, PhD, Department of Health and Physical Education, the Education University of Hong Kong, Tai Po, Hong Kong, China. yucw@eduhk.hk
Telephone: +852-29486685
Fax: +852-29487848

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Abstract

AIM: To determine the benefits of a 10-wk resistance

training programme on cardiovascular health in non-obese and active adolescents.

METHODS: This is a pragmatic randomised controlled intervention. The study was carried out in a Hong Kong Government secondary school. Thirty-eight lean and active boys and girls were randomised to either the resistance training group or the control group. Students in the resistance training group received in-school 10-wk supervised resistance training twice per week, with each session lasting 70 min. Main outcome measures taken before and after training included brachial endothelial dependent flow-mediated dilation, body composition, fasting serum lipids, fasting glucose and insulin, high sensitive C-reactive protein, 24-h ambulatory blood pressure and aerobic fitness.

RESULTS: The only training related change was in endothelial dependent flow-mediated dilation which increased from 8.5% to 9.8%. A main effect of time and an interaction ($P < 0.005$) indicated that this improvement was a result of the 10-wk resistance training. Main effects for time ($P < 0.05$) in a number of anthropometric, metabolic and vascular variables were noted; however, there were no significant interactions indicating the change was more likely an outcome of normal growth and development as opposed to a training effect.

CONCLUSION: Ten weeks of resistance training in school appears to have some vascular benefit in active, lean children.

Key words: Strength training; Children; Cardiometabolic risk factors; Endothelial function; School-based training program; High sensitive C-reactive protein; 24-h ambulatory blood pressure; Aerobic fitness

Core tip: We have shown that a school-based resistance training programme is adhered to and provides vascular benefit in lean children, lending support to the role school-based physical activity can play in the primary prevention of heart disease.

Yu CCW, McManus AM, So HK, Chook P, Au CT, Li AM, Kam JTC, So RCH, Lam CWK, Chan IHS, Sung RYT. Effects of resistance training on cardiovascular health in non-obese active adolescents. *World J Clin Pediatr* 2016; 5(3): 293-300 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i3/293.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i3.293

INTRODUCTION

The endothelium plays an integral role in maintaining vascular tone and reactivity and in preserving vascular health, but impaired endothelial function predisposes individuals to early atherosclerosis[1]. The cardio-protective property of physical activity is well established and resistance training, either on its own, or in combination with aerobic exercise, has proven to be particularly effective for both cardiovascular and endothelial function in adults with hypertension, chronic heart failure, or type Ⅱ diabetes[2-5]. In children and adolescents, there is growing evidence that resistance training not only increases muscle strength, but also contributes to an increase in bone strength, a desirable change in body composition, and an improvement in motor skills and sports performance[6]. We have shown considerable improvements in endothelial function following combined aerobic-resistance training and dietary modification programmes in overweight and obese children and adolescents[7]. Resistance training is potentially appealing and easy to administer within a school settings, but there is little evidence of the benefit of such training on cardiovascular and endothelial function in healthy active adolescents.

This study was therefore designed to evaluate the effectiveness of a resistance training intervention on aspects of vascular and metabolic health in normal weight 11 to 13 years old.

MATERIALS AND METHODS

Study design and subjects

Flyers were delivered to students and their parents attending a Government Secondary school in Hong Kong. Those who showed interest in the study were invited to attend an information seminar and 38 students (25 boys and 13 girls) aged 11 to 13 years old volunteered to participate. The school was chosen because it introduced a novel compulsory physical education (PE) programme comprising of one 70 min skill-based PE session per week (5 school days), plus 3 h per week of sport (students can join one of the following sports: Table-tennis, volleyball, soccer, badminton, basketball, squash, fencing, track and field, cross-country, swimming, cycling, or wushu). Although we did not assess physical activity, we believe that all the students can be classified as active on the basis of their participation in the extra sport programme. The study began at the start of the school term and all participants had been involved in the new PE programme for three weeks prior to joining the study.

All participants were classified as normal weight on the basis of having a body mass $\geqslant 40^{th}$ and $\leqslant 60^{th}$ percentile expressed in relation to height using sex, age and race specific normative charts[8]. None had congenital or chronic diseases that restricted them from physical activity. The study received ethical approval from the Institutional Review Board for Human Ethics of The University of Hong Kong and Hong Kong Hospital Authority West Cluster. Written informed consent was obtained from all participants and their legal guardians.

Procedures

Prior to the start of the training programme, our research team went to the school in the early morning to take fasting blood samples and assess body composition, pubertal stage, resting blood pressure and heart rate for all participants. Within one week participants attended the hospital laboratory twice for cardiorespiratory fitness testing and endothelial function of the brachial artery. During this baseline assessment period, the children were also fitted with an ambulatory 24-h blood pressure monitor at school early in a morning before their lessons started. The monitor was returned 24 h later to the school. This sequence of testing was repeated within 1-wk of completion of the 10-wk intervention, with the exception of pubertal rating. All baseline and post-training outcomes were assessed by individuals blinded to the grouping of the students.

After the baseline assessments, the 38 students were randomised to either the control group or resistance training group using gender specific sealed opaque envelopes. Students in the resistance training group (7 girls and 12 boys) received supervised resistance training twice per week for 10 wk, while students in the control group (6 girls and 13 boys) did not receive any resistance training. Both groups of students were asked to maintain their PE classes and their normal out-of-school lifestyle.

Intervention

The resistance training group joined twice weekly sessions in small groups (9 to 10 students per group), supervised by a professional trainer with two assistants. Each training session started with 10 min of warm-up and stretching exercises, followed by 40 min of resistance training (exercise order: Elbow extension, elbow flexion, trunk extension, trunk flexion, shoulder press, knee extension, knee flexion, push ups, squats, incline dip, hip abduction, and hip adduction), and ended with 5 min of stretching exercises to cool down. The training was carried out in circuit style and the participants were asked to complete three sets of 12 repetitions for each exercise in total. One set of a single exercise lasted for about 30 s and there was no rest between repetitions. The rest period between each set of single exercise items was about 16 s (therefore one set of all 13 exercises took about 9.7 min to finish). After that, the class moved on to the second and the third set of 13 exercises. Exercise order within each set of all exercises followed the principle of alternating upper-body exercises with lower-body exercises, or alternating pushing exercises with pulling exercises. This arrangement minimized the length of the rest periods required between exercises and maximizes the rest between body areas[9].

Training intensity was set at 12-RM (repetitions maximum), which implies the maximum amount of weight one can lift in 12 repetitions for most of the exercises (not including push-ups, incline dip, trunk extension, trunk flexion, and sit-ups). Twelve-RM was assessed at the first training session. This moderate intensity training programme is in keeping with published recommendations for safe resistance training in youth[10,11]. Equipment for the resistance training included dumbbells, sandbags, and exercise rubber tubing of varying resistances and fitness balls. After 4 wk the training load was increased by increasing the sets to four, whilst resistance remained constant.

Measurements

Anthropometric measures: Body mass was measured using electronic scales (Seca Delta Model 707, Hamburg, Germany) with subjects barefoot and dressed in light t-shirts and shorts. Body height was measured barefoot using a Harpenden stadiometer. Body fat was determined using foot-to-foot bio-electrical impedance (TBF-401, Tanita Co, Tokyo, Japan). The bio-electrical impedance measurement was arranged to be taken at the same day of fasting blood sampling at school to make sure that the measurement was taken in a fasting state and early in the morning. Participants emptied their bladder before the measurement.

Pubertal staging: Pubertal staging was assessed at baseline by a physician or nurse of our research team in school according to Tanner's indices for pubic hair, genitalia and breast development[12]. The highest rating for pubic hair, genitalia or breast development was recorded as the pubertal stage. Of the 38 participants, 2 were prepubertal (1 girl and 1 boy), 11 were stage 2 (1 girl, 10 boys), 19 were stage 3 (5 girls, 14 boys) and 6 were stage 4 (6 girls, no boys).

Endothelial function: Participants were studied fasting and at rest, between 900 and 1100 h. Brachial artery diameter was measured by high-resolution B-mode ultrasound (ATL 5000 system, L10-5 transducer, Bothell, Washington, United States) at rest, during reactive hyperaemia, again after 15 min rest, and after sublingual nitroglycerin spray (400 μg), as previously described[13,14]. Hyperaemia was induced by release of an occluding cuff, inflated to supra-arterial pressure for 5 min on the forearm distal to the site of measurement. Brachial artery diameter was measured continuously from 30 s before to > 2 min after cuff release. Flow-mediated vasodilatation (FMD) and nitroglycerin-mediated dilation (NMD) were recorded as the peak responses relative to the preceding rest measurements occurring within 90 s after cuff release and at 3 to 4 min after nitroglycerin administration. All scans were recorded on optic disc for subsequent off-line analysis, blinded as to which treatment group the subjects had been assigned. The scanning time took approximately 30 min for each student. We utilised a protocol established in our laboratory, which has been found to have good accuracy, reproducibility, and low interobserver error[15,16].

Cardiorespiratory fitness: Was assessed from a

peak oxygen uptake (peak VO_2) treadmill running test. The speed and gradient of the treadmill was increased gradually until volitional exhaustion. Gas samples were analyzed using the Medgraphics CPX/D™ metabolic cart (Medical Graphics Corporation, St. Paul, MN, United States). Heart rate was monitored continuously during the exercise test from heart rate telemetry (Polar Eletro Oy, Finland). Peak VO_2 was determined when two of the following three conditions were reached: (1) a respiratory exchange ratio > 1.0; (2) heart rate > 85% of age predicted maximum or levelled off; and (3) the student showed visible signs of exhaustion and refused to carry on despite strong verbal encouragement.

Laboratory investigations: A phlebotomist went to the school in the early morning and fasting (12 h) venous blood samples (4 mL) were drawn from all participants. Total cholesterol (TC) and triglyceride were assayed enzymatically using DP Modular Analytics, Roche Diagnostics Corp, Indianapolis, IN, United States. HDL cholesterol (HDL-C) was measured by cholesterol esterase/cholesterol oxidase coupling Trinder's reaction with pre-treatment steps using PEG modified enzyme and dextran sulphate. LDL cholesterol (LDL-C) was calculated using the Friedewald equation. Plasma glucose was measured by hexokinase method (DP Modular Analytics). Serum insulin and high sensitivity C-reactive protein (hsCRP) were determined by chemiluminescence immunoassay using the IMMULITE 1000 Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL, United States).

Blood pressure: Resting blood pressure was assessed in the laboratory from the right arm after at least 5 min of supine rest, using a standard mercury sphygmomanometer with cuffs of appropriate sizes. Korotkoff sound V was taken as the diastolic blood pressure. Heart rate was recorded by electrocardiogram. Ambulatory blood pressure (ABP) was monitored using an oscillometric monitor (SpaceLabs 90217, SpaceLabs Medical, Redmond, Washington, United States), which has been validated for use in children[17]. Systolic, diastolic and mean arterial BP were measured hourly during sleep and every 30 min when awake. The exact cut-off time dividing wake and sleep BP was defined individually according to a self-reported sleep habit diary. An appropriate sized cuff was placed on the non-dominant arm. Recordings were included in the analyses if they possessed a minimum of 14 successful readings during active wakefulness and at least 7 successful readings during sleep[17]. Individual mean systolic, diastolic and mean arterial BP were calculated for wake and sleep periods.

Statistical analysis

Histograms were produced for all variables to exclude any skew, in the presence of which the data were transformed before comparing group differences. Among all variables, fasting insulin was log transformed. Analysis of variance was used to compare baseline characteristics between the two groups. Group differences in the distribution of pubertal stage were examined using χ^2. Group (resistance training group, control group) by time (baseline, post-training) analyses of variance (ANOVA) with repeated measures were used to examine differences in the outcome measures. Analysis of covariance (ANCOVA), taking baseline scores as the covariate, was used to further deconstruct differences on fasting TC and HDL-C. A P value of 0.05 was set a priori.

RESULTS

Descriptive characteristics and markers of cardiovascular health at baseline and after the 10 wk intervention period are presented in Table 1. The distribution of pubertal ratings between the two groups was similar (resistance training group: Tanner 1 = 0, Tanner 2 = 5, Tanner 3 = 10, Tanner 4 = 4; Control group: Tanner 1 = 2, Tanner 2 = 6, Tanner 3 = 9, Tanner 4 = 2, χ^2 = 2.46; P = 0.483). There were no baseline differences between the two groups for any of the anthropometric variables. The mean attendance rate of the resistance training sessions was 83% and the students only missed sessions because of minor illness. All subjects in the resistance training group completed at least 80% of the 20 exercise sessions and were therefore all included in the final analyses. They were also able to finish all prescribed sets of exercises in each training session and there were no resistance training-related injuries.

Body height, body mass, body mass index and fat-free mass all increased significantly over the 10-wk period in both groups. No significant interactions confirmed none of the anthropometric changes over time were a result of the training programme.

Baseline differences between the resistance training group and control group were apparent for both TC and HDL-C, and ANCOVA was therefore utilised to compare values after 10 wk with pre-training levels as the covariate. No time or between group differences were found after removing the effect of baseline values for either TC or HDL-C (P > 0.05). LDL-C and insulin level decreased significantly in both groups over time.

Peak VO_2 expressed absolutely showed an increase in both groups over the 10-wk period, but when adjusted for body size, this increase was no longer apparent.

Thirty-two of the 38 participants agreed to be scanned for endothelial function before and after the intervention. Mean values for flow-mediated dilation and NMD at baseline and post 10 wk of training are provided by group in Table 2. Individual values for FMD at baseline and post 10 wk of training are presented graphically in Figure 1. A main effect of time [F(1,30) = 13.47; P < 0.001; η^2 = 0.310] and a significant interaction [F(1,30) = 9.37; P < 0.005; η^2 = 0.238] were apparent for FMD. Follow-up analyses indicated a greater increase in FMD in the resistance training group compared to the control group. Although there was a

Table 1 Descriptive characteristics at baseline and following the intervention by group

	Resistance training group (n = 19)		Control group (n = 19)		Time effect (P value)	Group effect (P value)	Interaction (P value)
	Baseline	After	Baseline	After			
Age, yr	12.3 ± 0.42	12.5 ± 0.42	12.1 ± 0.30	12.3 ± 0.30	< 0.001	0.100	1.000
Height, cm	151.4 ± 5.8	153.4 ± 5.5	151.0 ± 8.6	152.7 ± 8.8	< 0.001	0.800	0.300
Mass, kg	42.8 ± 6.7	44.3 ± 7.3	40.5 ± 7.1	41.9 ± 7.3	< 0.001	0.300	0.800
Body mass index, kg/m^2	18.6 ± 2.4	18.8 ± 2.5	17.7 ± 2.3	17.9 ± 2.1	0.048	0.200	0.700
Body fat, %	19.0 ± 6.1	19.0 ± 6.1	16.3 ± 3.7	16.3 ± 3.7	1.000	0.100	0.900
Fat free mass, %	34.9 ± 4.5	36.1 ± 4.9	33.9 ± 5.9	35.0 ± 6.1	< 0.001	0.900	0.600
SBP, mmHg	110 ± 9	107 ± 11	108 ± 11	107 ± 9	0.131	0.780	0.461
DBP, mmHg	68 ± 6	67 ± 8	67 ± 8	67 ± 7	0.652	0.751	0.557
TC, mmol/L	3.9 ± 0.6	3.7 ± 0.6	4.4 ± 0.5	4.2 ± 0.7	0.025	0.025	0.814
HDL-C, mmol/L	1.5 ± 0.2	1.5 ± 0.3	1.7 ± 0.4	1.8 ± 0.5	0.220	0.047	0.278
LDL-C, mmol/L	2.0 ± 0.6	1.8 ± 0.5	2.3 ± 0.5	2.0 ± 0.5	< 0.001	0.199	0.850
TG, mmol/L	1.0 ± 0.4	1.0 ± 0.4	0.9 ± 0.4	1.0 ± 0.4	0.554	0.756	0.848
Glucose, mmol/L	5.1 ± 0.3	5.0 ± 0.3	4.9 ± 0.3	4.9 ± 0.3	0.269	0.094	0.315
log insulin, pmol/L	4.4 ± 0.5	4.1 ± 0.3	4.0 ± 0.5	3.9 ± 0.5	0.027	0.099	0.169
hsCRP, mg/L	0.31 ± 0.45	0.25 ± 0.35	0.19 ± 0.18	0.65 ± 2.3	0.486	0.638	0.344
Peak VO_2, mL/min	1741 ± 322	1870 ± 446	1776 ± 466	1963 ± 540	0.003	0.700	0.500
Peak VO_2, mL/kg per minute	40.5 ± 7.1	41.8 ± 8.0	43.1 ± 8.8	45.6 ± 7.9	0.081	0.300	0.600

Data are presented as mean ± SD. P values were obtained from repeated measures ANOVA. SBP: Systolic blood pressure; DBP: Diastole blood pressure; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; hsCRP: High sensitive C-reactive protein; VO_2: Oxygen consumption.

Table 2 Endothelial function of the brachial artery at baseline and following the intervention by group

	Resistance training group (n = 17)		Control group (n = 15)		Time effect (P value)	Group effect (P value)	Interaction (P value)
	Baseline	After	Baseline	After			
FMD, %	8.5 ± 1.0	9.8 ± 1.3	8.8 ± 1.2	8.9 ± 0.9	0.001	0.451	0.005
NMD, %	21.7 ± 2.8	20.7 ± 1.8	22.5 ± 2.9	21.5 ± 2.7	0.011	0.336	0.985

Data are presented as mean ± SD. P values were obtained from repeated measures ANOVA. FMD: Flow-mediated dilation; NMD: Nitroglycerin-mediated dilation.

main effect of time for NMD, there was no interaction, with both groups showing a change in NMD over time (Table 2).

Mean ABP values awake and asleep are presented in Table 3. No main effects were found for either waking or sleeping diastolic ABP, nor interactions. There was no significant difference between the two groups for mean ambulatory systolic blood pressure during sleep or awake (Table 3). Sleeping systolic ABP did show a decline in both groups over the 10-wk period.

DISCUSSION

The key finding from this study was that 10 wk of resistance training resulted in enhanced endothelial function in lean, active youngsters. Improvements from baseline to 10 wk were noted in both groups for a number of anthropometric, metabolic and non-endothelial dependent vascular measures, but these were most likely simply a reflection of normal growth and development.

Accumulating evidence from the adult literature indicates that acute exercise promotes the number and activity of endothelial progenitor cells, increases blood flow and shear stress on the endothelium, which in turn causes an increase in the activity of endothelial nitric oxide synthase and vascular production of nitro-oxide[18]. Resistance exercise elevates blood flow for short periods of time under much higher pressure than sustained periods of moderate exercise and this may produce a more intensive stress stimulus for endothelial cells. In well-trained adult athletes, repetitive intensive exercise exposure has been shown to result in arterial remodelling, with and without change in dilatory capacity[19,20]. Other mechanisms such as hormonal and inflammatory effects, as well as peripheral resistance have been related to exercise-induced improvements in endothelial integrity[21]. The increase in FMD noted in the present study was apparent in the absence of any training-related change in blood pressure or markers of inflammation, and supports the proposition that resistance training most likely increases laminar shear stress, thus has a direct influence on endothelial function.

To the best of our knowledge, this is the first study to show that endothelial function can be enhanced in lean, active children following resistance training. Previous exercise interventions have focused upon normalising vascular dysfunction in groups of overweight and obese children. The relative increase in FMD from baseline

Table 3 Twenty-four hours ambulatory blood pressure at baseline and following the intervention by group

	Resistance training group (n = 19)		Control group (n = 19)		Time effect (P value)	Group effect (P value)	Interaction (P value)
	Baseline	After	Baseline	After			
Awake							
SBP, mmHg	113 ± 8	111 ± 7	110 ± 9	109 ± 8	0.100	0.200	0.700
DBP, mmHg	71 ± 5	70 ± 5	68 ± 4	67 ± 5	0.400	0.093	0.900
Mean BP, mmHg	85 ± 5	84 ± 5	82 ± 4	82 ± 5	0.400	0.100	0.800
Mean HR, beat/min	87 ± 9	86 ± 7	87 ± 9	83 ± 8	0.100	0.600	0.200
Asleep							
SBP, mmHg	103 ± 11	98 ± 8	101 ± 11	98 ± 9	0.041	0.800	0.600
DBP, mmHg	55 ± 7	54 ± 7	54 ± 6	54 ± 6	0.600	1.000	0.500
Mean BP, mmHg	73 ± 8	71 ± 7	73 ± 6	72 ± 6	0.200	1.000	0.600
Mean HR, beat/min	68 ± 6	70 ± 6	66 ± 8	68 ± 8	0.087	0.500	0.900

Data are presented as mean ± SD. P values were obtained from repeated measures ANOVA. SBP: Systolic blood pressure; DBP: Diastole blood pressure; HR: Heart rate.

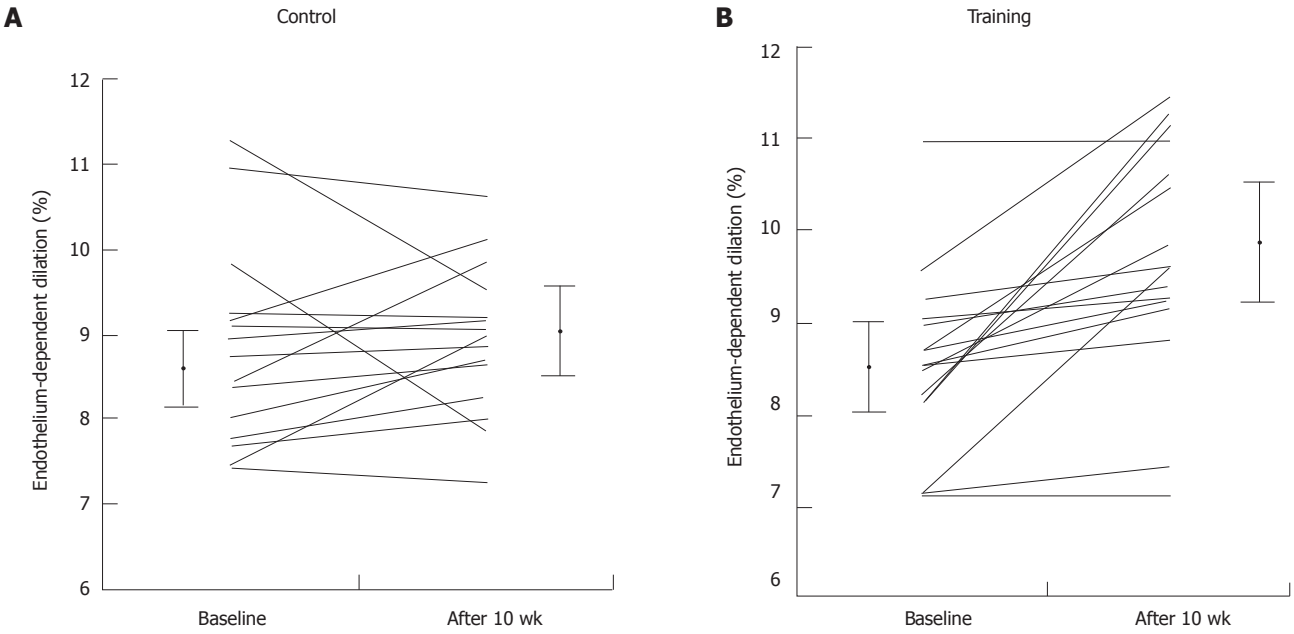

Figure 1 Individual values for flow-mediated dilation at baseline and after 10 wk of intervention in the control (A) and training group (B).

of 15% noted in our group of normal weight Chinese youngsters is marginally less than the improvement in FMD reported for overweight Chinese youngsters, where a relative increase in FMD from baseline of 18% was reported after a 6-wk diet and resistance training intervention[7].

The changes in anthropometric, metabolic and vascular variables in both groups over the 10-wk period could be in part due to active participation in the additional three hours of sport activities per week; however, these were not accompanied by an increase in aerobic fitness and are more likely a reflection of normal growth and development.

Currently there are no data on whether an increased FMD during childhood (either obese or non-obese) will translate into decreased risk of future cardiovascular risk, and only longitudinal studies will provide an answer to this question. However, various reports from the American Heart Association have reaffirmed the importance of primary cardiovascular disease prevention[22-24]. All children, not just those at risk, are thought to benefit from cardiovascular health promotion. Children and adolescents spend 7 to 8 h a day on average in school and it is therefore an ideal site for establishing appropriate behavioural patterns, particularly physical activity habits[25]. In Hong Kong the community places a strong emphasis on a student's academic performance and pays less attention to a student's physical activity. Physical activity levels in Hong Kong youngsters have been found to be low in comparison with other countries[26] with most of a child's active behaviour occurring in school, and nominal amounts of physical activity apparent in the home[27]. We have shown that a school-based resistance training programme is adhered to and provides vascular benefit in lean children, lending support to the role school-based physical activity can play in the primary prevention of heart disease.

This study is not without limitations. We have not

included strength measures in the current study. Muscular strength is likely to be improved after receiving resistance training in children and adolescents population[11,28], however, a primary consideration was compliance of participants to attend all investigations before and after the program (especially participants in the control group), and we felt assessment of strength measures would be too burdensome for participants. Participants in the resistance training group progressed to 4 sets of exercises at 12RM in most of the exercises by the end of the program and we accepted this as a reflection of their improvement in muscular strength. We did not directly assess physical activity, rather used school PE as a surrogate marker. PE in the majority of Hong Kong Government schools consists of 70 min every 10 d, of largely skill-based activity. The participants in this study received 250 min of PE every 7 d. We can probably assume that this population was engaged in more physical activity per week than many youngsters in Hong Kong; however, it would be beneficial to have a direct measure of physical activity habits in future studies.

With respect to the practical application of this study, the training programme in this study is designed in a circuit-style that is practical for schools. Schools and policy makers may consider the inclusion of resistance training as a part of a varied physical activity programme for promoting cardiovascular health in youth.

In conclusion, this study has shown that 10 wk of a school-based resistance training programme is effective in improving endothelial function in active, lean children. These findings stress even more the importance of schools offering plentiful and varied physical activity opportunities for the cardiovascular health of young people, in particular resistance exercise.

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COMMENTS

Background

The endothelium plays an integral role in maintaining vascular tone and reactivity and in preserving vascular health, but impaired endothelial function predisposes individuals to early atherosclerosis. The authors have previously reported that impairment of endothelium function in overweight and obese children can be improved following combined aerobic-resistance training and dietary modification programmes. Resistance training is easy to administer within a school settings, but there is little evidence of the benefit of resistance training on cardiovascular and endothelial function in healthy active adolescents.

Research frontiers

Primary prevention of cardiovascular disease through modification of lifestyle behaviors, such as exercise during childhood and adolescence is paramount because of the growing evidence that the origins of cardiovascular disease begin in childhood. Much of the research attention focusing on the role exercise plays in endothelial health has been on the obese child. Cross-sectional evidence has shown that the lean child is also at risk of vascular dysfunction because of insufficient physical activity and excessive sedentary behavior. This confirms the importance of strategies to encourage active lifestyles in children and adolescents, but requires better understanding of the role exercise plays in vascular health in lean children and adolescents.

Innovations and breakthroughs

Exercise and vascular function is a recent issue in healthy weight children and adolescents. This study addresses exercise induced alterations in endothelial function in healthy lean adolescents and provides novel insight into the benefits of resistance exercise training in this younger population.

Applications

The exercise training programme used in this study is designed in a circuit-style that is practical for schools. Schools and policy makers may consider the inclusion of resistance training as a part of a varied physical activity programme for promoting cardiovascular health in youth.

Terminology

Endothelium dependent flow-mediated dilation: A technique used to increase blood flow and therefore shear stress, stimulating the endothelium to release nitric oxide and induce vasodilation. Endothelial independent flow-mediated dilation: The use of an exogenous nitric oxide donor, such as nitroglycerin to induce vasodilation independent of the endothelium, reflecting vascular smooth muscle function.

Peer-review

The manuscript is well written. The study is well designed with detailed methodology to assess the change in body composition and cardiovascular function.

REFERENCES

1 **Verma S**, Anderson TJ. Fundamentals of endothelial function for the clinical cardiologist. *Circulation* 2002; **105**: 546-549 [PMID: 11827916 DOI: 10.1161/hc0502.104540]
2 **Cornelissen VA**, Fagard RH. Effect of resistance training on resting blood pressure: a meta-analysis of randomized controlled trials. *J Hypertens* 2005; **23**: 251-259 [PMID: 15662209 DOI: 10.1097/00004872-200502000-00003]
3 **Maiorana A**, O'Driscoll G, Dembo L, Cheetham C, Goodman C, Taylor R, Green D. Effect of aerobic and resistance exercise training on vascular function in heart failure. *Am J Physiol Heart Circ Physiol* 2000; **279**: H1999-H2005 [PMID: 11009490]
4 **Maiorana A**, O'Driscoll G, Cheetham C, Dembo L, Stanton K, Goodman C, Taylor R, Green D. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. *J Am Coll Cardiol* 2001; **38**: 860-866 [PMID: 11527646 DOI: 10.1016/S0735-1097(01)01439-5]
5 **Schjerve IE**, Tyldum GA, Tjønna AE, Stølen T, Loennechen JP, Hansen HE, Haram PM, Heinrich G, Bye A, Najjar SM, Smith GL, Slørdahl SA, Kemi OJ, Wisløff U. Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults. *Clin Sci* (Lond) 2008; **115**: 283-293 [PMID: 18338980 DOI: 10.1042/CS20070332]
6 **Behm DG**, Faigenbaum AD, Falk B, Klentrou P. Canadian Society for Exercise Physiology position paper: resistance training in children and adolescents. *Appl Physiol Nutr Metab* 2008; **33**: 547-561 [PMID: 18461111 DOI: 10.1139/H08-020]
7 **Woo KS**, Chook P, Yu CW, Sung RY, Qiao M, Leung SS, Lam CW, Metreweli C, Celermajer DS. Effects of diet and exercise on obesity-related vascular dysfunction in children. *Circulation* 2004; **109**: 1981-1986 [PMID: 15066949 DOI: 10.1161/01.CIR.0000126599.47470.BE]
8 **Leung SS**, Lau JT, Tse LY, Oppenheimer SJ. Weight-for-age and weight-for-height references for Hong Kong children from birth to 18 years. *J Paediatr Child Health* 1996; **32**: 103-109 [PMID: 8860382 DOI: 10.1111/j.1440-1754.1996.tb00904.x]
9 **Baechle TR**, Earle RW, Wathen D. Resistance training. In:

Baechle TR, Earle RW, editors. Essentials of strength training and conditioning/National Strength and Conditioning Association. 2nd ed. Champaign, IL: Human Kinetics, 2000: 404

10 **McCambridge TM**, Stricker PR. Strength training by children and adolescents. *Pediatrics* 2008; **121**: 835-840 [PMID: 18381549 DOI: 10.1542/peds.2007-3790]

11 **Faigenbaum AD**, Kraemer WJ, Blimkie CJ, Jeffreys I, Micheli LJ, Nitka M, Rowland TW. Youth resistance training: updated position statement paper from the national strength and conditioning association. *J Strength Cond Res* 2009; **23**: S60-S79 [PMID: 19620931 DOI: 10.1519/JSC.0b013e31819df407]

12 **Tanner J**. Growth at Adolescence. 2nd ed. Oxford: Blackwell Scientific Publications, 1962

13 **Corretti MC**, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, Deanfield J, Drexler H, Gerhard-Herman M, Herrington D, Vallance P, Vita J, Vogel R. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. *J Am Coll Cardiol* 2002; **39**: 257-265 [PMID: 11788217 DOI: 10.1016/S0735-1097(01)01746-6]

14 **Celermajer DS**, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 1992; **340**: 1111-1115 [PMID: 1359209 DOI: 10.1016/0140-6736(92)93147-F]

15 **Sorensen KE**, Celermajer DS, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Thomas O, Deanfield JE. Non-invasive measurement of human endothelium dependent arterial responses: accuracy and reproducibility. *Br Heart J* 1995; **74**: 247-253 [PMID: 7547018 DOI: 10.1136/hrt.74.3.247]

16 **Woo KS**, Chook P, Yu CW, Sung RY, Qiao M, Leung SS, Lam CW, Metreweli C, Celermajer DS. Overweight in children is associated with arterial endothelial dysfunction and intima-media thickening. *Int J Obes Relat Metab Disord* 2004; **28**: 852-857 [PMID: 15170465 DOI: 10.1038/sj.ijo.0802539]

17 **O'Brien E**, Asmar R, Beilin L, Imai Y, Mallion JM, Mancia G, Mengden T, Myers M, Padfield P, Palatini P, Parati G, Pickering T, Redon J, Staessen J, Stergiou G, Verdecchia P. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003; **21**: 821-848 [PMID: 12714851 DOI: 10.1097/00004872-200305000-00001]

18 **Yang Z**, Wang JM, Chen L, Luo CF, Tang AL, Tao J. Acute exercise-induced nitric oxide production contributes to upregulation of circulating endothelial progenitor cells in healthy subjects. *J Hum Hypertens* 2007; **21**: 452-460 [PMID: 17344910 DOI: 10.1038/sj.jhh.1002171]

19 **Rognmo O**, Bjørnstad TH, Kahrs C, Tjønna AE, Bye A, Haram PM, Stølen T, Slørdahl SA, Wisløff U. Endothelial function in highly endurance-trained men: effects of acute exercise. *J Strength Cond Res* 2008; **22**: 535-542 [PMID: 18550971 DOI: 10.1519/JSC.0b013e31816354b1]

20 **Walther G**, Nottin S, Karpoff L, Pérez-Martin A, Dauzat M, Obert P. Flow-mediated dilation and exercise-induced hyperaemia in highly trained athletes: comparison of the upper and lower limb vasculature. *Acta Physiol* (Oxf) 2008; **193**: 139-150 [PMID: 18294338 DOI: 10.1111/j.1748-1716.2008.01834.x]

21 **Meyer AA**, Kundt G, Lenschow U, Schuff-Werner P, Kienast W. Improvement of early vascular changes and cardiovascular risk factors in obese children after a six-month exercise program. *J Am Coll Cardiol* 2006; **48**: 1865-1870 [PMID: 17084264 DOI: 10.1016/j.jacc.2006.07.035]

22 **Hayman LL**, Williams CL, Daniels SR, Steinberger J, Paridon S, Dennison BA, McCrindle BW. Cardiovascular health promotion in the schools: a statement for health and education professionals and child health advocates from the Committee on Atherosclerosis, Hypertension, and Obesity in Youth (AHOY) of the Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004; **110**: 2266-2275 [PMID: 15477426 DOI: 10.1161/01.CIR.0000141117.85384.64]

23 **Hayman LL**, Meininger JC, Daniels SR, McCrindle BW, Helden L, Ross J, Dennison BA, Steinberger J, Williams CL. Primary prevention of cardiovascular disease in nursing practice: focus on children and youth: a scientific statement from the American Heart Association Committee on Atherosclerosis, Hypertension, and Obesity in Youth of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, and Council on Nutrition, Physical Activity, and Metabolism. *Circulation* 2007; **116**: 344-357 [PMID: 17592077 DOI: 10.1161/CIRCULATIONAHA.107.184595]

24 **Kavey RE**, Daniels SR, Lauer RM, Atkins DL, Hayman LL, Taubert K. American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. *Circulation* 2003; **107**: 1562-1566 [PMID: 12654618 DOI: 10.1161/01.CIR.0000061521.15730.6E]

25 **Pate RR**, Davis MG, Robinson TN, Stone EJ, McKenzie TL, Young JC. Promoting physical activity in children and youth: a leadership role for schools: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism (Physical Activity Committee) in collaboration with the Councils on Cardiovascular Disease in the Young and Cardiovascular Nursing. *Circulation* 2006; **114**: 1214-1224 [PMID: 16908770 DOI: 10.1161/CIRCULATIONAHA.106.177052]

26 **McManus AM**. Physical activity - a neat solution to an impending crisis. *J Sports Sci Med* 2007; **6**: 368-373 [PMID: 24149423]

27 **Johns DP**, Ha AS. Home and recess physical activity of Hong Kong children. *Res Q Exerc Sport* 1999; **70**: 319-323 [PMID: 10522290 DOI: 10.1080/02701367.1999.10608051]

28 **Yu CC**, Sung RY, Hau KT, Lam PK, Nelson EA, So RC. The effect of diet and strength training on obese children's physical self-concept. *J Sports Med Phys Fitness* 2008; **48**: 76-82 [PMID: 18212713]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Prevalence of recent immunisation in children with febrile convulsions

Leya Motala, Guy D Eslick

Leya Motala, Guy D Eslick, Whiteley-Martin Research Centre, Discipline of Surgery, Nepean Hospital, the University of Sydney, Penrith NSW 2751, Australia

Author contributions: Motala L and Eslick GD acquired, analysed, and interpreted the data; Motala L and Eslick GD drafted the manuscript; Eslick GD did statistical analysis; Eslick GD is the guarantor of the study; He had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; Eslick GD organised the study concept and design.

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Correspondence to: Guy D Eslick, Professor, Whiteley-Martin Research Centre, Discipline of Surgery, Nepean Hospital, the University of Sydney, Clinical Building, Level 3, P.O. Box 63, Penrith NSW 2751, Australia. guy.eslick@sydney.edu.au
Telephone: +61-2-47341373
Fax: +61-2-47343432

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Abstract

AIM: To determine the prevalence of recent immunisation amongst children under 7 years of age presenting for febrile convulsions.

METHODS: This is a retrospective study of all children under the age of seven presenting with febrile convulsions to a tertiary referral hospital in Sydney. A total of 78 cases occurred in the period January 2011 to July 2012 and were included in the study. Data was extracted from medical records to provide a retrospective review of the convulsions.

RESULTS: Of the 78 total cases, there were five medical records which contained information on whether or not immunisation had been administered in the preceding 48 h to presentation to the emergency department. Of these five patients only one patient (1.28% of the study population) was confirmed to have received a vaccination with Infanrix, Prevnar and Rotavirus. The majority of cases reported a current infection as a likely precipitant to the febrile convulsion.

CONCLUSION: This study found a very low prevalence of recent immunisation amongst children with febrile convulsions presenting to an emergency department at a tertiary referral hospital in Sydney. This finding, however, may have been distorted by underreporting of vaccination history.

Key words: Prevalence; Immunisation; Febrile con-

vulsion; Adverse event; Vaccination

Core tip: This study found a very low prevalence of recent immunisation amongst children with febrile convulsions. This finding, however, may have been distorted by underreporting of vaccination history. The use of large linked datasets may determine a more accurate estimate of the rate of febrile convulsions due to immunisation.

Motala L, Eslick GD. Prevalence of recent immunisation in children with febrile convulsions. *World J Clin Pediatr* 2016; 5(3): 301-305 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i3/301.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i3.301

INTRODUCTION

There has been much controversy in recent years about the risks *vs* the benefits of childhood vaccination[1,2]. Vaccines may have adverse effects which range from simple fever[3] to more severe febrile convulsions[3-10]. Febrile convulsions can be defined as any seizure that is associated with fever, and not due to intracranial infection or other known cause such as epilepsy or head trauma[4,11].

Of particular interest, has been the association between the influenza, diphtheria-tetanus toxoids-pertussis (DTP) and measles-mumps-rubella (MMR) vaccines and febrile convulsions. Western Australia observed a spike in emergency department presentations for high fever and febrile convulsions in young children after vaccination with the 2010 trivalent influenza vaccine (TIV)[5]. This resulted in a country-wide suspension of the use of TIV in children aged 5 years and under[5]. Further investigation into the matter then indicated that an association between TIV and febrile convulsions in children was prevalent across the majority of Australia[5]. Following these findings, a similar study performed in the United States revealed disproportionately higher rates of febrile convulsion associated with 2010-2011 TIV administration compared with other vaccines[12]. The majority (84%) of these convulsions occurred in children under 2 years of age, and most (86%) had an onset of convulsion on the same day or the day after the vaccination[12]. The suspension of the use of TIV in children under 5 in Australia was later lifted when it was found that the risk of febrile convulsions following TIV was specific to vaccination with Fluvax® and did not apply to the use of other seasonal influenza vaccines such as Vaxigrip® or Panvax®[3,6].

Although febrile convulsions generally have an excellent prognosis, they are the commonest cause of status epilepticus in childhood[4]. Their occurrence can be extremely distressing for family members of patients, and may have serious long-term consequences that are as yet unknown. A high rate of these seizures following vaccination would have important clinical implications as it may lead to poor vaccine uptake and the risk should be diminished where possible - perhaps, by the administration of alternate safer vaccines[3,6] or by the use of antipyretics and physical methods to reduce fever[3].

The aim of this study was to determine the prevalence of recent immunisation amongst children under the age of seven presenting with febrile convulsions to a teaching hospital in Western Sydney.

MATERIALS AND METHODS

Data collection

The study was approved by the Ethics Committee of the Sydney West Area Health Service. The study population included all patients presenting to Nepean Hospital Emergency Department with febrile convulsion based on the International Classification of Diseases (ICD-10-AM) codes (R56.0).

Data extraction

Two linked databases were set up in order to de-identify the data. The first database comprised of a unique patient identification number, name and medical records number. The following variables were collected from each medical record: Age (months); gender; weight; method of transport to hospital; primary diagnosis; additional diagnosis; number of febrile convulsions during current presentation; history of fever; antipyretic given prior to febrile convulsion; maximum temperature; length of convulsion; previous history of febrile convulsion; previous history of non-febrile convulsion; precipitant to previous febrile convulsion; history of current infection; history of vaccination/immunisation; number of vaccinations; time between vaccination and febrile convulsion; type of vaccination; history of concurrent illness; family history of febrile convulsions; family history of epilepsy; and length of stay.

Statistical analysis

Patient demographic and clinical characteristics have been reported as median and range for numeric-scaled features and percentages for discrete characteristics. Factors associated with febrile convulsion were identified using unconditional logistic regression. All *P* values calculated were two-tailed; the alpha level of significance was set at 0.05. All data was analysed using STATA version 12.0 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

RESULTS

Demographics

A total of 78 patients with a mean age of 23 mo (1-63

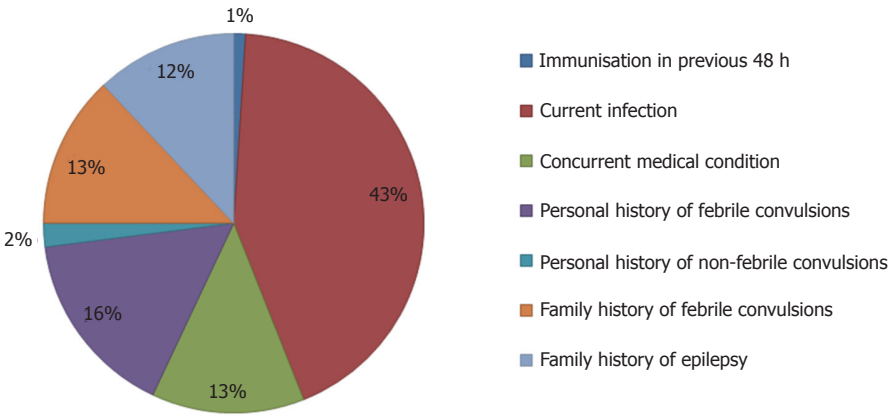

Figure 1 Risk factors for febrile convulsions.

mo; 60% male) presented to Nepean Hospital for febrile convulsions over the 19 mo period (January 2011 - July 30 2012).

Febrile convulsions

The primary diagnosis of febrile convulsion was made in 56.4% of cases, with the majority of the remaining patients being diagnosed with acute upper respiratory tract infections and a smaller number with acute intestinal infections. The mean maximum temperature reported was 39.5 ℃ (37.3 ℃-43 ℃). For each presentation, the mean number of febrile convulsive episodes was 1.7 (1-8 episodes), and the average length of convulsion was 3 min (30 s-20 min). Just over half the medical records (56%) had evidence of antipyretics administration prior to the convulsions. A large proportion of cases (89%) were given antipyretics before their convulsions, with the average time between drug administration and convulsion being 5 h and 45 min.

Risk factors

Five medical records contained information on whether or not immunisation had been administered in the 48 h preceding the febrile convulsion, with only one having clear information on immunisation (confirmed receipt of vaccination with Infanrix, Prevnar and Rotavirus) (Figure 1). Almost all patients (96%) reported a current infection as a possible precipitant to the febrile convulsion, and 25% had a concurrent medical condition such as developmental delay. For those aged > 2 years, a previous history of febrile convulsions was a significant risk factor (OR = 5.47; 95%CI: 1.92-15.60) for presentation. They were also more likely to have shorter convulsions (3 min or less) (OR = 1.67; 95%CI: 0.53-5.27). A positive family history of febrile convulsions but not epilepsy was also a potential risk factor in this age group (OR = 1.30; 95%CI: 0.44-3.84). These individuals were also more likely to have received an antipyretic at an appropriate time - that is from 20 min to 4 h prior to the convulsive episode (OR = 2.28; 95%CI: 0.52-9.99). Males were more likely to be given a primary diagnosis of febrile convulsions than females (OR = 1.72; 95%CI: 0.70-4.35).

Medical care

The mean length of stay was 2 d (1-4 d), with the most common follow-up diagnostic tests including electroencephalograms (15%) and brain magnetic resonance imaging (4%).

DISCUSSION

This study determined that there was a very low prevalence of recent immunisation amongst children with febrile convulsions presenting to a tertiary referral hospital in Western Sydney. This finding, however, may have been due to underreporting of vaccination history as the vast majority of medical records contained no information on whether or not immunisation was administered in the recent past. Only 6% of medical records contained information on immunisation.

Previous studies have shown that some vaccines such as MMR[10] and DTaP-IPV-Hib[8] were associated with an increased risk of febrile convulsions, but that this risk was small. Conversely, another study reported a significantly elevated risk of febrile seizures following receipt of DTP or MMR vaccine[7]. This study determined that a history of a current infection was the predominant precipitant for fever and thus convulsion, previous studies suggest that viral illness is the most common reason for hospitalisation with febrile convulsion[4].

Individuals older than 2 years of age were more likely to have a previous history of febrile convulsions. In terms of the average age at which febrile convulsions tend to occur, this study concurred with the findings of previous research[13] and established that this was at an age of about 2 years.

Males were more likely to be given a primary diagnosis of febrile convulsion than females. This may have been attributable to the fact that approximately 60% of febrile convulsions are known to occur in male

children[13,14], and may well indicate some degree of bias involved in diagnosis. Furthermore, male participants were found to be admitted to hospital more frequently - recent literature suggests that this excess of male admissions[15] is consistent with an increased vulnerability to illness amongst the gender[14].

The higher rate of appropriate antipyretic use that was observed amongst children with a personal history of febrile convulsions was possibly due to those parents being familiar with the occurrence of seizures and thus more cautious when fever arose. This study, much like previous reports, indicated higher rates of febrile convulsions in children with a personal or family history of these seizures[10,16].

One of the strengths of the study was that the aim, hypothesis and objectives were arrived at a priori examination of medical records. Furthermore, all medical records were thoroughly examined manually. The use of medical records as a source of data could also be considered a limitation of the study since some records were incomplete, however, this was not substantial. The sample size did not provide statistical significance for some of our results.

This study found a low prevalence of recent immunisation precipitating febrile convulsions in young children, but this finding may have been distorted by the low rates of accurate reporting of immunisation. A recommendation for future practice would, therefore, be that physicians directly request and record information on immunisation, particularly when dealing with cases of childhood febrile convulsions.

COMMENTS

Background

Febrile convulsions are an important reason for children presenting to hospital emergency departments. The causes of these febrile convulsions are varied but immunization/vaccination may be a factor.

Research frontiers

The authors' suggest that immunization associated febrile convulsions are an under-reported presentation to the emergency department. Specific studies to address this issue are required. Moreover, preventive strategies may be implemented to reduce the risk of febrile convulsions after immunization.

Innovations and breakthroughs

Vaccine safety is vitally important to the continued global approach to preventable infectious diseases both in childhood and adulthood. A greater understanding of minor and major adverse events following immunization are required. Recent high level evidence providing no link between vaccines and autism is a good example.

Applications

A greater knowledge of the potential adverse effects of immunization is important and education of patients with regards to preventive and recognition of adverse effects early is critical.

Terminology

The Measles, Mumps, Rubella vaccine protects against measles, mumps, and rubella (German measles). It is a mixture of live attenuated viruses of the three diseases, administered *via* injection. The (DTaP-IPV-Hib) includes diphtheria (D), tetanus (T) and acellular pertussis (aP) (whooping cough). Inactivated polio vaccine stands for "inactivated polio vaccine". Hib stands for *Haemophilus influenzae* type b.

Peer-review

Good study provided record based immunization history is of quality.

REFERENCES

1 **Shorvon S**, Berg A. Pertussis vaccination and epilepsy--an erratic history, new research and the mismatch between science and social policy. *Epilepsia* 2008; **49**: 219-225 [PMID: 18093146 DOI: 10.1111/j.1528-1167.2007.01478.x]

2 **Berg AT**. Seizure risk with vaccination. [accessed 2012 Jul 20]. Available from: URL: http//www.aesnet.org/files/dmFile/EPCvaccination.pdf

3 **Australian Government**, Department of Health and Ageing. Investigation into febrile convulsions in young children after seasonal influenza vaccination. [accessed 2012 Jul 20]. Available from: URL: http//www.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-factsheet-30jul10

4 **Al-Ajlouni SF**, Kodah IH. Febrile convulsions in children. *Saudi Med J* 2000; **21**: 617-621 [PMID: 11500722]

5 **Gold MS**, Effler P, Kelly H, Richmond PC, Buttery JP. Febrile convulsions after 2010 seasonal trivalent influenza vaccine: implications for vaccine safety surveillance in Australia. *Med J Aust* 2010; **193**: 492-493 [PMID: 21034379]

6 **Australian Technical Advisory Group on Immunisation (ATAGI) and Therapeutic Goods Administration (TGA) Joint Working Group**. Report of an analysis of febrile convulsions following immunisation in children following monovalent pandemic H1N1 vaccine (Panvax/Panvax Junior, CSL). [accessed 2012 Jul 20]. Available from: URL: http//www.tga.gov.au/safety/alerts-medicine-seasonal-flu-100928.htm

7 **Barlow WE**, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mullooly JP, Black SB, Shinefield HR, Ward JI, Marcy SM, DeStefano F, Chen RT, Immanuel V, Pearson JA, Vadheim CM, Rebolledo V, Christakis D, Benson PJ, Lewis N. The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *N Engl J Med* 2001; **345**: 656-661 [PMID: 11547719 DOI: 10.1056/NEJMoa003077]

8 **Sun Y**, Christensen J, Hviid A, Li J, Vedsted P, Olsen J, Vestergaard M. Risk of febrile seizures and epilepsy after vaccination with diphtheria, tetanus, acellular pertussis, inactivated poliovirus, and Haemophilus influenzae type B. *JAMA* 2012; **307**: 823-831 [PMID: 22357833 DOI: 10.1001/jama.2012.165]

9 **Jacobsen SJ**, Ackerson BK, Sy LS, Tran TN, Jones TL, Yao JF, Xie F, Cheetham TC, Saddier P. Observational safety study of febrile convulsion following first dose MMRV vaccination in a managed care setting. *Vaccine* 2009; **27**: 4656-4661 [PMID: 19520201 DOI: 10.1016/j.vaccine.2009.05.056]

10 **Hak E**, Bonten MJ. MMR vaccination and febrile seizures. *JAMA* 2004; **292**: 2083; author reply 2083-2084 [PMID: 15523064 DOI: 10.1001/jama.292.3.351]

11 **Stehr-Green P**, Radke S, Kieft C, Galloway Y, McNicholas A, Reid S. The risk of simple febrile seizures after immunisation with a new group B meningococcal vaccine, New Zealand. *Vaccine* 2008; **26**: 739-742 [PMID: 18187240 DOI: 10.1016/j.vaccine.2007.12.001]

12 **Leroy Z**, Broder K, Menschik D, Shimabukuro T, Martin D. Febrile seizures after 2010-2011 influenza vaccine in young children, United States: a vaccine safety signal from the vaccine adverse event reporting system. *Vaccine* 2012; **30**: 2020-2023 [PMID: 22361303 DOI: 10.1016/j.vaccine.2011.12.042]

13 **Habib Z**, Akram S, Ibrahim S, Hasan B. Febrile seizures: factors affecting risk of recurrence in Pakistani children presenting at the Aga Khan University Hospital. *J Pak Med Assoc* 2003; **53**: 11-17 [PMID: 12666845]

14 **Hon KL**, Nelson EA. Gender disparity in paediatric hospital admissions. *Ann Acad Med Singapore* 2006; **35**: 882-888 [PMID: 17219000]

15 **Al-Khathlan NA**, Jan MM. Clinical profile of admitted children with febrile seizures. *Neurosciences* (Riyadh) 2005; **10**: 30-33 [PMID: 22473180]

16 **Jones T**, Jacobsen SJ. Childhood febrile seizures: overview and implications. *Int J Med Sci* 2007; **4**: 110-114 [PMID: 17479160 DOI: 10.7150/ijms.4.110]

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ORIGINAL ARTICLE

Retrospective Study

Subclinical hypothyroidism in atopic South Italian children

Marcella Pedullà, Vincenzo Fierro, Pierluigi Marzuillo, Ester Del Tufo, Anna Grandone, Laura Perrone, Emanuele Miraglia del Giudice

Marcella Pedullà, Vincenzo Fierro, Pierluigi Marzuillo, Ester Del Tufo, Anna Grandone, Laura Perrone, Emanuele Miraglia del Giudice, Department of Woman, Child and General and Specialized Surgery, Seconda Università degli Studi di Napoli, 80138 Napoli, Italy

Author contributions: Pedullà M drafted the manuscript; Pedullà M, Fierro V and Marzuillo P participated in the conception and the design of the study; Del Tufo E and Grandone A examined the patients, collected anthropometric data; Perrone L and Miraglia del Giudice E supervised the design and execution of the study.

Institutional review board statement: The approved protocol from the Institutional Review Board at the Second University of Naples.

Informed consent statement: An informed consent was obtained from the parents and the children all enrolled after the nature of the investigation was explained.

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Correspondence to: Pierluigi Marzuillo, MD, Department of Woman, Child and General and Specialized Surgery, Seconda Università degli Studi di Napoli, Via L. De Crecchio n° 2, 80138 Napoli, Italy. pierluigi.marzuillo@gmail.com
Telephone: +39-081-5665420
Fax: +39-081-5665427

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Abstract

AIM: To verify if subclinical hypothyroidism (SCH) could be associated to atopy in children.

METHODS: Seven hundred and thirty-two Caucasian children from South Italy presenting symptoms of allergic disease were enrolled and submitted to atopy, obesity, chronic low grade inflammation, and SCH work up.

RESULTS: Four hundred and forty-five out of 705 (63.12%) children affected by allergic disease were diagnosed as atopic and 260 (36.88%) as not atopic. The SCH prevalence was 6.3%. Significant higher prevalence of SCH among atopic children with average (group 2) and high (group 3) low grade chronic inflammation compared to atopic children with mild (group 1) low grade chronic inflammation was present. Moreover, group 1 and group 2 presented an OR to show SCH of 2.57 (95%CI: 1.55-6.26) and 2.96 (95%CI: 1.01-8.65), respectively. Both in atopic and not atopic children we found C3 serum levels significantly higher in group 3 respect to group 2 and group 1. Noteworthy, among atopic patients, also total immunoglobulin E (IgE) serum levels, were significantly higher in group 3 compared to group 2 and group 1 children. In atopic children, C3 and total IgE serum values increased in parallel with the increase of C-reactive protein values, while in not atopic children this phenomenon was not evident.

CONCLUSION: The possibility exists that an increasing atopic inflammation contributes to SCH occurrence. So far this is the first report in literature showing an

association between SCH and atopy but further studies are needed to confirm our data.

Key words: Thyroid derangement; Atopy; Children; Low grade chronic inflammation; Subclinical hypothyroidism

Core tip: A high subclinical hypothyroidism (SCH) prevalence has been associated in childhood to obesity and the chronic low grade inflammation found obese children has been involved in this relationship. In our population, obesity does not influence SCH prevalence. Interestingly, we found a SCH prevalence twice higher compared to all other patients and a significant higher risk to show SCH in atopic children affected by the highest C-reactive protein values characterizing low-grade inflammation.

Pedullà M, Fierro V, Marzuillo P, Del Tufo E, Grandone A, Perrone L, Miraglia del Giudice E. Subclinical hypothyroidism in atopic South Italian children. *World J Clin Pediatr* 2016; 5(3): 306-310 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i3/306.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i3.306

INTRODUCTION

Subclinical hypothyroidism (SCH) is defined as a thyroid stimulating hormone (TSH) serum level above the statistically defined upper limit of the reference range despite normal serum free T4 (fT4) and free T3 (fT3) concentration. In addition to genetic cause, SCH has been associated to childhood obesity[1], with some slight myocardial dysfunction[2].

It has been recently demonstrated that atopy can be related to childhood obesity and that chronic low grade inflammation related to it was involved in this relationship[3-5].

The aim of our study is to verify if, as well as to obesity, SCH could be also associated to atopy in children.

MATERIALS AND METHODS

Seven hundred thirty-two Caucasian children from South Italy (age in years 6.03 ± 3.63) presenting symptoms of allergic disease (erythema, pruritus, eczematous rash, wheals, ocular and nasal pruritus and wheezing) attending consecutively from January 2013 to July 2015 the Department of Pediatrics of the Second University of Naples were enrolled. None showed any clinical symptoms of thyroid disease. All the enrolled children were submitted to atopy, obesity, chronic low grade inflammation, and SCH work up. Body mass index (BMI) was calculated by dividing weight in kilograms by height squared in meters (kg/m^2). Obesity was defined by a BMI $\geqslant$ 95th percentile[6].

In all patients, after an overnight fasting, a blood sample was obtained to evaluate C-reactive protein (CRP) and Complement C3 serum levels, measured using an Olympus AU 560 apparatus by an enzymatic colorimetric method, total and specific IgE by a fluorenzymeimmunoassay (ImmunoCap and ImmunoCap 0-100), thyroid hormones (TSH, fT3, and fT4) and anti-thyroid peroxidase antibodies (TPO-Ab) and anti-thyroglobulin antibodies (Tg-Ab), determined by high-specific solid-phase technique-chemiluminescence immunoassays (Perkinelmer, Turku, Finland).

The diagnosis of atopy suspected for clinical history and symptoms, was confirmed by levels of serum total IgE (normal value from 25 to 60 mo of age < 81 kU/L, from 61 to 156 mo of age < 101 kU/L) and specific immunoglobulin E (IgE) assay (> 0.36 kUA/L) as well as by Skin Prick Tests (SPTs). None had taken steroids or received immuno-suppressive therapy for at least 3 mo before investigation. Antihistamine therapy had been stopped at least 2 wk before SPTs were performed and serum samples were collected.

According to atopy diagnosis the children enrolled in the study were divided in two groups: Atopic and not atopic children.

Chronic low grade inflammation is diagnosed by slightly raised concentrations of inflammatory markers in the systemic circulation[7]. Therefore, to better assess the chronic low grade inflammation status we applied both in atopic and not atopic children the cut-off point described by Pearson *et al*[8] for assessing cardio vascular disease (CVD) risk. Thus we divided children in three different CRP serum values gradation groups: group 1 low grade (CRP < 0.1 mg/dL), group 2 average grade (CRP 0.1-0.3 mg/dL) and group 3 high grade (CRP > 0.3-< 1 mg/dL) of chronic low grade inflammation.

Twenty-seven children with CRP serum values greater than 1 mg/dL were excluded from the study given the possibility of an ongoing infection.

SCH was diagnosed when TSH value was higher than 5 mUI/mL, as indicated by the "European Thyroid Association Guidelines for the Management of Subclinical Hypothyroidism in Pregnancy and in Children"[9,10], with fT3, fT4, and antithyroid antibodies values in the normal range for age and no clinical signs or symptoms of hypothyroidism[10].

Informed consent was obtained from all enrolled children and their parents and in accordance with the approved protocol from the Institutional Review Board at the University of Naples.

Skewness and Kurtosis tests were used to evaluate if the distribution of continuous variables was normal. According to distribution, the values were expressed as mean ± SD or median and minimum-maximum values. To analyze categorical variables was used *t* test for unpaired data. A χ^2 test was also used to analyze the differences between the frequencies. Mann-Whitney *U* test was used for comparison of continuous variables which did not exhibit normal distribution. A *P* value < 0.05 was considered significant.

Table 1 Clinical and laboratory differences between atopic and not atopic children affected by allergic disease

	Atopic children	Not atopic children	*P*
Patients, *n*	459/732 (62.7%)	273/732 (37.3%)	
Age expressed in years (mean age ± SD)	6.24 ± 3.55	5.82 ± 3.71	0.128
Gender (male)	245/459 (53.37%)	137/274 (50%)	0.37
Family history of atopy	365/420 (86.9%)	195/235 (80%)	0.17
Family history of thyroid disease	191/421 (45.36%)	94/235 (40%)	0.18
BMI (kg/m^2)	16.6 (10.9-36.8)	16.4 (10.7-30.17)	0.069
SCH affected (%)	33/445 (7.41%)	13/260 (5%)	0.21
SCH obeses (%)	1/33 (3%)	1/13 (7.69%)	0.48
CRP (mg/dL)	0.06 (0-10.3)	0.08 (0-7.9)	0.123
TSH (UI/mL)	2.33 (0.35-12.2)	2.24 (0.52-6.98)	0.269

P value < 0.05 was considered significant. BMI: Body mass index; SCH: Subclinical hypothyroidism; CRP: C-reactive protein; TSH: Thyroid stimulating hormone.

Table 2 Atopic and not atopic children divided into three groups on the basis of the C-reactive protein serum levels

	Atopic children			*P*	Not atopic children			*P*
	Group 1	Group 2	Group 3		Group 1	Group 2	Group 3	
CRP (mg/dL)	< 0.1	0.1-0.3	> 0.3-< 1		< 0.1	0.1-0.3	> 0.3-< 1	
SCH	18/272 (6.62%)	7/121 (5.78%)	8/52 (15.38%)	[1]0.033 OR: 2.57 (1.55-6.26) [3]0.04 OR 2.96 (1.01-8.65)	8/151 (5.29%)	3/81 (3.70%)	2/28 (7.14%)	
C3 (mg/dL)	115 (20-174)	122 (50-172)	138 (103-192)	[1]1.86e^{-8} [2]0.027 [3]0.00021	116.5 (10-170)	126 (73-177)	139 (109-170)	[1]0.000053 [2]0.0085 [3]0.024
Total IgE (kUI/L)	120 (100-2270)	123.5 (100-4328)	162.1 (124-5000)	[1]0.000017 [3]0.00045	17.4 (1.9-98)	22.45 (1.9-93)	22.43 (1.9-88.9)	

[1]Group 1 *vs* group 3; [2]Group 1 *vs* group 2; [3]Group 2 *vs* group 3. SCH: Subclinical hypothyroidism; CRP: C-reactive protein.

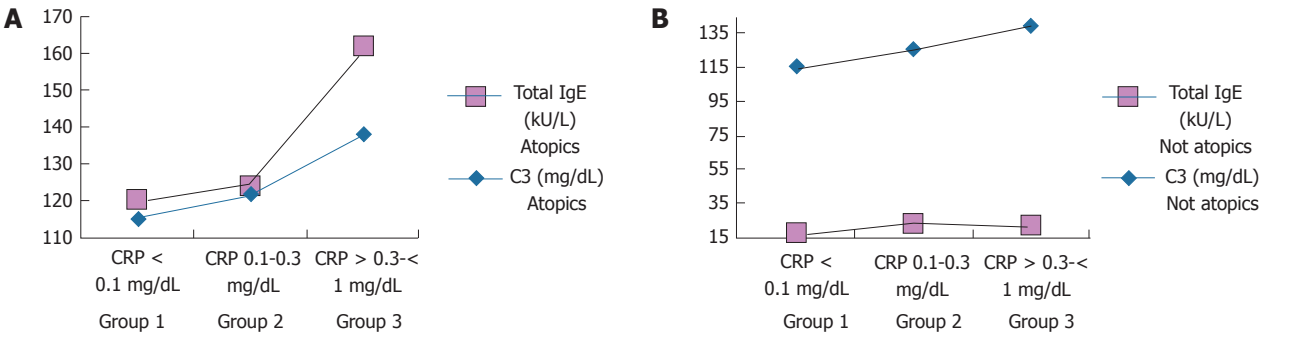

Figure 1 Complement C3 and total IgE serum levels values according to low grade inflammation in both atopic (A) and not atopic (B) children affected by allergic disease. CRP values < 0.1 mg/dL identify children with low grade of chronic low grade inflammation (group 1). CRP values between 0.1 and 0.3 mg/dL identify children with average grade of chronic low grade inflammation (group 2). CRP values > 0.3 and < 1 mg/dL identify high grade of chronic low grade inflammation (group 3). In atopic children, C3 and total IgE serum values increased in parallel with the increase of CRP values, while in not atopic children this phenomenon is not evident. A: For C3, group 1 *vs* group 3, $P = 1.86e^{-8}$; group 1 *vs* group 2, $P = 0.027$; group 2 *vs* group 3, $P = 0.00021$. For total IgE, group 1 *vs* group 3, $P = 0.000017$; group 1 *vs* group 2, $P > 0.05$; group 2 *vs* group 3, $P = 0.00045$; B: For C3, group 1 *vs* group 3, $P = 0.000053$; group 1 *vs* group 2, $P = 0.0085$; group 2 *vs* group 3, $P = 0.024$. For total IgE, group 1 *vs* group 3, $P > 0.05$; group 1 *vs* group 2, $P > 0.05$; group 2 *vs* group 3, $P \geqslant 0.05$.

Odds ratio (OR) was calculated to evaluate the association of Atopy and SCH prevalence. OR was considered significant when a 95%CI excluded unity. Statistical analysis were performed using Stat-Graphics Centurion 3.0 for Windows.

RESULTS

On the basis of atopy work-up 459 out of 705 (62.7%) children affected by allergic disease were diagnosed as atopic and 273 (37.3%) as not atopic. The overall prevalence of SCH was 6.3%.

In Table 1 we described clinical and laboratory differences between these two groups of children. No significant differences were found.

Table 2 shows clinical and laboratory data of both atopic and not atopic children divided into 3 different groups on the basis of increasing CRP serum values:

group 1 (CRP < 0.1 mg/dL), group 2 (CRP 0.1-0.3 mg/dL) and group 3 (CRP > 0.3-< 1 mg/dL). First we compared the prevalence of SCH among all the groups and no significant differences were found.

On the contrary, among atopic children, significant higher prevalence of SCH in group 3 and group 2 compared to group 1 was found (P = 0.033 and P = 0.04, Table 2). Moreover, group 3 and group 2 atopic children presented an OR to show SCH of 2.57 (95%CI: 1.55-6.26) and 2.96 (95%CI: 1.01-8.65) respectively.

Both in atopic and not atopic children we found C3 serum levels significantly higher in group 3 respect to group 2 and group 1 (Table 2). Noteworthy, among atopic patients, also total IgE serum levels, were significantly higher in group 3 compared to group 2 and group 1 children.

Figure 1 shows in both atopic (A) and not atopic (B) children complement C3 and total IgE serum levels values according to the different grading of CRP values.

In atopic children, C3 and total IgE serum values increased in parallel with the increase of CRP values, but no significant correlation was found. C3 and total IgE serum values in not atopic children showed a completely independent trend.

DISCUSSION

In our study atopic children showed a 7.41% prevalence of SCH while not atopic children allergic found in alike disease affected a 5% SCH prevalence. These frequencies are in line with the estimated prevalence of this thyroid disorder in the pediatric population[11,12].

A high SCH prevalence has been associated in childhood to obesity and the chronic low grade inflammation found obese children has been involved in this relationship[13]. In our population, obesity does not influence SCH prevalence.

Interestingly, we found a SCH prevalence twice higher (15.38%) compared to all other patients and a significant higher risk to show SCH [2.57 (95%CI: 1.55-6.26)] in atopic children affected by the highest CRP values characterizing low grade inflammation (group 3 atopics).

Atopy and the associated allergic disease are now regarded as systemic inflammatory disease that could affect the risk of atherosclerosis[14], impaired glucose tolerance[15], and coronary artery disease[16]. The chronic low grade inflammation involved in the pathogenesis of localized allergic disease causes a systemic inflammatory response that potentially could promote also SCH.

Moreover, in our atopic children the highest low grade chronic inflammation (CRP > 0.3-< 1 mg/dL) seems to correspond to the highest atopic inflammation as measured by total serum IgE values (Figure 1). The possibility exists that an increasing atopic inflammation contributes to SCH occurrence. A limitation of our study could be a recruitment bias because the patients enrolled were affected severe allergic disease needing of a specialist evaluation.

So far this is the first report in literature showing an association between SCH and atopy but further studies are needed to confirm our data.

COMMENTS

Background

Recent studies demonstrate that atopy can be associated to childhood obesity and that chronic low grade inflammation could be involved in this relationship. The aim of the study was to verify if subclinical hypothyroidism (SCH) could be also associated to atopy in children.

Research frontiers

Important areas of research related to the study are represented by the field of pediatric endocrinology and allergology. More in particular, the study aimed to hypothesize, throughout the verification of an association, the mechanisms by which atopy could lead to SCH.

Innovations and breakthroughs

This is the first report in literature showing an association between SCH and atopy with a possible causal link represented by chronic low grade inflammation.

Applications

The study can result in future researches confirming the authors' findings and, moreover, understanding the pathophysiological basis underlining the association between atopy and SCH.

Terminology

SCH is defined as a thyroid stimulating hormone serum level above the statistically defined upper limit of the reference range despite normal serum free T4 and free T3 concentration.

Peer-review

The association among obesity, chronic inflammation and SCH is a very interesting topic.

REFERENCES

1 **Grandone A**, Santoro N, Coppola F, Calabrò P, Perrone L, Del Giudice EM. Thyroid function derangement and childhood obesity: an Italian experience. *BMC Endocr Disord* 2010; **10**: 8 [PMID: 20441588]

2 **Brienza C**, Grandone A, Di Salvo G, Corona AM, Di Sessa A, Pascotto C, Calabrò R, Toraldo R, Perrone L, del Giudice EM. Subclinical hypothyroidism and myocardial function in obese children. *Nutr Metab Cardiovasc Dis* 2013; **23**: 898-902 [PMID: 22748710 DOI: 10.1016/j.numecd.2012.04.006]

3 **von Mutius E**, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. *Thorax* 2001; **56**: 835-838 [PMID: 11641506 DOI: 10.1136/thorax.56.11.835]

4 **Ford ES**. C-reactive protein concentration and cardiovascular disease risk factors in children: findings from the National Health and Nutrition Examination Survey 1999-2000. *Circulation* 2003; **108**: 1053-1058 [PMID: 12925465 DOI: 10.1161/01.CIR.0000080913.81393.B8]

5 **Cibella F**, Cuttitta G, La Grutta S, Melis MR, Bucchieri S, Viegi G. A cross-sectional study assessing the relationship between BMI, asthma, atopy, and eNO among schoolchildren. *Ann Allergy Asthma Immunol* 2011; **107**: 330-336 [PMID: 21962093 DOI: 10.1016/j.anai.2011.08.001]

6 **Cacciari E**, Milani S, Balsamo A, Spada E, Bona G, Cavallo L, Cerutti F, Gargantini L, Greggio N, Tonini G, Cicognani A. Italian cross-sectional growth charts for height, weight and BMI (2 to 20 yr). *J Endocrinol Invest* 2006; **29**: 581-593 [PMID: 16957405 DOI: 10.1007/BF03344156]

7 **Trayhurn P**, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. *Br J Nutr* 2004; **92**: 347-355 [PMID: 15469638 DOI: 10.1079/BJN20041213]

8 **Pearson TA**, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003; **107**: 499-511 [PMID: 12551878]

9 **Lazarus J**, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European thyroid association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J* 2014; **3**: 76-94 [PMID: 25114871 DOI: 10.1159/000362597]

10 **Taubner K**, Schubert G, Pulzer F, Pfaeffle R, Körner A, Dietz A, Thiery J, Kiess W, Kratzsch J. Serum concentrations of anti-thyroid peroxidase and anti-thyroglobulin antibodies in children and adolescents without apparent thyroid disorders. *Clin Biochem* 2014; **47**: 3-7 [PMID: 24103918 DOI: 10.1016/j.clinbiochem.2013.09.017]

11 **Gawlik A**, Such K, Dejner A, Zachurzok A, Antosz A, Malecka-Tendera E. Subclinical hypothyroidism in children and adolescents: is it clinically relevant? *Int J Endocrinol* 2015; **2015**: 691071 [PMID: 25892992 DOI: 10.1155/2015/691071]

12 **Wu T**, Flowers JW, Tudiver F, Wilson JL, Punyasavatsut N. Subclinical thyroid disorders and cognitive performance among adolescents in the United States. *BMC Pediatr* 2006; **6**: 12 [PMID: 16623938]

13 **Wärnberg J**, Nova E, Romeo J, Moreno LA, Sjöström M, Marcos A. Lifestyle-related determinants of inflammation in adolescence. *Br J Nutr* 2007; **98** Suppl 1: S116-S120 [PMID: 17922948]

14 **Knoflach M**, Kiechl S, Mayr A, Willeit J, Poewe W, Wick G. Allergic rhinitis, asthma, and atherosclerosis in the Bruneck and ARMY studies. *Arch Intern Med* 2005; **165**: 2521-2526 [PMID: 16314550]

15 **Wang Z**, Zhang H, Shen XH, Jin KL, Ye GF, Qiu W, Qian L, Li B, Zhang YH, Shi GP. Immunoglobulin E and mast cell proteases are potential risk factors of impaired fasting glucose and impaired glucose tolerance in humans. *Ann Med* 2013; **45**: 220-229 [PMID: 23110545 DOI: 10.3109/07853890.2012.732234]

16 **Deliargyris EN**, Upadhya B, Sane DC, Dehmer GJ, Pye J, Smith SC, Boucher WS, Theoharides TC. Mast cell tryptase: a new biomarker in patients with stable coronary artery disease. *Atherosclerosis* 2005; **178**: 381-386 [PMID: 15694948]

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ORIGINAL ARTICLE

Retrospective Study

Potential carrier priming effect in Australian infants after 7-valent pneumococcal conjugate vaccine introduction

Mohamed Tashani, Sanjay Jayasinghe, Zitta B Harboe, Harunor Rashid, Robert Booy

Mohamed Tashani, Sanjay Jayasinghe, Harunor Rashid, Robert Booy, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, the Children's Hospital at Westmead, Sydney 2145, Australia

Mohamed Tashani, Sanjay Jayasinghe, Harunor Rashid, Robert Booy, the Discipline of Child and Adolescent Health, Sydney Medical School, University of Sydney, Sydney 2145, Australia

Zitta B Harboe, Neisseria and Streptococcus Reference Laboratory, Department of Microbiology and Infection Control, Statens Serum Institut, 2100 Copenhagen, Denmark

Harunor Rashid, Robert Booy, Marie Bashir Institute for Infectious Diseases and Biosecurity, School of Biological Sciences and Sydney Medical School, University of Sydney, Sydney 2006, Australia

Robert Booy, World Health Organization Collaborating Centre for Mass Gatherings and High Consequence/High Visibility Events, Flinders University, Adelaide 5001, Australia

Author contributions: All authors contributed equally to this manuscript; Booy R contributed to conceptualizing the idea; Tashani M conducted the literature review and performed data collection and analysis; Jayasinghe S provided support in accessing, collecting and analysing the data; Harboe ZB provided additional data from overseas; and Rashid H helped in writing and revision of this manuscript; the authors have seen and agreed to the submitted version of the paper, that all who have been acknowledged as contributors have agreed to their inclusion.

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Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data.

Conflict-of-interest statement: Professor Robert Booy has received funding from Baxter, CSL, GSK, Merck, Novartis, Pfizer, Roche, Romark and Sanofi Pasteur for the conduct of sponsored research, travel to present at conferences or consultancy work; all funding received is directed to research accounts at the Children's Hospital at Westmead; Dr Harunor Rashid has received fees from Pfizer and Novartis for consulting or serving on an advisory board; the other authors have declared no conflict of interest in relation to this work.

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Correspondence to: Mohamed Tashani, DCH, MBBCH, MPH, MHM, MIPH, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, the Children's Hospital at Westmead, Locked Bag 4001, Sydney 2145, Australia. mohamed.tashani@health.nsw.gov.au
Telephone: +61-29-8451232
Fax: +61-29-8451418

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Abstract

AIM: To investigate evidence of clinical protection

in infants after one dose of 7-valent pneumococcal conjugate vaccine (7vPCV) owing to carrier priming.

METHODS: Using Australian National Notifiable Diseases Surveillance System data, we conducted a descriptive analysis of cases of vaccine type invasive pneumococcal disease (VT-IPD) during "catch-up" years, when 7vPCV was carrier primed by prior administration of DTPa vaccine. We compared the number of VT-IPD cases occurring 2-9 wk after a single dose of 7vPCV (carrier primed), with those < 2 wk post vaccination, when no protection from 7vPCV was expected yet. Further comparison was conducted to compare the occurrence of VT-IPD cases *vs* non-VT-IPD cases after a single carrier-primed dose of 7vPCV.

RESULTS: We found four VT-IPD cases occurring < 2 wk after one carrier primed dose of 7vPCV while only one case occurred 2-9 wk later. Upon further comparison with the non-VT-IPD cases that occurred after one carrier primed dose of 7vPCV, two cases were detected within 2 wk, whereas seven occurred within 2-9 wk later; suggesting a substantial level of protection from VT-IPD occurring from 2 wk after carrier-primed dose of 7vPCV.

CONCLUSION: This data suggest that infants may benefit from just one dose of 7vPCV, likely through enhanced immunity from carrier priming effect. If this is proven, an adjusted 2-dose schedule (where the first dose of PCV is not given until after DTPa) may be sufficient and more cost-effective.

Key words: Carrier priming; Conjugate vaccine; Infant; Invasive pneumococcal disease

Core tip: With the inclusion of newer conjugate vaccines with higher number of serotypes in the immunisation schedule, literature suggests that prior immunisation with tetanus/diphtheria-containing vaccines could enhance the immunogenicity of subsequently administered glycoconjugate vaccine, a phenomenon known as "carrier priming". This analysis provides evidence of substantial clinical protection ensued after one dose of 7-valent pneumococcal conjugate vaccine as result of carrier priming. This phenomenon could be implemented to enhance the immunogenicity of conjugate vaccines among vulnerable populations such as infants in resource-poor settings, travellers, immigrants and refugees.

Tashani M, Jayasinghe S, Harboe ZB, Rashid H, Booy R. Potential carrier priming effect in Australian infants after 7-valent pneumococcal conjugate vaccine introduction. *World J Clin Pediatr* 2016; 5(3): 311-318 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i3/311.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i3.311

INTRODUCTION

Streptococcus pneumoniae (SPn) is responsible for 33% of childhood mortalities due to pneumonia worldwide[1]. Invasive pneumococcal disease (IPD) is caused by SPn and is defined as an infection confirmed by the isolation of pneumococci from a normally sterile body site, such as the blood stream and cerebrospinal fluid whereas non-invasive disease includes otitis media, sinusitis and bronchitis[2]. The incidence of IPD is often used as a measure of pneumococcal disease burden[3]. The 7-valent pneumococcal conjugate vaccine (7vPCV) was introduced to the Australian National Immunisation Program (NIP) for vaccination against SPn for medically at-risk and Indigenous children in 2001 and for all children from January 2005[4]. The dosage schedule used was three doses at 2, 4 and 6 mo of age along with other vaccines such as diphtheria, tetanus and acellular pertussis (DTPa). A concurrent catch up vaccination program was implemented for two years targeting children up to two years of age, many of whom would have received DTPa vaccine prior to their first catch up dose of 7vPCV. The use of the 3 + 0 schedule is strongly supported by a systematic review of several randomized controlled clinical trials (RCTs) of pneumonia and IPD in developing country settings[5]. A 3-dose 2-4-6 mo schedule result in the optimum antibody levels after the primary series for many serotypes. However, interestingly, the 2-dose 3-5 mo schedule demonstrated higher antibody levels for five serotypes than the 3-dose schedule (at 2-3-4 mo) and equivalent antibody responses for serotypes 6B and 23F suggesting that the optimal timing of doses is perhaps more important than the number of doses[6].

The PCV is currently available in less than 60% of countries across the world[7] as the cost of the vaccine is an important barrier. Affordability of the vaccine could be improved through adoption of schedules with reduced doses by taking the advantage of a phenomenon called "carrier priming" when PCV is administered after DTPa vaccination[8]. Carrier priming is defined as an enhanced antibody response to a glycoconjugate vaccine when an individual has been previously primed with the carrier protein[9].

PCVs utilise carrier proteins such as tetanus toxoid, diphtheria toxoid or cross-reacting material 197 of diphtheria toxin. It is apparent that there is a high resemblance between these carrier proteins and the contents of DTPa vaccine. The carrier priming effect is attributed to the development of carrier-specific T-cells in response to a preceding immunisation with a vaccine (such as DTPa) that contains antigens similar to the carrier proteins in conjugate vaccines; this has been demonstrated in various studies[8].

The catch-up vaccination program implemented in 2005 accompanying the introduction of universal 7vPCV vaccination program in Australia provides a unique opportunity to examine the potential protective effect of carrier priming on IPD. We hypothesise that

due to the effect of carrier priming, the number of vaccine type-IPD (VT-IPD) cases 2-9 wk following the administration of the first dose of 7vPCV (through catch up program in those children primed with previous dose of DTPa), would be less frequent than that of the VT-IPD cases within the first two weeks post-vaccination (where no protection is expected yet). In this analysis, we compared the number of IPD occurring after the 2nd week post-vaccination until the 9th week (the time of the next dose) to that occurring two weeks post-vaccination.

MATERIALS AND METHODS

Data source and case definition

We conducted a retrospective descriptive analysis by obtaining data from the National Notifiable Diseases Surveillance System (NNDSS), Australia. IPD has been a notifiable disease in Australia since the year 2001. Laboratories, medical practitioners and allied health providers are required to report IPD cases to the health authorities. De-identified data on notified cases are reported by authorities electronically to NNDSS.

A case of IPD is defined as an identification of SPn through culture or nucleic acid testing from any normally sterile body site. The onset date is considered as the date of diagnosis. Demographic and clinical information including Indigenous status, age, vaccination status and serotype of the isolated pneumococci were collected from each case of IPD. According to the Australian NIP, all cases $\geqslant$ 2 mo old were presumed to receive dose one of DTPa. The VT-IDP was defined as the isolation of one of the serotypes contained in 7vPCV (4, 6B, 9V, 14, 18C, 19F and 23F). Isolation of other serotypes was defined as non-vaccine type-IPD (NVT-IDP). Eligibility criteria of IPD cases for analysis were non-Indigenous, infant (aged $\leqslant$ 12 mo) of both genders with no documented underlying pre-existing medical conditions.

We undertook the following comparisons: (1) the first analysis in this paper compares the number of VT-IPD within two weeks after a single carrier primed dose of 7vPCV with that occurred during 2-9 wk; (2) the second analysis compares the number of VT-IPD cases *vs* NVT-IPD cases after a single carrier primed dose of 7vPCV during and two weeks after vaccination; (3) the third analysis compares the number of VT-IPD cases after a single carrier primed dose of 7vPCV with the number of VT-IPD cases after non-carrier-primed dose of 7vPCV during and two weeks after vaccination; and (4) the final analysis explores herd immunity after the introduction of 7vPCV to assess the herd effect during the transitional period (when most of the analysed cases occurred). Herd immunity was explored by detecting numbers of VT-IPD among infants < 2 mo before, during and after the introduction of 7vPCV.

Ethics approval

Permission to access NNDSS data for the study was granted by the data custodian Communicable Disease Network Australia of the Australian Department of Health. Australian Capital Territory Health Human Research Ethics Committee approval was obtained as a prerequisite for data access (Reference number ETHLR.13.318).

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 22 software program (SPSS, Inc., Chicago, IL, United States) was used to carry out descriptive data analyses. Categorical variables were compared by using the one-sided fisher's exact test. A P value $\leqslant$ 0.05 was considered statistically significant.

RESULTS

A total of 23632 IPD cases were identified and scanned for study eligibility. The number of cases included in the study was 184 among non-Indigenous Australian children who developed IPD after at least one dose of 7vPCV and were born between 1st January 2001 (when 7vPCV became available in the private market) until 31st December 2006 (when the 7vPCV catch up program ended). Of these, 108 (58.7%) were males. The majority of cases were from New South Wales [61 (33.2%)], Victoria [50 (27.2%)] and Queensland [42 (22.3%)]. Serotype was determined in 174 cases (94.5%). Final analysis in this study included 22 IPD cases with median ages as shown in Figure 1.

While examining a carrier-priming protective effect after one dose of 7vPCV, we found that four VT-IPD cases (serotypes: 23F, 4, 14 and 19F) occurred within two weeks after one carrier primed dose of 7vPCV. We did not expect the vaccine to work effectively for two weeks; we found that only one case (serotype 19F) occurred 2-9 wk later (Figure 2), indicating that one carrier primed dose could provide a substantial protection after two weeks.

Further analysis revealed that two NVT-IPD cases (serotypes: 6C and 22F) occurred within two weeks after the first carrier primed dose of 7vPCV whereas seven NVT-IPD cases (serotypes: 35B, 38 and five 10A) were reported 2-9 wk after vaccination (Figure 3). Compared to the number of VT-IPD cases after the carrier primed dose, this suggests a protective effect (P = 0.06) against VT-IPD occurring after only one carrier primed dose (Table 1).

Upon further comparison with the non-carrier primed VT-IPD cases, two VT-IPD cases (serotypes: 18C and 14) occurred within two weeks after the first dose of 7vPCV while six VT-IPD cases (serotypes: 18C, 14, 23F, 6B and two 19F) occurred 2-9 wk after vaccination (Figure 4); which although not quite significant, may indicate that protection ensued (P = 0.08) (Table 2). However, age would be a confounder in the latter comparison as the primed cases were older with possibly more mature immunity.

Considering the fact that most of the cases included in our analysis took place during the transitional years

Table 1 Contingency table comparing the numbers of vaccine type invasive pneumococcal disease and non-vaccine type invasive pneumococcal disease cases 9 wk after single carrier primed dose of the 7-valent pneumococcal conjugate vaccine among non-Indigenous Australian infants (2001-2006)

	Two weeks after carrier primed dose of 7vPCV	2-9 wk after carrier primed dose of 7vPCV
Number of VT-IPD cases	4	1
Number of NVT-IPD cases	2	7
[1]*P* value	0.06	

[1]One-sided fisher's exact test. 7vPCV: 7-valent pneumococcal conjugate vaccine; VT-IPD: Vaccine type invasive pneumococcal disease; NVT-IPD: Non-vaccine type invasive pneumococcal disease.

Table 2 Contingency table comparing the numbers of vaccine type invasive pneumococcal disease cases 9 wk after carrier primed and non-carrier primed dose of the 7-valent pneumococcal conjugate vaccine among non-Indigenous Australian infants (2001-2006)

	Two weeks after dose of 7vPCV	2-9 wk after dose of 7vPCV
Number of VT-IPD cases after carrier primed 7vPCV	4	1
Number of VT-IPD cases after non-carrier primed 7vPCV	2	6
[1]*P* value	0.08	

[1]One-sided fisher's exact test. 7vPCV: 7-valent pneumococcal conjugate vaccine; VT-IPD: Vaccine type invasive pneumococcal disease.

of 2005-2006, we explored herd immunity during this transitional period to evaluate its effect. The trends shown in Table 3 and Figure 5 demonstrate little evidence of clinical protection (herd immunity) among young infants aged < 2 mo (before first vaccine dose). This suggests that herd immunity was unlikely to have contributed to the protection of young infants against IPD during observation period of our study. Therefore, the explanation for protection is likely to be the direct effect of one PCV dose enhanced by prior carrier priming.

DISCUSSION

Our analysis suggests that infants may receive some protection even from a single dose of 7vPCV if conjugate vaccines are offered after DTPa vaccination; this could be attributed to enhanced protection through a carrier priming effect even after one dose of vaccine. This is consistent with other incidental findings among infants, adults and even in animal models where prior exposure to DTPa or one of its components was shown to enhance the immunogenicity of subsequent PCV[6,10-13]. There is evidence from other settings that children who had not carrier primed would still be susceptible to IPD at 2-8 wk after one dose of 7vPCV (unpublished Danish IPD data, Z Harboe personal communication). It has been shown elsewhere that one dose of 7vPCV provides

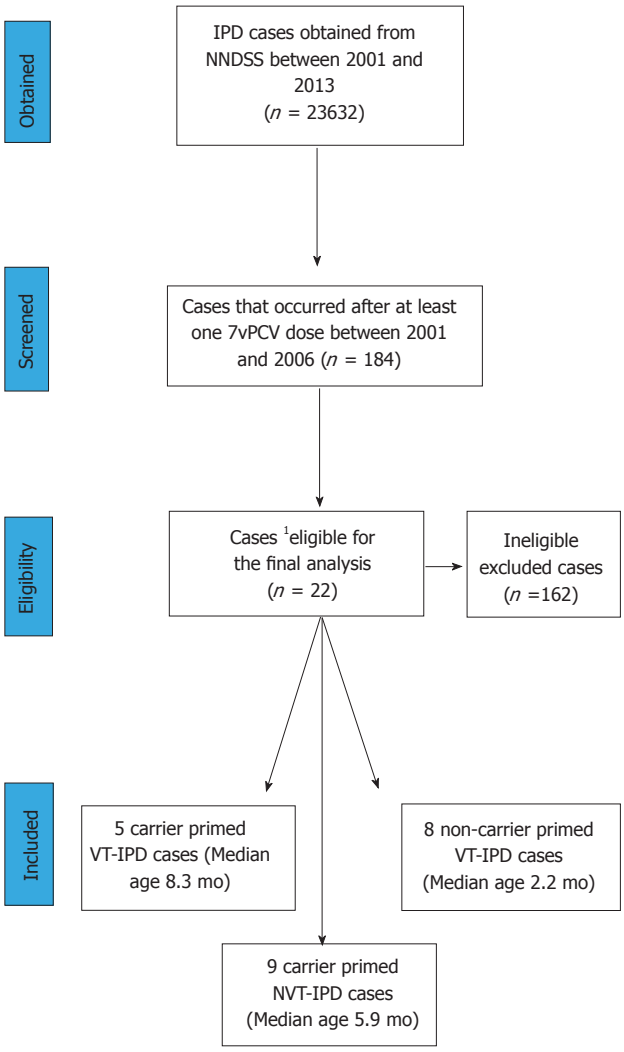

Figure 1 Flowchart showing the selection process of analysed cases and their median ages. [1]Australian non-Indigenous immunocompetent infants with receipt of first dose of 7vPCV after diphtheria, tetanus and acellular pertussis vaccine. NNDSS: National Notifiable Diseases Surveillance System; 7vPCV: 7-valent pneumococcal conjugate vaccine; VT-IPD: Vaccine type invasive pneumococcal disease; NVT-IPD: Non-vaccine type invasive pneumococcal disease.

no significant protection to young infants in the absence of carrier priming effect[14].

Our limited data suggested that herd protection in infants was not prominent in the first two years of vaccine introduction which is not surprising as the impact on carriage takes some years, and the proportion of infants and children that were vaccinated was still low[15].

PCV is highly effective, but it is also one of the most expensive vaccines on the routine paediatric schedule, at about USD $100/dose[16]. Among Australian children < 5 years of age there were approximately 700 cases of IPD and 16 associated deaths in the year prior to universal 7vPCV introduction. In 5 years of 7vPCV use IPD due to VT declined by 97% and total IPD by 68% in these children[17]. The percentage of the world's birth cohort living in countries with PCV in their NIPs rose from 1% in 2000 to 58% in 2014[7]. This suggests that efforts to increase PCV use globally are succeeding;

Table 3 Invasive pneumococcal disease cases among non-Indigenous Australian children < 6 mo (2001-2010)

	Year	2001-2002			2003-2004			2005-2006			2007-2008			2009-2010		
	Age	< 2 mo	2 mo-< 4 mo	4 mo-< 6 mo	< 2 mo	2 mo-< 4 mo	4 mo-< 6 mo	< 2 mo	2 mo-< 4 mo	4 mo-< 6 mo	< 2 mo	2 mo-< 4 mo	4 mo-< 6 mo	< 2 mo	2 mo-< 4 mo	4 mo-< 6 mo
VT-IPD	Vaccinated	0	1	0	0	2	0	0	7	2	1	0	0	0	1	4
	Not vaccinated	7	14	26	7	19	37	12	2	0	3	2	1	1	2	0
NVT-IPD	Vaccinated	0	0	0	0	0	0	0	5	8	2	9	14	2	8	18
	Not vaccinated	8	7	13	14	6	13	13	3	3	7	3	5	14	3	4

VT-IPD: Vaccine type invasive pneumococcal disease; NVT-IPD: Non-vaccine type invasive pneumococcal disease.

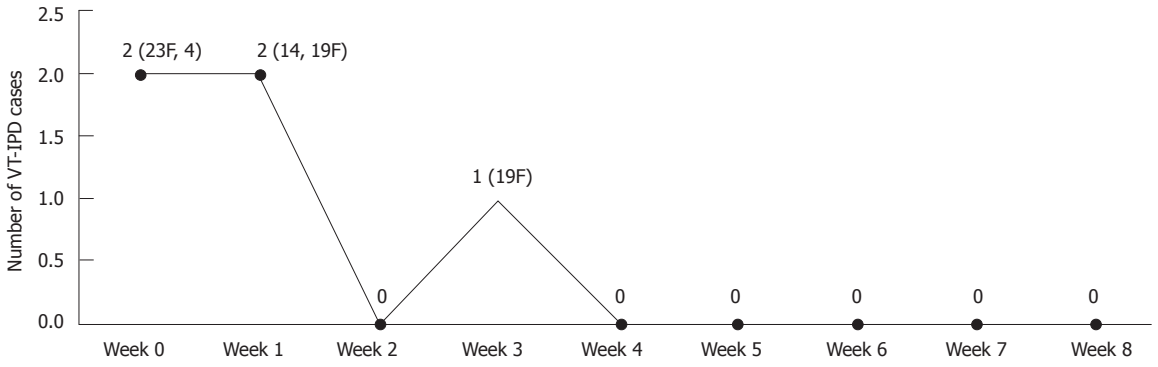

Figure 2 Number of vaccine type invasive pneumococcal disease cases 9 wk after a single carrier primed dose of the 7-valent pneumococcal conjugate vaccine among non-Indigenous Australian infants (2001-2006). VT-IPD: Vaccine type invasive pneumococcal disease.

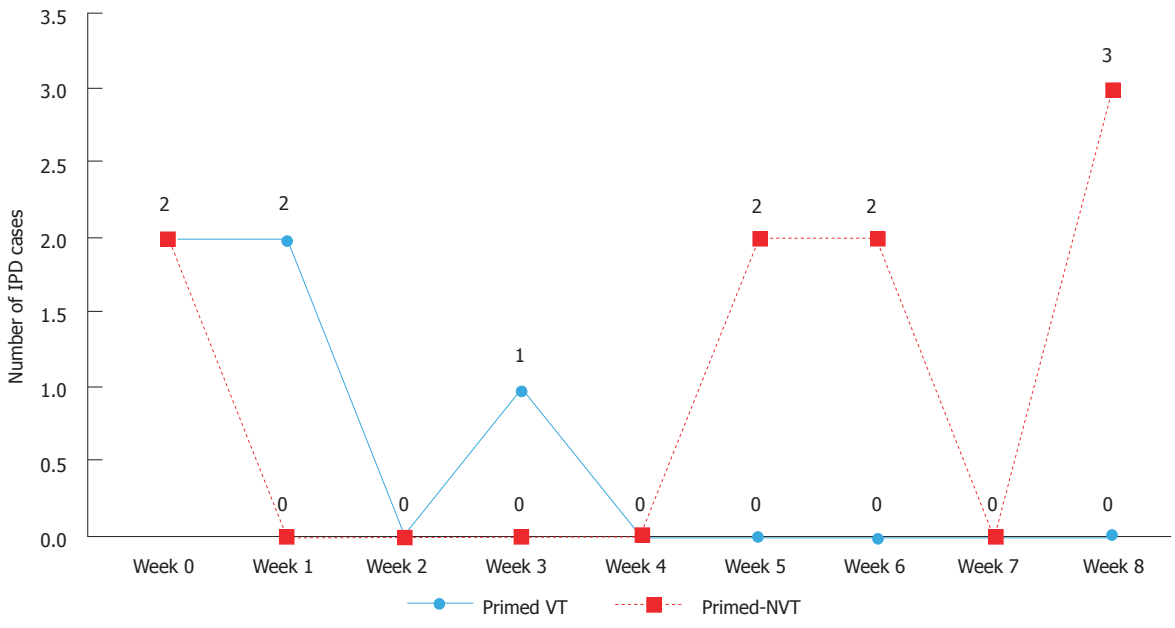

Figure 3 Number of vaccine type invasive pneumococcal disease compared to non-vaccine type invasive pneumococcal disease cases 9 wk after single carrier primed dose of 7-valent pneumococcal conjugate vaccine among non-Indigenous Australian infants (2001-2006). IPD: Invasive pneumococcal disease; VT: Vaccine type; NVT: Non VT.

however, important gaps in PCV introduction remain, notably in the World Health Organization South-East Asia Region that includes several countries with large birth cohorts but limited financial capacities to purchase these costly vaccines[18].

The implication of carrier priming raises hope for developing countries where IPD is still a major cause of morbidity and mortality[19,20]. The serotypes in the current PCV formulations account for 49%-88% of deaths in Africa, Asia and Latin America where IPD morbidity

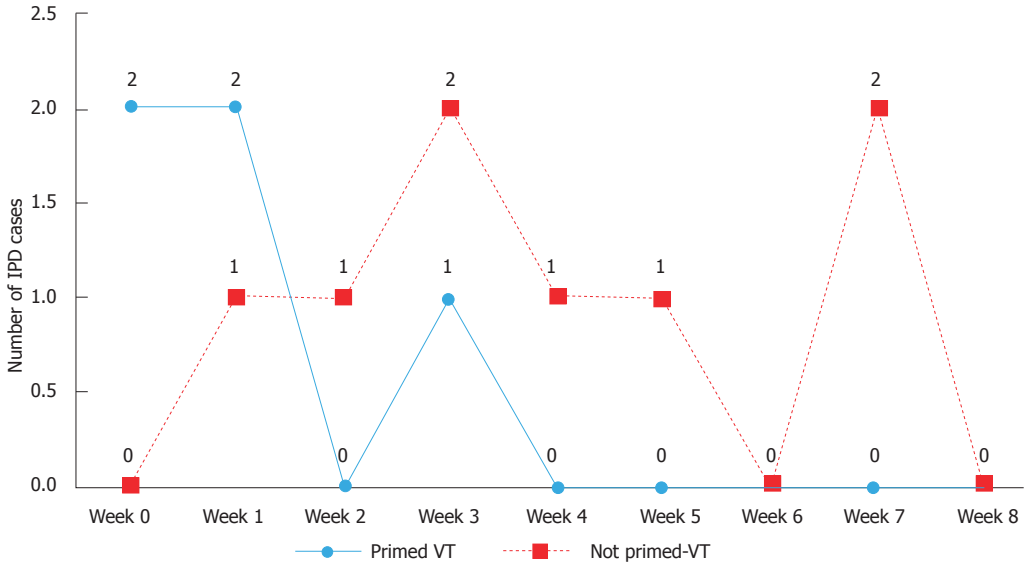

Figure 4 Number of vaccine type invasive pneumococcal disease cases 9 wk after a single carrier primed dose of 7-valent pneumococcal conjugate vaccine compared to the vaccine type invasive pneumococcal disease cases after non-carrier primed single 7-valent pneumococcal conjugate vaccine dose among non-Indigenous Australian infants (2001-2006). IPD: Invasive pneumococcal disease; VT: Vaccine type.

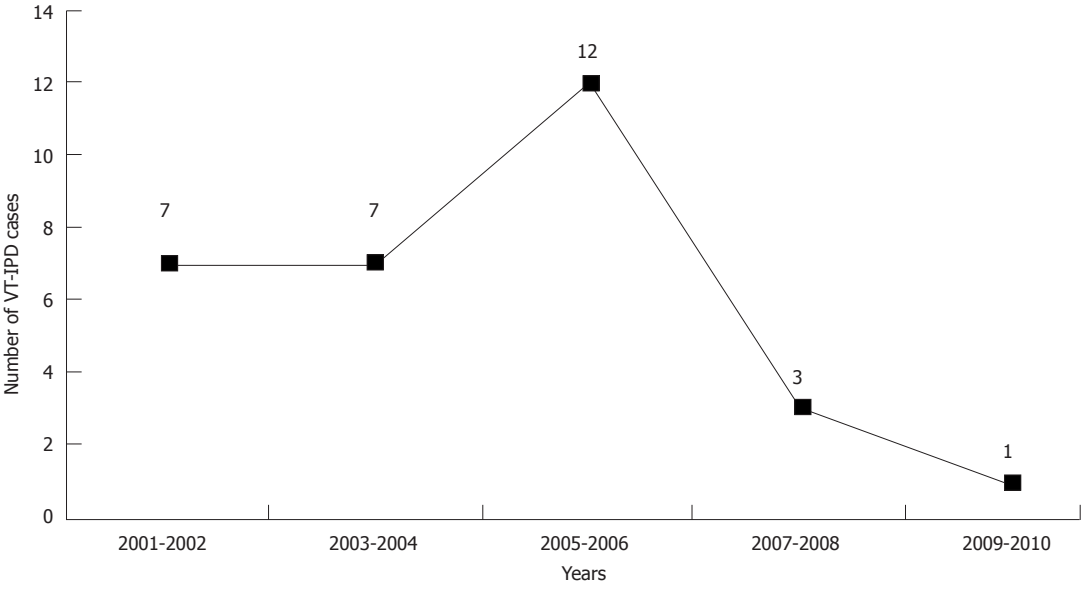

Figure 5 Number of vaccine type invasive pneumococcal disease cases among non-Indigenous Australian in children aged < 2 mo (2001-2010). VT-IPD: Vaccine type invasive pneumococcal disease.

and mortality are the highest, yet many children do not have access to these vaccines[21]. Achieving sufficient immunity against pneumococcal disease in spite of sparing a dose of vaccine could be of great value to these countries.

Simply minimizing the number of doses of PCV would not likely to be beneficial unless the carrier priming effect is also harnessed. A study in Fiji by Russell *et al*[22,23] was conducted to explore the immunogenicity of the reduced dose schedule of 7vPCV in order to determine optimal pneumococcal vaccination strategy for poor settings. They found that the immunogenicity of three PCV doses is better than two doses with potentials for a two dose PCV primary series to offer similar protection as provided by three doses for most serotypes. They also noted that a significant protection from one dose of PCV would not continue for children throughout the highest risk period for IPD and an early booster at 6 or 9 mo of age ("1 + 1" schedule) deserves a further investigation for use in the developing world[22,23]. However, in their variable schedules/methods, they only administered DTPa with the first dose of PCV, and missed the chance to examine the effect of carrier priming.

This paper sheds light on the need for further RCTs designed specifically to detect/provide conclusive evidence of the positive impact of carrier priming. If priming occurs, there is a possibility in the third world that if DTPa vaccine is given first, at anywhere between

2 and 6 wk of age, a subsequent single dose of PCV may be at least partially protective, and a second dose 4 wk later highly protective so that a third dose may not be required, either making a substantial saving in vaccine cost or allowing the third dose of PCV to be used at a more strategic time, *e.g.*, between 9 and 12 mo of age. We believe that this theory is applicable to other conjugate vaccines, *e.g.*, Hib and meningococcal conjugate vaccines, irrespective of the carrier protein. Furthermore, carrier-priming phenomenon could be implemented to reinforce immunisation schedules in resource-poor settings.

We are currently investigating this innovative concept of carrier priming by RCT among adult travellers to mass gathering, where we offer DTPa before, with and after conjugate vaccines to examine the effect.

A limitation of the study is that it is retrospective and observational with a limited number of cases included in the final analysis. Additionally, the exact dates of receipt of DTPa were not accessible as the NDDS system registers only the vaccines related to the disease, in this case PCV. However, the Australian surveillance data indicated that the coverage of DTPa was ⩾ 90% during that time[24]. This is the first established descriptive analysis looking at clinical evidence of carrier priming for prevention of pneumococcal disease.

In conclusion, these data suggest a favourable level of evidence of the effectiveness of one dose of PCV; this could be attributed to enhanced immunity through a carrier priming effect. If priming really occurs, an adjusted 2-dose schedule (where the first PCV is given following DTPa) may be sufficient and more cost-effective for vulnerable populations, particularly those that have used PCV for several years so that herd immunity is also operating.

COMMENTS

Background

Conjugate vaccines such as pneumococcal conjugate vaccine (PCV) have a carrier protein to enhance its immunogenicity. These carrier proteins have some similar antigens to the contents of diphtheria, tetanus and pertussis vaccine (DTP). This similarity may bring a potential interaction between PCV and DTP. This occurs as upon administering DTP before PCV which leads to development of carrier-specific T-cells resulting in an enhance immunogenicity of PCV, a phenomenon called carrier priming.

Research frontiers

Invasive pneumococcal diseases carry substantial morbidity and mortality particularly in developing countries and among vulnerable populations. Currently, infants are required to receive at least three doses of (the expensive) PCV. In this analysis, the authors propose investigating the use of carrier priming to enhance the immunogenicity of PCV in order to spare one of the three doses.

Innovations and breakthroughs

Most studies exploring conjugate vaccine interactions, examine concurrent co-administration. This unique analysis examines sequential administration and its effect on the protectiveness conjugate vaccines.

Applications

If carrier priming used judicially to enhance the immunogenicity of PCV, an adjusted 2-dose schedule (where the first PCV is given after DTPa) may be sufficient and cost-effective.

Terminology

Invasive pneumococcal disease (IPD): Infection confirmed by the isolation of pneumococci from a normally sterile body site, such as the blood stream, cerebrospinal fluid and joint fluid. Vaccine type invasive pneumococcal disease (VT-IPD): IPD caused by one of the pneumococcal serotype that is included in the pneumococcal vaccine. Non-vaccine type invasive pneumococcal disease (NVT-IPD): IPD caused by one of the pneumococcal serotype that is not included in the pneumococcal vaccine. Carrier priming: Enhanced antibody response to a glycoconjugate vaccine when an individual has been previously primed with the carrier protein. Carrier primed IPD case: IPD case that occurred after one dose of PCV that was administered at least one dose of DTP vaccine. Non-carrier primed VT-IPD cases: IPD case that occurred after one dose of PCV without previous exposure to at least one dose of DTP vaccine.

Peer-review

This is an interesting descriptive analysis investigating evidence for clinical protection in infants after one dose of the 7-valent PCV as a result of possible prior carrier priming from Tdap vaccine administration. It provides evidence for efficacy of reduced PCV schedule if administered following Tdap vaccination. This is valuable especially for developing countries as saving cost.

REFERENCES

1 **Rudan I**, O'Brien KL, Nair H, Liu L, Theodoratou E, Qazi S, Lukšić I, Fischer Walker CL, Black RE, Campbell H. Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. *J Glob Health* 2013; **3**: 010401 [PMID: 23826505 DOI: 10.7189/jogh.03.010401]

2 **Randle E**, Ninis N, Inwald D. Invasive pneumococcal disease. *Arch Dis Child Educ Pract Ed* 2011; **96**: 183-190 [PMID: 21555595]

3 **World Health Organisation**. Pneumococcal vaccines WHO position paper - 2012. Available from: URL: http: //www.who.int/wer/2012/wer8714.pdf

4 **Australian Government Department of Health**. The Australian Immunisation Handbook 2013. 10th ed. [updated 2015 Jun]. Available from: URL: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/7B28E87511E08905CA257D4D001DB1F8/$File/Aus-Imm-Handbook.pdf

5 **Conklin L**, Knoll MD, Loo J, Fleming-Dutra K, Park D, Johnson TS, Kirk J, Goldblatt D, O'Brien KL, Whitney CG. Landscape analysis of pneumococcal conjugate vaccine dosing schedules: A systematic review (Sub-report on the 3-dose schedules. A project of the AVI Technical Assistance Consortium (AVI-TAC) Final Report 1. 0. 2011). Available from: URL: http://www.who.int/immunization/sage/3_Conklin_L_PCV_Dosing_Landscape_Report_Oct_17_2011_FINAL_nov11.pdf

6 **Spijkerman J**, Veenhoven RH, Wijmenga-Monsuur AJ, Elberse KE, van Gageldonk PG, Knol MJ, de Melker HE, Sanders EA, Schouls LM, Berbers GA. Immunogenicity of 13-valent pneumococcal conjugate vaccine administered according to 4 different primary immunization schedules in infants: a randomized clinical trial. *JAMA* 2013; **310**: 930-937 [PMID: 24002279 DOI: 10.1001/jama.2013.228052]

7 **Murray J**, Agócs M, Serhan F, Singh S, Deloria-Knoll M, O' Brien K, Mwenda JM, Mihigo R, Oliveira L, Teleb N, Ahmed H, Wasley A, Videbaek D, Wijesinghe P, Thapa AB, Fox K, Paladin FJ, Hajjeh R, Schwartz S, Van Beneden C, Hyde T, Broome C, Cherian T. Global invasive bacterial vaccine-preventable diseases surveillance--2008-2014. *MMWR Morb Mortal Wkly Rep* 2014; **63**: 1159-1162 [PMID: 25503919]

8 **Pobre K**, Tashani M, Ridda I, Rashid H, Wong M, Booy R. Carrier priming or suppression: understanding carrier priming enhancement of anti-polysaccharide antibody response to conjugate vaccines. *Vaccine* 2014; **32**: 1423-1430 [PMID: 24492014 DOI: 10.1016/j.vaccine.2014.01.047]

9 **Kurikka S**. Priming with diphtheria-tetanus-pertussis vaccine enhances the response to the Haemophilus influenzae type b tetanus conjugate vaccine in infancy. *Vaccine* 1996; **14**: 1239-1242 [PMID: 8961512 DOI: 10.1016/S0264-410X(96)00025-4]

10 **Goldblatt D**, Southern J, Andrews N, Ashton L, Burbidge P, Woodgate S, Pebody R, Miller E. The immunogenicity of 7-valent pneumococcal conjugate vaccine versus 23-valent polysaccharide vaccine in adults aged 50-80 years. *Clin Infect Dis* 2009; **49**: 1318-1325 [PMID: 19814624 DOI: 10.1086/606046]

11 **Lucero MG**, Puumalainen T, Ugpo JM, Williams G, Käyhty H, Nohynek H. Similar antibody concentrations in Filipino infants at age 9 months, after 1 or 3 doses of an adjuvanted, 11-valent pneumococcal diphtheria/tetanus-conjugated vaccine: a randomized controlled trial. *J Infect Dis* 2004; **189**: 2077-2084 [PMID: 15143476 DOI: 10.1086/420849]

12 **Peeters CC**, Tenbergen-Meekes AM, Poolman JT, Beurret M, Zegers BJ, Rijkers GT. Effect of carrier priming on immunogenicity of saccharide-protein conjugate vaccines. *Infect Immun* 1991; **59**: 3504-3510 [PMID: 1894357]

13 **Shelly MA**, Pichichero ME, Treanor JJ. Low baseline antibody level to diphtheria is associated with poor response to conjugated pneumococcal vaccine in adults. *Scand J Infect Dis* 2001; **33**: 542-544 [PMID: 11515767]

14 **Mahon BE**, Hsu K, Karumuri S, Kaplan SL, Mason EO, Pelton SI. Effectiveness of abbreviated and delayed 7-valent pneumococcal conjugate vaccine dosing regimens. *Vaccine* 2006; **24**: 2514-2520 [PMID: 16417951 DOI: 10.1016/j.vaccine.2005.12.025]

15 **van Hoek AJ**, Sheppard CL, Andrews NJ, Waight PA, Slack MP, Harrison TG, Ladhani SN, Miller E. Pneumococcal carriage in children and adults two years after introduction of the thirteen valent pneumococcal conjugate vaccine in England. *Vaccine* 2014; **32**: 4349-4355 [PMID: 24657717 DOI: 10.1016/j.vaccine.2014.03.017]

16 **Centers of Disease Control and Prevention**. CDC vaccine price list (web page). 2013. Available from: URL: http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/2013/2013-07-01.html

17 **Jayasinghe S**, Chiu C, Menzies R, Lehmann D, Cook H, Giele C, Krause V, McIntyre P. Evaluation of impact of 23 valent pneumococcal polysaccharide vaccine following 7 valent pneumococcal conjugate vaccine in Australian Indigenous children. *Vaccine* 2015; **33**: 6666-6674 [PMID: 26519550 DOI: 10.1016/j.vaccine.2015.10.089]

18 **Centers for Disease Control and Prevention (CDC)**. Progress in introduction of pneumococcal conjugate vaccine - worldwide, 2000-2012. *MMWR Morb Mortal Wkly Rep* 2013; **62**: 308-311 [PMID: 23615674]

19 **Berkley JA**, Lowe BS, Mwangi I, Williams T, Bauni E, Mwarumba S, Ngetsa C, Slack MP, Njenga S, Hart CA, Maitland K, English M, Marsh K, Scott JA. Bacteremia among children admitted to a rural hospital in Kenya. *N Engl J Med* 2005; **352**: 39-47 [PMID: 15635111 DOI: 10.1056/NEJMoa040275]

20 **Brent AJ**, Ahmed I, Ndiritu M, Lewa P, Ngetsa C, Lowe B, Bauni E, English M, Berkley JA, Scott JA. Incidence of clinically significant bacteraemia in children who present to hospital in Kenya: community-based observational study. *Lancet* 2006; **367**: 482-488 [PMID: 16473125 DOI: 10.1016/s0140-6736(06)68180-4]

21 **Johnson HL**, Deloria-Knoll M, Levine OS, Stoszek SK, Freimanis Hance L, Reithinger R, Muenz LR, O'Brien KL. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. *PLoS Med* 2010; **7**: pii: e1000348 [PMID: 20957191 DOI: 10.1371/journal.pmed.1000348]

22 **Russell FM**, Carapetis JR, Burton RL, Lin J, Licciardi PV, Balloch A, Tikoduadua L, Waqatakirewa L, Cheung YB, Tang ML, Nahm MH, Mulholland EK. Opsonophagocytic activity following a reduced dose 7-valent pneumococcal conjugate vaccine infant primary series and 23-valent pneumococcal polysaccharide vaccine at 12 months of age. *Vaccine* 2011; **29**: 535-544 [PMID: 21044669 DOI: 10.1016/j.vaccine.2010.10.046]

23 **Russell FM**, Balloch A, Tang ML, Carapetis JR, Licciardi P, Nelson J, Jenney AW, Tikoduadua L, Waqatakirewa L, Pryor J, Byrnes GB, Cheung YB, Mulholland EK. Immunogenicity following one, two, or three doses of the 7-valent pneumococcal conjugate vaccine. *Vaccine* 2009; **27**: 5685-5691 [PMID: 19616498 DOI: 10.1016/j.vaccine.2009.06.098]

24 **Hull B**, Deeks S, Menzies R, McIntyre P. Immunisation coverage annual report, 2007. *Commun Dis Intell Q Rep* 2009; **33**: 170-187 [PMID: 19877535]

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ORIGINAL ARTICLE

Observational Study

Single institution experience with the Ladd's procedure in patients with heterotaxy and stage I palliated single-ventricle

Kurt D Piggott, Grace George, Harun Fakioglu, Carlos Blanco, Sukumar Saguna Narasimhulu, Kamal Pourmoghadam, Hamish Munroe, William Decampli

Kurt D Piggott, Grace George, Harun Fakioglu, Carlos Blanco, Sukumar Saguna Narasimhulu, Kamal Pourmoghadam, Hamish Munroe, William Decampli, the Heart Center at Arnold Palmer Hospital for Children, Pediatric Cardiac Intensive Care Medicine, Orlando, FL 32806, United States

Author contributions: Piggott KD, George G, Fakioglu H, Blanco C, Pourmoghadam K, Munroe H, Decampli W contributed to study conception and design; Piggott KD and George G contributed to data analysis and interpretation and writing of article; Narasimhulu SS, Munroe H and Decampli W contributed to editing reviewing and final approval of article.

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Correspondence to: Kurt D Piggott, MD, the Heart Center at Arnold Palmer Hospital for Children, Pediatric Cardiac Intensive Care Medicine, 92 W. Miller Street, MP307, Orlando, FL 32806, United States. kurt.piggott@orlandohealth.com
Telephone: +1-407-7662948
Fax: +1-321-8414260

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Abstract

AIM: To investigate and describe our current institutional management protocol for single-ventricle patients who must undergo a Ladd's procedure.

METHODS: We retrospectively reviewed the charts of all patients from January 2005 to March 2014 who were diagnosed with heterotaxy syndrome and an associated intestinal rotation anomaly who carried a cardiac diagnosis of functional single ventricle and were status post stage I palliation. A total of 8 patients with a history of stage I single-ventricle palliation underwent Ladd's procedure during this time period. We reviewed each patients chart to determine if significant intraoperative or post-operative morbidity or mortality occurred. We also described our protocolized management of these patients in the cardiac intensive care unit, which included pre-operative labs, echocardiography, milrinone infusion, as well as protocolized fluid administration and anticoagulation regimines. We also reviewed the literature to determine the reported morbidity and mortality associated with the Ladd's procedure in this particular cardiac physiology and if other institutions

have reported protocolized care of these patients.

RESULTS: A total of 8 patients were identified to have heterotaxy with an intestinal rotation anomaly and single-ventricle heart disease that was status post single ventricle palliation. Six of these patients were palliated with a Blaylock-Taussig shunt, one of whom underwent a Norwood procedure. The two other patients were palliated with a stent, which was placed in the ductus arteriosus. These eight patients all underwent elective Ladd's procedure at the time of gastrostomy tube placement. Per our protocol, all patients remained on aspirin prior to surgery and had no period where they were without anticoagulation. All patients remained on milrinone during and after the procedure and received fluid administration upon arrival to the cardiac intensive care unit to account for losses. All 8 patients experienced no intraoperative or post-operative complications. All patients survived to discharge. One patient presented to the emergency room two months after discharge in cardiac arrest and died due to bowel obstruction and perforation.

CONCLUSION: Protocolized intensive care management may have contributed to favorable outcomes following Ladd's procedure at our institution.

Key words: Congenital heart disease; Heterotaxy; Single-ventricle; Pediatrics; Ladd's procedure; Congenital heart disease

Core tip: Babies born with congenital heart disease consisting of a functional single-ventricle present a complicated subset of patients to care for. When these patients also have heterotaxy and an intestinal rotational anomaly combined with their heart defect, determining when and how to safely perform a Ladd's procedure is challenging for clinicians involved in their care. Having experienced practitioners involved and using protocolized care may help reduce surgical morbidity and mortality in these patients.

Piggott KD, George G, Fakioglu H, Blanco C, Narasimhulu SS, Pourmoghadam K, Munroe H, Decampli W. Single institution experience with the Ladd's procedure in patients with heterotaxy and stage I palliated single-ventricle. *World J Clin Pediatr* 2016; 5(3): 319-324 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i3/319.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i3.319

INTRODUCTION

Heterotaxy syndrome is a relatively rare phenomenon with an incidence of approximately 1 in 10000 live births. It accounts for about 3% of cases of congenital heart disease[1]. Heterotaxy is synonymous with "visceral heterotaxy" and "heterotaxy syndrome" and is defined as an abnormality where the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right access of the body. The heterotaxy syndrome is typically associated with complex cardiovascular malformations. These malformations can vary from relatively common defects such as ventricular septal defects to complex anatomy not amenable to complete repair and resultant single ventricle physiology[2].

Intestinal rotation and fixation abnormalities (IRA) are commonly associated with heterotaxy syndrome. Normal intestinal rotation and fixation occurs between days 32 and 56 in the human fetus[3]. IRA is a spectrum of disease that depends on the stage of intestinal rotation or fixation that was interrupted. IRA occurs in 40%-90% of children with heterotaxy syndrome[4,5]. Practice among institutions pertaining to IRA is extremely variable and ranges from observation and conservative management for asymptomatic patients to surgical intervention with a Ladd procedure early in life.

A Ladd procedure may be performed in patients with IRA in an attempt to reduce the risk of bowel ischemia and infarction. During the Ladd procedure, peritoneal bands (Ladd's bands) are divided, and the mesentery of the small bowel is widened. An appendectomy is performed and the bowel is rearranged to a nonrotated state with the small bowel on the right side of the peritoneal cavity and the colon on the left.

The decision of whether or not to perform an elective Ladd procedure in a patient with heterotaxy syndrome becomes more complicated when the patient has complex cardiac anatomy resulting in the need for single ventricle palliation. These patients are at risk for complications such as hypoxia, shunt thrombosis, bowel ischemia and coronary ischemia to name a few. This physiology may increase the risk of morbidity and mortality, particularly in the young infant age group. As such, procedures including major abdominal surgery carry an increased risk of complications and instability.

Our institutional approach to patients with heterotaxy sydrome, IRA and functional single ventricle has been to perform a Ladd procedure if: (1) there are signs of bowel obstruction or ischemia; or (2) there is feeding intolerance and the patient requires a gastrostomy or jejunostomy tube, then a Ladd procedure is performed at the same time.

Substantial morbidity and mortality has been reported in these complex patients[4-7]. Over a period of several years, we have attempted to protocolize as much as possible our pre-operative and post-operative approach to all stage I single ventricle palliated patients, in hopes of minimizing morbidity and mortality. We report our experience with 8 patients carrying a diagnosis of heterotaxy syndrome, IRA and functional single ventricle status post stage I palliation who underwent Ladd procedure at the time of nissen fundoplication and gastrostomy tube or jejunostomy tube placement. The purpose of this paper is to share our current protocol and experience as well as to

retrospectively determine if complications occurred during or after the Ladd's procedure.

MATERIALS AND METHODS

Following approval by the Arnold Palmer Medical Center institutional review board, we conducted a retrospective chart review. We searched our surgical database for all patients with heterotaxy syndrome and functional single ventricle who underwent a cardiac procedure at Arnold Palmer Hospital for Children between January 2005 and March 2014. For the subset of patients who were diagnosed with an IRA and underwent a Ladd procedure, we collected data including patient sex, age at the time of Ladd procedure, cardiac and segmental anatomy, type of gastrointestinal surgery, intraoperative or post-operative complications from the Ladd procedure and mortality associated with the procedure. We also reviewed each patient's hospital records and clinic notes to ascertain their most up to date feeding status, evidence of post-operative bowel obstruction, or need for further gastrointestinal (GI) procedures.

RESULTS

A total of 8 patients were identified with heterotaxy, IRA and functional single ventricle. All 8 patients had undergone first stage single ventricle palliation. Two patients underwent stenting of the ductus arteriosus. The remaining 6 patients underwent placement of systemic-pulmonary artery shunts. Four of the patients who underwent shunt placement also underwent repair of total anomalous pulmonary venous connection. Each of the 8 patients had an upper GI series with small bowel follow through confirming IRA. Two patients had modified barium swallows showing aspiration. Seven of the 8 patients underwent placement of gastrostomy tube as well as nissen fundoplication at the time of the Ladd procedure. The other patient underwent Roux-en-Y jejunostomy at the time of the Ladd procedure. None of these patients experienced intraoperative complications. One patient had mild postoperative hypotension upon immediate arrival to the cardiovascular intensive care unit, which was responsive to fluid resuscitation. One patient had transient oxygen desaturation upon arrival to the cardiovascular intensive care unit which was found to be mucous plugging and responded immediately to manual bag mask ventilation and suctioning. Neither of these events were considered complications of the procedure as neither of these events recurred and additionally, these can be seen as common, postoperative events in any patient undergoing a procedure.

All eight patients survived to discharge. One patient died as an outpatient. She presented 2 mo after discharge to the emergency department in cardiopulmonary arrest and was found to have bowel perforation and hemodynamic collapse, likely secondary to bowel obstruction. Six patients are currently free from bowel obstruction. One patient had continued feeding intolerance and had suspicion of partial bowel obstruction but was managed conservatively and is currently tolerating full feedings by gastrostomy tube and did not require additional surgery. One patient is feeding entirely per oral, three entirely by gastrostomy tube and the remaining 3 are fed by a combination of oral and gastrostomy tube. Table 1 shows the details for each of the 8 patients with heterotaxy syndrome.

DISCUSSION

Children born with complex cardiac anatomy resulting in a functional single ventricle present a challenging group of patients. Their unstable physiology and typically unbalanced circulation puts all single ventricle patients at risk for morbidity and mortality after stage Ⅰ palliation. This mortality has improved over the years, however it has still been reported between 10% and 25%[6,7]. Patients with heterotaxy syndrome and functional single ventricle have been reported to have a mortality rate as high as 41%[8]. For this reason, procedures and exposures to general anesthesia should be minimized.

Patients with heterotaxy syndrome have an incidence of IRA between 40% and 90%[4,5,9]. It is understood and agreed upon that patients with heterotaxy and IRA who develop feeding intolerance need immediate evaluation for IRA. However, there is no consensus on whether or not to evaluate asymptomatic patients with heterotaxy for IRA. Additionally, significant institutional variance remains on whether or not to perform an elective Ladd procedure if an IRA is discovered in an asymptomatic patient and if so, the appropriate timing of the procedure. This decision becomes even more complicated when the patient has a functional single ventricle and unbalanced circulation.

In 2013, Pockett *et al*[10] described their institutional experience of performing elective Ladd procedure in all heterotaxy patients with IRA. They reported a high rate of serious complications (57%) after Ladd procedure in patients with heterotaxy syndrome. They felt that it was likely the limited cardiopulmonary reserve that shunt-dependent and single-ventricle patients have that led to the high rate of complications[10].

In 2013, Sharma *et al*[11] reported significant morbidity and mortality in patients undergoing Ladd procedure both prior to and after stage Ⅰ palliation. Two patients had Ladd procedure prior to stage Ⅰ palliation. One had recurrent necrotizing enterocolitis and died. Two patients had Ladd procedure after stage Ⅰ palliation, both of whom developed shunt thrombosis, one of which died. They also reported no mortalities in 5 asymptomatic patients who underwent elective Ladd procedure after second-stage palliation.

Our programmatic approach to heterotaxy syndrome with functional single ventricle is to evaluate for IRA in all patients with heterotaxy. However, we have chosen to intervene surgically only in those patients who develop signs of bowel obstruction or feeding intolerance. All 8 patients described above had feeding

Table 1 Heterotaxy patients

Reason for GI surgery	Studies	Segmental anatomy	Cardiac anatomy	Visceral abnormality	Cardiac procedure	GI surgery	Age at ladd	Intra/postop Complications	Outcome	Current GI status
Poor PO intake, severe GE Reflux	UGI/SBFT	I, D, D	Unbalanced CAVC, PA, LSVC	IRA	PDA stent	Ladd, Roux-en-Y jejunostomy	6 wk	None	Alive	At 5 yr had jejunal perforartion resulting in laparotomy and Nissen. Feeds PO and Gtube
Poor PO intake, severe GE Reflux	UGI/SBFT	A, D, D	Unbalanced CAVC, TAPVR, PA, RPA stenosis	IRA	3.5 mm central shunt placement, TAPR repair, RPA plasty	Ladd, Nissen/ Gtube	6 wk	None	Alive	No obstruction or GI surgeries. Feeds PO and Gtube
Severe GE Reflux, Vocal cord paralysis with aspiration	UGI/SBFT Mod. Barium Swallow	I, D, S	Dextrocardia, TA, Unbalanced CAVC, Coarctation	IRA	Norwood with 3.5 mm Modified BT shunt	Ladd, Nissen/ Gtube	8 wk	None	Alive	No obstruction or GI surgeries. Gtube is removed and now eats entirely PO
Poor PO intake, severe GE Reflux	UGI/SBFT	A, L, D	Unbalanced CAVC, TAPVR, PA	IRA	3.5 Modified BT shunt, TAPVR repair, PA plasty	Ladd, Nissen/ Gtube	8 wk	None	Outpatient death from bowel perforation	N/A
Poor PO intake, TE Fistula repair, severe GE Reflux	UGI/SBFT	S, D, D	DORV, right atrial isomerism, BLSVC, CAVC, PS	IRA	PDA stent	Ladd, Nissen/ Gtube	5 wk	None	Alive	No obstruction or further GI surgeries. Gtube fed only
Poor PO feeding, GE Reflux,	UGI/SBFT	I, D, D	Dextrocardia, Unbalanced CAVC, TAPVR, PA	IRA	3.5 mm central shunt, TAPVR repair, PA plasty	Ladd, Nissen/GT	6 wk	None	Alive	No obstruction or GI surgeries. Feeds PO and Gtube
Poor PO intake, feeding intolerance, GE Reflux	UGI/SBFT	I, D, D	Unbalanced CAVC, Pulmonary atresia	IRA	3.5 mm Modified BT shunt	Ladd, Nissen/ Gtube	6 wk	None	Alive	No obstruction or GI surgeries, All feeds *via* Gtube
Poor PO feeding, GE reflux, aspiration	UGI/SFT, Modified barium swallow	A, L, L	Unbalanced CAVC, TAPVR, Pulmonary atresia	IRA	4.0 mm Modified BT shunt, TAPVR repair	Ladd, Nissen/ Gtube	5 wk	None	Alive	No obstruction or GI surgery. All feeds *via* Gtube

PA: Pulmonary atresia; BT: Blaylock-Taussig; CAVC: Complete atrioventricular canal; TAPVR: Total anomalous pulmonary venous return; GI: Gastrointestinal; GT: Gastrostomy tube; GE: Gastroesophageal; PO: Per oral; TA: Tricuspid atresia; IRA: Intestinal rotation and fixation anomaly; UGI/SBFT: Upper GI with small bowel follow through; DORV: Double outlet right ventricle.

intolerance and were found by upper GI series with small bowel follow through to have IRA. All patients had a Ladd procedure at the time of gastrostomy or jejunostomy tube placement. As a program, we maintain a philosophy of not performing prophylactic Ladd procedures in asymptomatic patients and we would prefer to wait until after the stage two palliation to perform a Ladd's procedure, when the circulation is more balanced. However, all 8 patients had feeding difficulties resulting in the need for an alternate source of enteral feeding. We have maintained the philosophy that if the patient requires GI surgery for an alternate feeding source that we will perform the Ladd's procedure at that time. To date all patients have required an alternate feeding source and therefore underwent successful Ladd's at that time. To date we have not encountered any patients with heterotaxy syndrome, functional single-ventricle and IRA who developed bowel obstruction requiring urgent Ladd procedure.

At our institution over a period of several years, we have protocolized the pre-operative and post-operative management of patients with functional single-ventricle, status post stage I palliation who are to undergo general anesthesia for any procedure. All patients have preopera-

tive labs performed to evaluate for signs of infection and to monitor hemoglobin, assuring adequate oxygen carrying capacity pre-operatively. All patients get a pre-operative echocardiogram 1-2 d prior to the procedure to evaluate shunt patency and systolic function of the systemic ventricle and all patients regardless of echocardiographic findings, are placed on a milrinone infusion at a dose of 0.5 mg/kg per minute 24 h prior to the procedure and it is continued during the surgery and for 24 h following surgery in an attempt to support the ventricular function during the stress of anesthesia and a major gastrointestinal surgery. Aspirin is not stopped prior to surgery. We have chosen to accept some risk of bleeding in order to have continued antiplatelet affect and avoid any period without some anticoagulation affect in hopes of preserving shunt patency. All patients receive aggressive intraoperative and postoperative fluid resuscitation in addition to maintenance fluids regardless of hemodynamic data to replace assumed fluid losses from gastrointestinal surgery and to prevent intravascular depletion in hopes of minimizing risk of shunt thrombosis. All patients receive a minimum of one 20 mL/kg fluid bolus upon arrival to the cardiac intensive care unit. All patients are placed on postoperative antibiotics for a minimum of 48 h. Anesthesia is performed by experienced cardiac anesthesiologists. The surgery is performed by experienced pediatric surgeons and the patients recover in our dedicated cardiovascular intensive care unit with 24 h in-house attending physician coverage.

While there is still no consensus on the need for evaluation of heterotaxy patients for the presence of IRA and the need for elective Ladd procedure in asymptomatic patients, there will continue to be a need for Ladd procedure in patients with heterotaxy syndrome. As an institution, we do agree with previous reports that suggest waiting until completion of the second stage of palliation to undergo elective Ladd's procedure. However, we feel that if a gastrointestinal surgery, such as gastrostomy tube, is necessary during the stage I palliated phase, that our practice of doing a Ladd's procedure at the same time is acceptable.

It is important to realize that Ladd procedure does not guarantee that a patient will free of partial or complete bowel obstruction later in life as is suspected in our only patient who died following bowel perforation as an outpatient 2 mo after discharge.

While the 8 patients we have presented is a small number, we believe that it does show that a protocolized pre-operative and post-operative management strategy may improve morbidity and possibly survival in this complex patient population. This subset of patients is extremely challenging and each institution must weigh the risk and benefit of the procedure with their own experiences and resources available to care for these patients. While our protocol and results appear satisfactory, we fully recognize that this is a very small group of patients and to say that this strategy is entirely safe and that it would work for every program is not possible. The combination of heterotaxy syndrome, functional single-ventricle and IRA describes a relatively unique and rare subset of patients. For this reason, further research containing larger cohorts of patients in this field is needed and will likely require data sharing and multi-institution studies.

Our paper does have significant limitations including the fact that it is a retrospective, single institution review and additionally it contains a small cohort of patients.

COMMENTS

Background

Heterotaxy, while rare is often associated with heart defects. When these defects result in single-ventricle physiology and are associated with intestinal rotational anomalies. A Ladd's procedure can carry a high rate of morbidity and mortality in the complex subset of patients and should be undertaken with caution and with the appropriate expertise to care for these patients.

Research frontiers

To our knowledge, no paper has described a protocolized approach to the care of this complicated care of patients undergoing a Ladd's procedure.

Innovations and breakthroughs

The major conclusion from this paper is that with an experienced providers and protocolized approach to the Ladd's procedure in this patient population, morbidity and mortality may be reduced.

Applications

With the current literature reporting high rates of morbidity and mortality when performing the Ladd's procedure in stage I palliated, functional single-ventricle patients, a protocolized approach may improve outcomes.

Terminology

Heterotaxy is defined as an abnormality where the internal thoraco-abdominal organs demonstrate abnormal arrangement across the left-right access of the body.

Peer-review

An interesting article that provides a different perspective in the management of patients with heterotaxy, intestinal rotation anomaly and single-ventricle undergoing the Ladd's procedure.

REFERENCES

1 **Hoffman JI**, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002; **39**: 1890-1900 [PMID: 12084585 DOI: 10.1016/S0735-1097(02)01886-7]

2 **Jacobs JP**, Anderson RH, Weinberg PM, Walters HL, Tchervenkov CI, Del Duca D, Franklin RC, Aiello VD, Béland MJ, Colan SD, Gaynor JW, Krogmann ON, Kurosawa H, Maruszewski B, Stellin G, Elliott MJ. The nomenclature, definition and classification of cardiac structures in the setting of heterotaxy. *Cardiol Young* 2007; **17** Suppl 2: 1-28 [PMID: 18039396 DOI: 10.1017/S1047951107001138]

3 **Langman J**, Sadler T. Langman's medical embryology. 9th ed. Philadelphia: Lippincott Williams & Wilkins, 2003

4 **Pockett CR**, Dicken BJ, Rebeyka IM, Ross DB, Ryerson LM. Heterotaxy syndrome and intestinal rotation abnormalities: a survey of institutional practice. *J Pediatr Surg* 2013; **48**: 2078-2083 [PMID: 24094961 DOI: 10.1016/j.jpedsurg.2013.03.001]

5 **Nakada K**, Kawaguchi F, Wakisaka M, Nakada M, Enami T, Yamate N. Digestive tract disorders associated with asplenia/polysplenia syndrome. *J Pediatr Surg* 1997; **32**: 91-94 [PMID: 9021579 DOI: 10.1016/S0022-3468(97)90103-2]

6 **Azakie T**, Merklinger SL, McCrindle BW, Van Arsdell GS, Lee KJ, Benson LN, Coles JG, Williams WG. Evolving strategies and improving outcomes of the modified norwood procedure: a 10-year single-institution experience. *Ann Thorac Surg* 2001; **72**: 1349-1353 [PMID: 11603459 DOI: 10.1016/S0003-4975(01)02795-3]
7 **Forbess JM**, Cook N, Roth SJ, Serraf A, Mayer JE, Jonas RA. Ten-year institutional experience with palliative surgery for hypoplastic left heart syndrome. Risk factors related to stage I mortality. *Circulation* 1995; **92**: II262-II266 [PMID: 7586421]
8 **Song J**, Kang IS, Huh J, Lee OJ, Kim G, Jun TG, Yang JH. Interstage mortality for functional single ventricle with heterotaxy syndrome: a retrospective study of the clinical experience of a single tertiary center. *J Cardiothorac Surg* 2013; **8**: 93 [PMID: 23591028 DOI: 10.1186/1749-8090-8-93]
9 **Ladd WE**. Surgical diseases of the alimentary tract in infants. *N Engl J Med* 1936; **215**: 705-710 [DOI: 10.1056/NEJM193610152151604]
10 **Pockett CR**, Dicken B, Rebeyka IM, Ross DB, Ryerson LM. Heterotaxy syndrome: is a prophylactic Ladd procedure necessary in asymptomatic patients? *Pediatr Cardiol* 2013; **34**: 59-63 [PMID: 22644418 DOI: 10.1007/s00246-012-0385-6]
11 **Sharma MS**, Guleserian KJ, Forbess JM. Ladd's procedure in functional single ventricle and heterotaxy syndrome: does timing affect outcome? *Ann Thorac Surg* 2013; **95**: 1403-1407; discussion 1407-1048 [PMID: 23434253 DOI: 10.1016/j.athoracsur.2012.11.018]

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ORIGINAL ARTICLE

Observational Study

Significant variations in nutritional supplementation amongst neonates in the United Kingdom

Morris Gordon, Sahira Isaji, Fiona Tyacke

Morris Gordon, Sahira Isaji, Fiona Tyacke, Department of Paediatric, Blackpool Victoria Hospital, Preston FY3 8NR, United Kingdom

Morris Gordon, School of Medicine and Dentistry, University of Central Lancashire, Preston PR1 2HE, United Kingdom

Author contributions: Gordon M conceived the study, supported the analysis and led the write up; Isaji S and Tyacke F jointly performed the data collection, analysis and added to the write up; all authors approved the final manuscript.

Institutional review board statement: The study was reviewed by the local Research and Development/audit Department.

Informed consent statement: Obtained by all participants before telephone participation, all information recorded was anonymous.

Conflict-of-interest statement: Isaji S and Tyacke F have none to declare; Gordon M has received travel grants and educational grants from various companies to attend scientific and educational meetings, including Danone/nutricia, Abbott, Ferring, Casen Fleet, Vifor, Clinova, Tillots, Warner Chiclott, Norgine and Biogaia. They had no involvement in this or any other study.

Data sharing statement: Data is available on request from the author morris@betterprescribing.com.

Manuscript source: Invited manuscript

Correspondence to: Dr. Morris Gordon, School of Medicine and Dentistry, University of Central Lancashire, HA118, Harrington building, Preston PR1 2HE, United Kingdom. morris@betterprescribing.com
Telephone: +44-7816-687791

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Abstract

AIM: To ascertain United Kingdom adherence to European society of Paediatric Gastroenterology, Hepatology and Nutrition guidance (ESPGHAN).

METHODS: A national cross sectional questionnaire study of neonatal units across England was completed between January and March 2014. All 174 units in the country were attempted to be contacted to complete a telephone survey. This included all level 1, 2 and 3 units. They were initially contacted by phone and asking any senior member of the team about their current practice and procedures. The first ten telephone interviews were completed with two researchers present to ensure consistency of approach. If no response was received or no details were available, one further attempt was made to contact the unit. The results were recorded in a proforma and then collated and entered into a spreadsheet for analysis. Comparison to United Kingdom adherence to ESPGHAN guidance was completed.

RESULTS: Response rate was 53%. There was variation in use of all supplements. The survey collected data from 91 neonatal units (53% response rate). It was found that 10% of neonatal units had no fixed policy on supplements. The protocols regarding supplementation involved predominantly folic acid, vitamin A, vitamin D

and iron, with much variation in doses and regimens. The criteria for prescribing supplements was largely based on age (47%) with only 7% using a weight targets to initiate supplements. Summary data regarding the appropriateness of each nutritional supplement for a variety of different weights are presented, as well as comparison to ESPGHAN guidance which suggests issues with both underdoing of Breast Fed infants and overdosing of infants on several artificial formulas which already contain significant amounts of these nutritional elements.

CONCLUSION: There is significant heterogeneity in neonatal policies when prescribing supplements to neonates. National policies which take international guidance into account are recommended.

Key words: Neonatal; Nutritional additives; Preterm nutrition; Term nutrition; Iron

Core tip: Nutritional supplementation in neonates is common in neonatal units, but there is no clear United Kingdom guidance. This study set out to ascertain United Kingdom practice with a national cross-sectional study with reference to European society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) nutritional guidance. Fifty-five percent of the 174 units in the country were contacted. There was variation in use of all supplements. Comparison to ESPGHAN guidance suggests issues with both underdoing of Breast Fed infants and overdosing of preterm infants on several artificial formulas which already contain significant amounts of nutritional elements. National policies which take international guidance into account are recommended, with similar research needed in other countries.

Gordon M, Isaji S, Tyacke F. Significant variations in nutritional supplementation amongst neonates in the United Kingdom. *World J Clin Pediatr* 2016; 5(3): 325-329 Available from: URL: http://www.wjgnet.com/2219-2808/full/v5/i3/325.htm DOI: http://dx.doi.org/10.5409/wjcp.v5.i3.325

INTRODUCTION

Nutritional needs of both preterm and term neonates are not the same as older children and are subject to rapid changes. A number of nutritional supplements have been studied in relation to prematurity, notably vitamin A, D, iron and folic acid - these form the basis of supplementation recommendations in neonates. Preterm infants have higher nutrient requirements than term infants but inappropriate or absent supplementation can be detrimental to their health[1]. Preterm infants have a low vitamin A status at birth[1]. Evidence shows vitamin A supplement significantly reduces the risk of chronic lung disease and reduces mortality, however excessive levels can lead to symptoms[2].

Preterm infants are susceptible to developing iron deficiency, particularly more premature infants and those being exclusively breastfed without supplementation. As iron plays a role in various tissue functions this would support the need supplementation in preterm infants[3]. Vitamin D is needed for bone health and low levels can cause rickets and seizures secondary to low calcium[4]. Folic acid is used for the prevention of anaemia of prematurity. Levels are high at birth but fall rapidly in the first few weeks of life more notably in the lowest birthweight neonates[5].

Nutritional supplements are almost ubiquitous for infants admitted to United Kingdom neonatal units. Compositions of vitamin supplements vary, for example, Dalavit and Abidec are both commonly used, but Dalavit contains nearly 4 times the amount of vitamin A[1] as Abidec. Doses of supplements should be adjusted according to the type of milk the infant is receiving. Breast milk is best for preterm and low birth weight babies - better long term health outcomes have been well documented, but higher doses of supplements or the addition of fortifiers is required in order to reach the recommended daily intake of vitamins and minerals.

There are currently no national guidelines on nutritional supplementation, but local protocols exist based on growth and nutrition studies and guidance provided by expert groups[6]. The aim of this study was to establish current practices in neonatal supplementation in neonatal units across England[6] and to compare these dosing regimens to guidance provided by European society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[7].

MATERIALS AND METHODS

A national cross sectional questionnaire study of Neonatal units across England was conducted between January and March 2014[6]. This included all level 1, 2 and 3 units. They were initially contacted by phone and asking any senior member of the team about their current practice and procedures. Eligible staff included senior nurses, advanced neonatal nurse practitioners and senior medical staff.

Firstly, the existence of a local policy was established. Then, details of the supplements used, their brands, dosing, criteria for initiation and the impact of gestational age, weight and feeding type were recorded.

The first ten telephone interviews were completed with two researchers present to ensure consistency of approach and then further interviews were conducted by either researcher. If no response was received or no details were available, one further attempt was made to contact the unit.

The results were recorded in a proforma and then

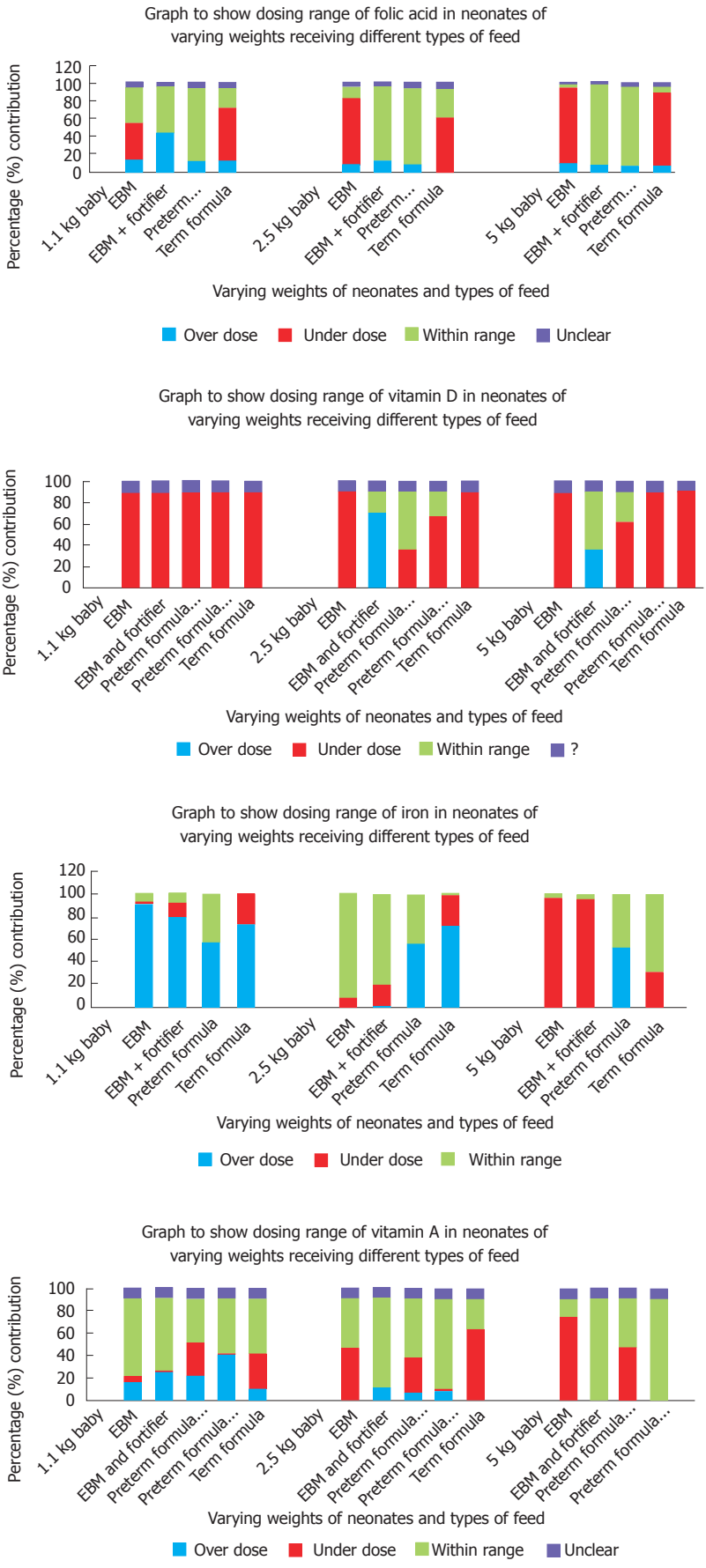

Figure 1 Dosing range results for various nutritional supplements. EBM: Expressed breast milk.

Table 1 Nutritional content of breast milk and artificial formulae (brand names of United Kingdom formula preparations used)[5]

Type of feed (based on 180 mL of feed)	Vitamin A (μgRE)	Vitamin D (μg)	Folic acid (μg)	Iron (mg)
EBM	104	0.07 μg/kg per day	9	0.126
EBM + 2 × 2.2 g Nutriprem (C and G) Breast Milk Fortifier	522	9.1 μg/kg per day	63	Neg
EBM + 2 × 2 g SMA BMF	486	13.68 μg/kg per day	54	Neg
SMA gold Prem 1	333	6.1 μg/kg per day	52	2.5
SMA Gold Prem 2	180	2.7 μg/kg per day	27	2.16
C and G Nutriprem 1	650	5.4 μg/kg per day	63	2.9
C and G Nutriprem 2	180	3.06 μg/kg per day	36	2.16
C and G 1	97.2	2.16 μg/kg per day	23.4	0.954
Aptamil 1	97.2	2.16 μg/kg per day	23.4	0.954
SMA 1	119	2.2 μg/kg per day	19.8	1.2
HiPP 1	126	2.16 μg/kg per day	18	0.9
Neocate LCP	100.8	2.16 μg/kg per day	15.84	1.8
ESPGHAN recommendation	400-1000 μg RE/ kg per day	20-25 μg/d	35-100 μg/kg per day	2-3 mg/kg per day (from 2-6 wk)

EBM: Expressed breast milk.

collated and entered into a spreadsheet for analysis. Comparison to ESPGHAN guidance was completed.

RESULTS

The survey collected data from 91 neonatal units (53% response rate), with a representative sample of hospital size and level of neonatal care achieved[6]. It was found that 10% of neonatal units had no fixed policy on supplements. The protocols regarding supplementation involved predominantly folic acid, vitamin A, vitamin D and iron.

In regards to folic acid, when supplementing expressed breast milk (EBM), 36% of hospitals prescribed 50 μg of folic acid daily, whilst 37% of units prescribed no folic acid. For remaining units, the dose varied from 50 μg daily to 1 mg weekly of folic acid.

Similar results were obtained when looking at the vitamins A and D data. Dalavit and Abidec doses varied in each hospital. Two units had no fixed regime and was based on which supplement (Dalavit or Abidec) was available at the time of prescribing.

When considering iron supplementation[7], over 65% of units prescribed iron supplementation with various feeds types whereas 27% did not supplement with iron at all. Doses across the different units varied between 0.5 mL sytron once daily to 2.5 mL twice daily. Forty-six percent of units recognised that no additional iron supplementation is needed for babies receiving preterm formula. The criteria for prescribing supplements was largely based on age (47%) with only 7% of units interviewed using a weight based set of criteria to initiate supplements. A small number of hospitals had no fixed criteria, and certain hospitals (24%) used both age and weight.

Summary data regarding the appropriateness of each nutritional supplement for a variety of different weights are presented in Figure 1. Table 1 demonstrates the amount of each of the supplements that are delivered purely through feeding with breast milk, fortified breast milk and with a variety of artificial milks.

DISCUSSION

Dosing of all nutritional additives varied greatly across the country[6]. Only a small proportion of units actually achieved dosing within ESPGHAN recommended limits in all supplements[7]. More than 80% of units are in-fact overdosing smaller infants iron potentially causing toxicity.

In general, overdosing of supplements was seen in smaller babies. Larger babies are more commonly receiving doses within the recommended limits. However, the criterion was seen to be based on either birth weight, gestational age or both. ESPGHAN recommends that the infant's dry weight should be used when calculating the dose of supplements[5]. This would mean weighing the baby on a regular basis and adjusting doses accordingly. This practice was not being done in any unit surveyed; doses calculated from birth seem to remain static until discontinued.

Whilst there is clearly no national policy on this issue, there are local networks that carry guidance. Whilst it was outside the scope of this study to investigate these in great detail, the local network in Greater Manchester included a total of 8 units surveyed. Not only did the dose of vitamin A vary but units were also using different brands. Supplementing with folic acid was completely absent in one hospital but the use of iron was consistent. This highlights that current practice is clearly leading to massive variations in both strategy and outcome for babies. With such wide variation in dosing and differing criteria for initiation there is great potential for causing harm to infants, from either insufficient or excessive supplementation. Consistent dosing and one policy for all feed types are also not ideal and can put smaller babies in particular at risk.

Table 1 highlights certain dosing issues that could become tenants of a national policy. It is clear that neonates on preterm formula generally do not need

further vitamin A, folic acid or iron supplementation, but require vitamin D. Neonates on EBM will require all additional supplementation, but those on fortifier will only require iron supplements. It seems that iron supplementation is not indicated for any babies on artificial formulas, as changing requirements have been considered in the changing constituents of preterm *vs* term formulations. It is also important to assess whether the supplements need to continue on discharge as both requirements and content of formulas change with age.

These principles and the huge variation in practical prescribing that have been highlighted by this study support the need for a standardised supplementation regime based on available evidence, with arrangements to update regular to consider changes in artificial formulas and fortification. This will allow the nutritional needs of infants to be met in an appropriate and safe manner. Further research is indicated to assess if similar problems exists in other countries.

There is significant heterogeneity in neonatal policies when prescribing supplements to neonates. National policies which take international guidance into account are recommended. Further research is indicated to assess if similar problems exists in other countries.

COMMENTS

Background

Nutritional requirements amongst preterm and term neonates differ from older infants and change rapidly. Preterm infants have higher nutrient requirements than term infants but inappropriate or absent supplementation can be detrimental to their health.

Research frontiers

There are currently no national guidelines on nutritional supplementation, although there is international guidance from ESPGHAN.

Innovations and breakthroughs

This study confirms that despite international guidance that is evidence informed, practice across the country does not align to this or any prescribed guidance. Indeed, practice varies significantly and this potential means neonates may be under or overdosing on supplements.

Applications

It is advised that readers consider the evidence base of their local guidance and how this compares to national and international guidance.

Terminology

ESPGHAN: European society of Paediatric Gastroenterology, Hepatology and Nutrition.

Peer-review

In the paper, the authors present a useful and interesting study regarding nutritional supplementation in preterm babies in the United Kingdom.

REFERENCES

1 **Larmour K**, Shaw V. Nutrition: enteral nutrition for the preterm infant. 2016. Available from: URL: http//www.gosh.nhs.uk/health-professionals/clinical-guidelines/nutrition-enteral-nutrition-preterm-infant

2 **Mactier H**, Weaver LT. Vitamin A and preterm infants: what we know, what we don't know, and what we need to know. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**: F103-F108 [PMID: 15724031 DOI: 10.1136/adc.2004.057547]

3 **Rao R**, Georgieff MK. Iron therapy for preterm infants. *Clin Perinatol* 2009; **36**: 27-42 [PMID: 19161863 DOI: 10.1016/j.clp.2008.09.013]

4 **Baker RD**, Greer FR. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). *Pediatrics* 2010; **126**: 1040-1050 [PMID: 20923825 DOI: 10.1542/peds.2010-2576]

5 **Roberts PM**, Arrowsmith DE, Rau SM, Monk-Jones ME. Folate State of Premature Infants. *Arch Dis Child* 1969; **44**: 637-642

6 **Gordon M**, Isaji S, Karlsen F. Nutritional supplementation amongst preterm and term neonates. Proceedings of the 48th annual meeting of the European society of Paediatric gastroenterology, hepatology and nutrition. 2015-05-06. Available from: URL: http//espghan.org/uploads/media/ESPGHAN_A4_Abstract_2015_v2.pdf

7 **Agostoni C**, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, Domellöf M, Embleton ND, Fusch C, Genzel-Boroviczeny O, Goulet O, Kalhan SC, Kolacek S, Koletzko B, Lapillonne A, Mihatsch W, Moreno L, Neu J, Poindexter B, Puntis J, Putet G, Rigo J, Riskin A, Salle B, Sauer P, Shamir R, Szajewska H, Thureen P, Turck D, van Goudoever JB, Ziegler EE. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2010; **50**: 85-91 [PMID: 19881390 DOI: 10.1097/MPG.0b013e3181adaee0]

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ORIGINAL ARTICLE

Observational Study

Hypothesis on supine sleep, sudden infant death syndrome reduction and association with increasing autism incidence

Nils J Bergman

Nils J Bergman, School of Child and Adolescent Health, University of Cape Town, Rondebosch 7700, South Africa

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Correspondence to: Dr. Nils J Bergman, MB ChB, MPH, MD, School of Child and Adolescent Health, University of Cape Town, Private Bag X3, Rondebosch 7700, South Africa. nils@ninobirth.org
Telephone: +27-21-5315819
Fax: +27-21-5315819

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Abstract

AIM: To identify a hypothesis on: Supine sleep, sudden infant death syndrome (SIDS) reduction and association with increasing autism incidence.

METHODS: Literature was searched for autism spectrum disorder incidence time trends, with correlation of change-points matching supine sleep campaigns. A mechanistic model expanding the hypothesis was constructed based on further review of epidemiological and other literature on autism.

RESULTS: In five countries (Denmark, United Kingdom, Australia, Israel, United States) with published time trends of autism, change-points coinciding with supine sleep campaigns were identified. The model proposes that supine sleep does not directly cause autism, but increases the likelihood of expression of a subset of autistic criteria in individuals with genetic susceptibility, thereby specifically increasing the incidence of autism without intellectual disability.

CONCLUSION: Supine sleep is likely a physiological stressor, that does reduce SIDS, but at the cost of impact on emotional and social development in the population, a portion of which will be susceptible to, and consequently express autism. A re-evaluation of all benefits and harms of supine sleep is warranted. If the SIDS mechanism proposed and autism model presented can be verified, the research agenda may be better directed, in order to further decrease SIDS, and reduce autism incidence.

Key words: Autism; Autism spectrum disorder; Incidence; Prevalence; Prone sleep; Sudden infant death syndrome; Supine sleep; Time trends

Core tip: An earlier article presents evidence that supine sleep is a stressor, with sympathetic arousal that protects infants with defects in auto-resuscitation from sudden infant death syndrome. This article argues that a possible side-effect in the population being subjected to supine sleep is an increase in the expression of features contributing to diagnosis of autism spectrum disorder. In a literature search, five countries were identified (Denmark, United Kingdom, Australia, Israel, United States) with published time trends of autism, and with change-points coinciding with supine sleep campaigns. The stressor hypothesis for both conditions are amenable to testing, a better understanding of both is likely to improve outcomes.

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INTRODUCTION

Supine sleep campaigns have successfully achieved global reductions in sudden infant death syndrome (SIDS), which is well documented in 13 countries[1]. In all these countries the reduction was fairly immediate and in proportion to the population uptake of supine sleep following the public health messages. Reductions achieved a plateau, somewhat higher in the United States than in Scandinavia[2]. Continued intensive supine sleep messages have not lowered mortality further. Indeed, in the United States unexplained infant deaths appear to have increased[3]. The underlying mechanism for SIDS has not been explained, nor the mechanism whereby prone sleep exerts a potentially harmful effect. That prone sleep is harmful has indeed been the assumption, since the association was so clear.

This author has recently presented a hypothesis for the mechanisms of SIDS and the protective mechanism of supine sleep[4]. Briefly, this hypothesis elaborates on the Triple Risk Model for SIDS[5], the three aspects being an underlying vulnerability, a critical developmental period, and an exogenous stressor or risk factor. The key element of this model is that there is an underlying defect: The great majority of SIDS cases have identified brainstem abnormalities, which have not yet been found in controls[5,6]. This author proposes that these defects are specific to various stages of auto-resuscitation[7], and it is the failure of these which is the proximal or immediate cause of SIDS. Tobacco specifically augments defects in the gasping mechanism that initiates auto-resuscitation[8]. However, at an intermediate level of causation, auto-resuscitation is a necessary response to "adverse autonomic events" (AAE), whereby the autonomically immature organism responds in a primitive reptilian autonomic defence style, through a purely parasympathetic discharge orchestrated by the ventrolateral periaqueductal gray matter[9]. This is not compatible with mammalian physiology, therefore a robust auto-resuscitation mechanism is activated. Distal mechanisms include those that induce the AAEs, or conversely reduce them, along with the critical period and the risk factors of the Triple Risk Model. In healthy infants without defect, such AAE's appear to be common, and auto-resuscitation is robust. REM sleep processes negative emotions[10], and is likely the key period of SIDS risk[11,12] with increasing frequency of AAEs. In SIDS subjects, neural gliosis suggests that there have been repeated episodes of "near-misses" with hypoxic damage, prior to a lethal event[13]. It is possible that the same defects in serotonin metabolism identified in SIDS cases may contribute also to sleep disruption, increased REM sleep and decreased quiet sleep has been documented in such cases. Further, serotonin is also involved in anxiety and autonomic arousal[14], which may contribute further to increased AAE.

The association with prone sleep has made it the focus of research as to mechanisms of harm. No such harmful effects have been ascertained. This author argues from a biologically based developmental paradigm, that prone sleep is in fact the normal and healthy form of sleep[4], as a near universal mammalian phenomenon (exceptions include bats and sloths). Supine sleep in human infants qualifies as a stressor in a number of respects, primarily in producing a raised level of state organisation, and autonomic arousal[4]. This is indeed protective for such infants that have a brainstem defect, the effect may be due to decreased frequency of REM sleep, but perhaps more through an element of sympathetic autonomic stressor arousal, that counteracts the primitive parasympathetic dissociation defence mechanism[4].

The defect has not been found in post-mortem control cases[6], and SIDS qualifies as a "rare disease"[15]. The lethality of the defect is clearly not absolute, otherwise it would not be responsive to supine sleep. Conjecture can be based on existing data: in the United States neonatal mortality has halved, this would fit a population with a defect prevalence of 1.0/1000 with a 50% lethality. Sweden had a mortality around 1.0/1000, this has fallen to 0.25/1000; perhaps a 5/1000 defect prevalence with a 20% lethality reduced to 5% by supine sleep. The number needed to treat from such a "treatment" is high, perhaps above 1000. Clearly, current information does not allow an exact figure, but this is likely the order of magnitude, or else controls with defect would be found.

Consideration should then be given to potential side-effects of such an intervention applied to a whole population. Plagiocephaly was identified early[16], occurring in 1 of 60 supine sleeping infants, but will only

rarely have long lasting major impact. More importantly, supine sleep in the first months of life leads to delayed motor development at 6 mo and up to a year[4,17]. Recent developments in epigenetics and developmental neuroscience have relevance here. Prolonged stressor effects result in elevated cortisol levels that mediate gene methylation changes during sensitive periods of early development. "Perinatal life is a critical time for DNA methylation and for susceptibility to environmental factors"[18], methylation generally down-regulates genes, with adverse effects[18]. Sleep cyclicity is another factor essential for the development of healthy neuronal circuits[19]. Supine sleep may therefore have two separate mechanisms that disrupt early development, as evidenced by delayed motor development.

The first two months of life are a critical period for socio-emotional development[20]. This entails neural circuitry from the amygdala and associated limbic structures (emotional brain) to the medial and orbito-prefrontal cortex and executive function, also called the social brain[20]. The establishment of early resilience requires that social oxytocin circuits are connected also to reward-related dopamine circuits[21], a likely consequence of early bonding and secure attachment. A predictable consequence of such disruption is autism spectrum disorder (ASD), from here just "autism". Autism has recently been redefined in the DSM-5[22], encompassing persistent deficits in social communication and interaction, along with restricted and repetitive patterns of behaviour, beginning in early childhood and impairing everyday functioning. The emotional social deficit has been attributed to methylation of oxytocin receptors[18,23], and repetitive behaviours may be attributable to dopamine pathway disruption[24,25].

There has been extensive debate in the literature, with some arguing that the increase in autism is due to diagnostic changes and other factors[26,27]. These include methodological variations in conducting surveys[26,28], definitions of autism displaying variability[29] (including new definition in DSM-5, predicted by some to decrease the identified incidence[30,31], or make little difference[32-34]), broadening of diagnostic concepts[27], increased awareness[35-37], diagnostic substitution[38,39], and altered ranking of co-morbidities[28,40]. This debate has led to some relevant reflection: Hrdlicka and Dudova[41] argue there is a need for a "broader model of social disorders". While "autism" as a diagnosis may be welcomed by parents seeking economic support for care of a challenged child, autism could be seen as a smaller piece of a broader group of "social inhibition disorders"[41], all of which require support without discrimination[28,40,42].

The above notwithstanding, "a significant portion of the time trend remains unexplained"[43], an actual increase cannot be ruled out[43-47]. Keyes *et al*[48] analysed Californian data by birth cohorts, showing a consistent increase over time, with no evidence of an characteristic factor contributing to increase. The Autism and Developmental Disabilities Monitoring Network (ADDM)[49] likewise reports on birth cohorts, using a standardised approach in case finding and diagnosis for self-selected sites in the United States, incidence has risen from 6.6 to 14.7 (1994 to 2002 birth cohorts).

The hypothesis presented in this paper assumes that a portion of the increased incidence of autism is real, and proposes that supine sleep is contributing to that real increase. Since supine sleep campaigns have been introduced in many countries, with measurable change in infant sleeping position in the community, such change should according to this hypothesis be reflected in change points in the incidence of autism, attributable to "change in risk factor prevalence"[50]. Further, only susceptible infants will express such autism, therefore an incidence plateau should be achieved within a time period that matches the sleeping behaviour change in the community. Establishing this requires accurate data based on birth cohorts. Most cases are believed to be diagnosed by the age of 8 years[49], although current trends do show that additional cases are diagnosed in the teen years[51].

MATERIALS AND METHODS

A literature search was undertaken for published incidence or prevalence data on autism for countries with clear dates for supine sleep campaigns, and with time line series that straddle a period before and after such campaigns. The focus period was the decade before supine sleep campaigns (1980's), through the campaign decade, and for the decade after (2000's), allowing for full expression of incidence. Data on actual sleep position in community over time are scarce[42], as reported in author's previous paper[4], aligning to such data would be preferable otherwise. Search was conducted through PubMed, using terms "autism" or "ASD", with "incidence", "prevalence" and "trends". This was followed up in Google Scholar, and subsequent internet searches on key words found in articles. Data were collated in Excel in country-specific graphs. Statistical analysis was not undertaken, merely identification of change points aligned to supine sleep campaigns.

Based on the putative insight that supine sleep is a stressor, a mechanistic hypothesis for increase in autism was generated. This integrates genetics, epigenetics, stress biology and developmental neuroscience with current theories and understanding of ASD.

RESULTS

Epidemiological findings

Data for autism incidence from five countries are presented in Table 1 and Figure 1, with incidence time series straddling supine sleep campaigns.

There is a broadly consistent temporal relationship

Table 1 Countries with time series prevalence data on supine sleep and autism

Country	Campaign	Supine sleep data	Ref.
Denmark	1990	-	[1]Madsen *et al*[45] Parner *et al*[109]
United Kingdom	1991	Gilbert *et al*[42]	[1]Taylor *et al*[52] Blaxill[64] Smeeth *et al*[112]
Australia	1991	-	[1]Nassar *et al*[53] Atladottir *et al*[51] Parner *et al*[109]
Israel	1993	Inbar *et al*[115] Tauman *et al*[116]	[1]Gal *et al*[55]
United Sates	1994	Willinger *et al*[65]	Blaxill[64] Boyle *et al*[56] [1]MMWR[49] Keyes *et al*[48]

[1]References provide data used in Figure 1. MMWR: Morbidity and Mortality Weekly Report.

between supine sleep campaigns and the change-points for autism increase for Denmark in 1990[45], United Kingdom in 1991[52], Australia in 1991[53], Israel in 1993[54,55], and the United States in 1994[49,56]. Note the data for Israel are as reported from a national database for medical insurance cover, so rather than the usual 8 years, the mean age at diagnosis was 39 mo[54], providing a close match of change-point with supine sleep campaign date. Uptake of supine sleep following launch of campaigns[42] correlates with rates of later autism increase. The change-points span a five-year period in five separate countries, making any other extrinsic or secular factor less likely.

The quality of supine sleep data is poor[42], but where such exists there is an improved correlation, since population supine sleep increase started before actual campaigns in the United States, United Kingdom and Australia. Norway has long term supine sleep data, the only data known to author that precedes safe sleep campaigns, based on a retrospective survey of parent recall conducted in 1992 and going back 25 years[57]. This showed a correlation of decreasing supine sleep with increasing SIDS, and a corresponding decrease of SIDS following supine sleep campaign[58]. Autism data from earlier years was not found, published data does not cover the putative change-point[59-61], a comment from such later reports is that this represents a "tenfold increase in all ASD" compared to previous reports[59].

McDonald and Paul[62] "used data sets from Denmark, California, Japan, and a worldwide composite of studies" on autism, seeking change-points that may assist in identifying an "exposure to controllable exogenous stressors". They identified a worldwide change-point around 1988-1989. They identify Japan as being alone in having no change-point, this may reflect the patchy uptake of supine sleep from independent prefectures[63], with no standardised denominators for comparisons. Blaxill[64] provides a detailed review of

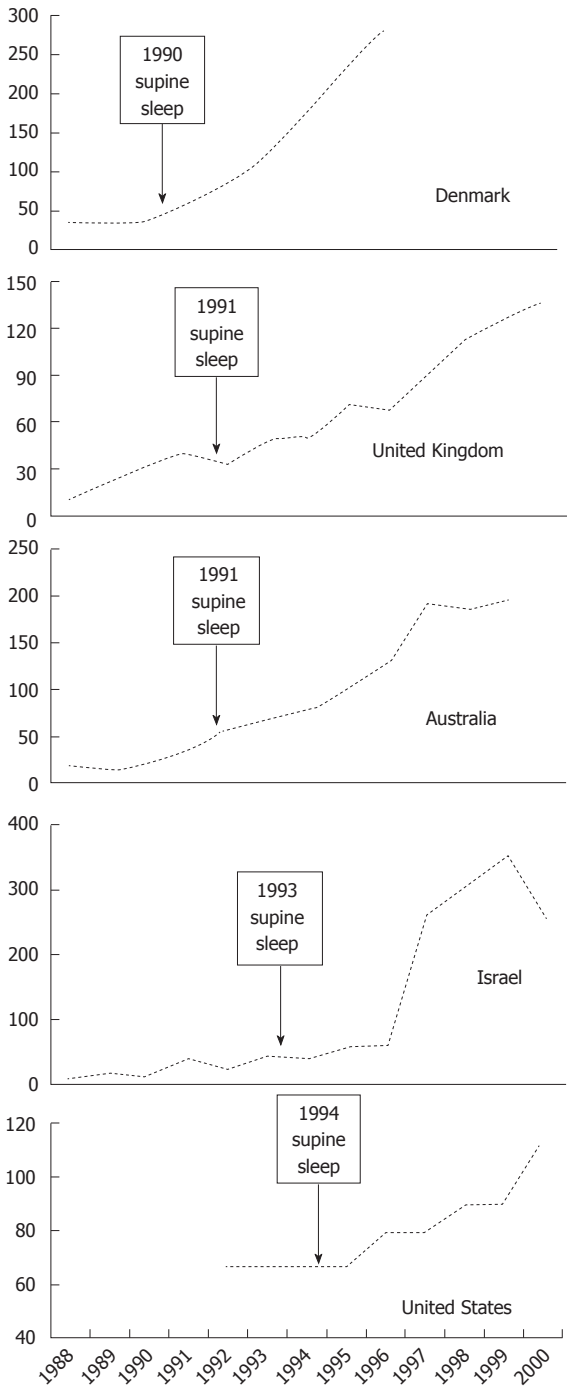

Figure 1 Epidemiological associations with autism rates (dashed line, rate per 10000) and supine sleep campaigns (block arrows). Autism incidence plotted by reported year of birth cohort, except Israel which is reported from year of insurance claim for infants average 39 mo old (source references in Table 1).

time trends in autism prevalence in the United Kingdom and the United States. These results show slight increases preceding the formal campaigns, which may reflect population uptake of supine sleep prior to formal campaigns, or other factors. For the United Kingdom, Gilbert *et al*[42] shows change before 1990, for the United States this can be seen in the NISP data for sleeping position[65] and CDC data for SIDS[66]. Note however

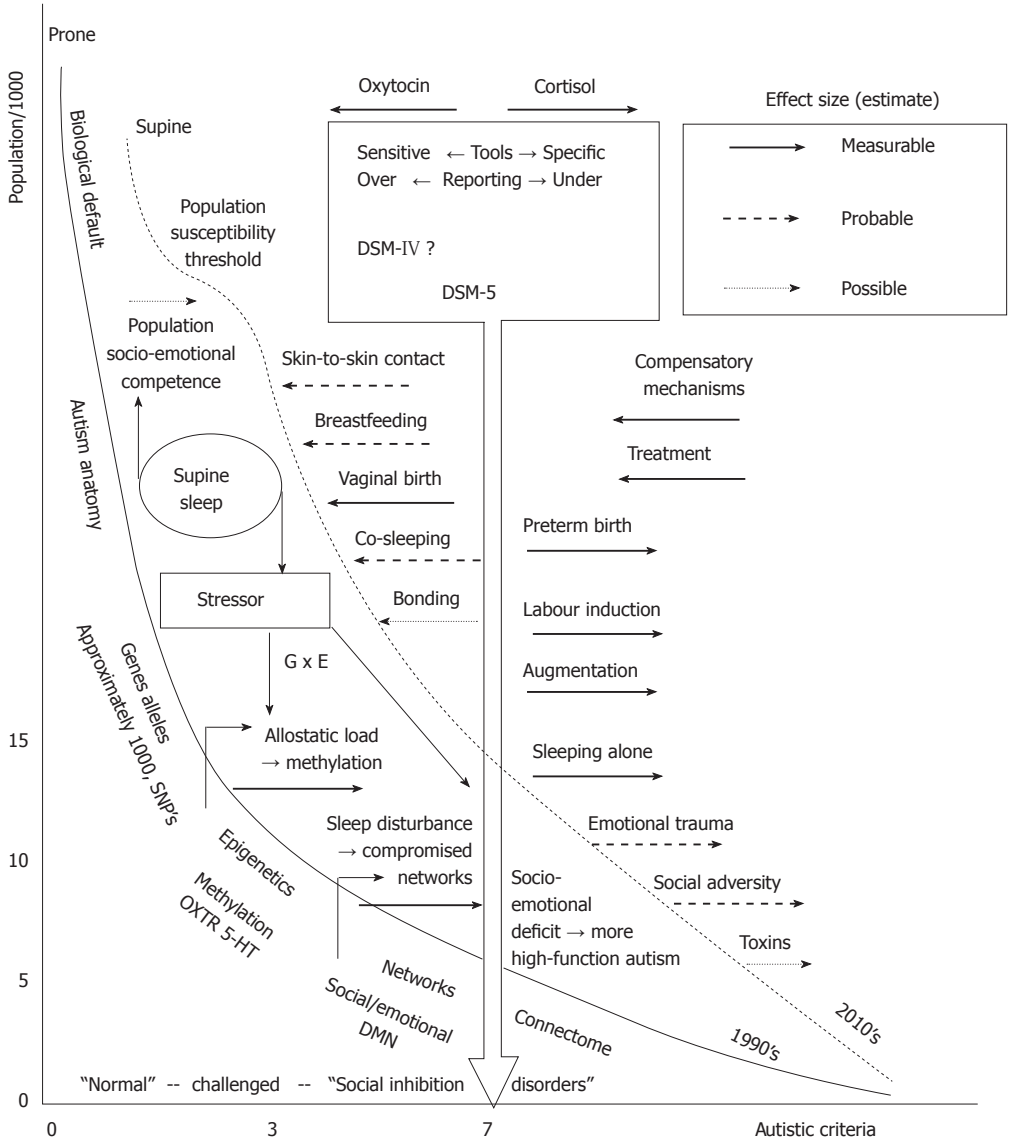

Figure 2 Model for proposed mechanisms of impact of supine sleep on expression of autistic criteria in a population. Autism diagnosis according to DSM-5 is indicated by block arrow, issues debated concerning real incidence in arrow box. Solid black line represents "1990's" incidence of 8 years old final and actual criteria, dashed black line represents the rightward shift that supine sleep is proposed to have made to current time ("2010's"), with mechanisms indicated between the curves, see text for details. Autism incidence increases by right shift of the curve along the X axis, as reflected on Y axis. Other factors identified that increase and decrease expression of autistic criteria are to the right of the dashed curve. 5-HT: Serotonin; DMN: Default mode network; DSM: Diagnostic and Statistical Manual; G x E: Gene environment interaction; OXTR: Oxytocin receptor.

that countries with clear change-points all had supine sleep campaigns with launch dates.

Resulting model for hypothesis on supine sleep and autism

It is acknowledged that the quality of this data leaves much to be desired. However, the original case for association with prone sleep and SIDS was based on similar quality data. In either case, an epidemiological association requires a biologically plausible hypothesis of causation, which in turn can be tested. The hypothesis for supine sleep's effect on autism incidence is presented as an integrated mechanism model in Figure 2. The "busyness" of the model is commensurate with the complexity of the subject. The population incidence is on the Y axis, plotted against the sum of individual symptom criteria of autism on the X axis. The majority of the population may have one or no autistic feature. However numbers of "healthy" people may have autistic features[67], but are coping well and without "impaired everyday functioning" (criteria D, DSM-5). Some may have impaired functioning and have some autistic features, perhaps part of another "social inhibition disorder"[41]. Given the high heritability and variable expression of "autism genes", relatives of confirmed cases are likely to be clustered to the right of the larger population, closer to the diagnostic cut-off[68].

The DSM-5 does not provide diagnostic cut-off as a numeric, nor any sense of severity, but an arbitrary score of 7 is here marked by the blocked arrow as the

diagnostic cut-off point for autism. The diagnostic cut-off line can be (administratively) shifted separately from the reality in the population. The new DSM-5 is believed to decrease the incidence[30], and is therefore more to the right than the DSM-Ⅳ cut-off. Diagnostic and screening tools, and new International Classification of Diseases editions, with various sensitivity and specificity, may be to the left or right of the block arrow. This could be depicted as a zone, and even be quantified, but makes little difference to the hypothesis presented here.

The curves represent the "population autistic criteria", but could equally be seen as the "population emotional and social competence curves"; the focus of this paper is however on the extreme right of the curve where autism is diagnosed. Aligning with the ADDM, the model is regarded as applying to 8 years old, assuming all cases of autism are expressed or diagnosed by this age. The solid curve represents the "true" or real incidence of "population autistic criteria" in the population in the early 1990's, the dashed line the real incidence in the 2010's. Prior under-diagnosis would provide incidence to the left of solid line curve, later over-diagnosis provides figures to the right of the dashed curve. For realistic scale the curves are approximately aligned to the DSM-5 diagnostic cut-off with reported ADDM incidence data of 1992 and 2002 birth cohorts[49]. The curves should however be seen as a generic and conceptual model. Effectively this presents autism as having doubled in incidence during this period, conveyed by a right shift of the "population autistic criteria" curve. Note this is a modest increase in comparison to other data sources, factoring in secular artefactual increases, as described in the introduction.

To the left of the solid curve are itemised basic components of autism etiology and pathology. Space precludes a description of these, review references are provided on "autism anatomy"[69], "genes and alleles"[70-74], "epigenetics"[18,23], "networks"[75], and the "connectome"[76,77]. The latter suggests that autism is a neural network disease, providing a unifying view of the genes, epigenes, effects of environment, hormones and receptors and all the anatomical parts identified. Underlying genetic defects are necessary, and in some cases sufficient, to "cause" autism[72,78].

Right shift - exacerbating factors

To the right of the block arrow are external factors other than the hypothesised effect of supine sleep that are known or believed to increase autism incidence (right shift of curve, dashed line). This hypothesis does not address prenatal adverse factors.

Being born preterm exposes the developing brain to an environment that makes profound changes to a broad range of genes, even in children who do not go on to develop autism[79], and even those born late preterm[80]. The incidence of preterm birth has increased in the ten year period depicted, but so have also efforts to improve the quality of care: Preterm birth may therefore account for a small portion of the increase depicted.

In a population sample (North Carolina) a significant effect on autism was found following induction and augmentation of labour[81]. Caesarean birth can for similar reasons be included in this argument[82]. Though of relatively short duration, these interventions directly disrupt key oxytocin circuits of the connectome in autism[83,84]. These interventions may interfere with the normal pulsatile function of oxytocin[85]. Oxytocin administration has been in use for many years preceding 1994, only in so far as the use has increased after 1994 may this have made a minor contribution to the observed increase. In terms of gene-environment interaction[86], induction and augmentation involve approximately a one day "adversity dose". A single anaesthetic and surgical procedure for an infant does not appear to be enough "adversity dose" to impact the curve[87]. Schieve *et al*[50] review evidence on factors associated with autism as above, and have quantified the possible impact the above factors may have had on the increase in autism, concluding their contribution has been negligible.

"Toxic stress" as defined in early childhood development[88] would also produce a right shift. However, much of the underlying etiology of autism begins in the uterine and early birth period[78]. Even in great adversity, if the early uterine environment and the early perinatal period was "good-enough", some resilience will be in place. The contribution to increasing autism may thus be relatively small, even if many other developmental and social ills follow. This hypothesis requires that "toxic stress" be expressed early to increase the incidence of autism. Repeated emotional and social traumas during the first year of life have been linked to autism[89]. Toxic stress during the First 1000 Days will certainly further exacerbate early changes that took place[90], and so the sum contribution of childhood adversity to right shift is at most moderate, but more likely mild as other factors preceded.

A large number of environmental factors and toxins have been proposed as contributing to the increase in autism. Many of them are plausible in so far as they can impact on epigenetic mechanisms and neurodevelopmental processes. However none of them can easily be linked to the increase since the early 1990's. A possible contributor is advancing parental age[91], which may be acting through increased genetic and allelic changes.

Left shift - protective factors

To the left of the block arrow are protective factors. Skin-to-skin contact and breastfeeding support oxytocin networks[92], so shift the curve to the left. The paradigm could however be that they represent the basic biologically normal condition of the original and normative curve for "population autistic criteria" (prone sleep, solid curve), in which autism is infrequently caused

solely by adverse genomic phenomena. Prone sleep can be regarded as part of a package of normal biological expectation of human reproduction. Co-sleeping is controversial, but is an integral part of human life course sciences[93]. In the context of preterm birth, and perhaps family history of autistic features, consciously increasing the dose of leftward factors (enhancing oxytocin) may be an informed choice for some parents. Higher maternal intake of folate and some other nutrients may lower autism risk[94]. In the ecobiodevelopmental model presented by Shonkoff *et al*[88], "life science theory" is presented as a key concept alongside epigenetics and neuroscience. In the model, all of the protective factors listed are in fact directly out of "life science theory". This encompasses a holistic approach to reproduction, where no single factor acts in isolation.

Compensatory mechanisms develop in the majority of autism cases later in life[95], but some may be apparent and effective at 8 years, and provide a left shift to the curve. Successful treatment likewise, if only by accomplishing everyday functioning: It appears the underlying neurology does not change that much[96].

Biological rationale for hypothesised impact of supine sleep

The hypothesis that supine sleep produces rightward shift, *i.e.*, increases autism incidence, is depicted between the solid and dashed curves. Supine sleep can be seen as a population-wide novel environmental factor introduced in the early 1990's, before which the solid line of the model represents the baseline "population autism criteria".

Supine sleep may bring two separate and distinct stressor disruptions to early development. In the context of the current public health recommendations, it does so over an extended and critical period, more so than many of the "right shifting" factors described above. First is the autonomic stressor effect, sufficient to cause motor developmental delay[17]. High sympathetic tone elevates cortisol and other mediators, which may lead to gene methylation[90,97]. Oxytocin receptor gene methylation has been measured accurately[89], showing a correlation with autism severity, with methylation reported as percentages[98]. Changes may be acute or act over time, as described in the allostasis and allostatic load concept[86]. The Developmental Origins of Health And Disease concept clarifies that developmental disruptions caused by stressors occur at critical periods during development, impacting only the specific developmental goal of that time[99]. One result of stress in the period from 0-2 mo may be disruption of socio-emotional networks, and other parts of the connectome implicated in autism[76]. The default mode network is implicated in autism, this may likely be disturbed antenatally[72,78,100], but could be further dysregulated by the stress of supine sleep.

Second, good quality sleep cycling is necessary for consolidation of memory in adults[101], and even more for neurodevelopment in infants and children[19]. Supine sleep disturbs sleep architecture, with autonomic effects equivalent to anxious arousal and with adverse effect on normal sleep cyclicity[102]. The consolidation and integration of diverse neural networks is necessary for developing the capacities required for Theory of Mind[103]. Oxytocin is core to developing emotional and social networks, and future Theory of Mind[104]. Birth itself and early bonding are highly reliant on oxytocin, which is critical to the parturition process, to early breastfeeding and to bonding[105,106]. Breastfeeding and early bonding are maintained by skin-to-skin contact, which in and of itself supports oxytocin, and the neurobiological processes associated with oxytocin. Continued contact allows mother to be sensitive and attuned to her infant's cues[107], and the infant to establish a trajectory toward a secure attachment.

Ecologically, supine sleep may be part of a package that acts synergistically to disrupt development. Supine sleep and swaddling often go together, the latter per se increases stress, even when practised only the first day there is a measurable adverse impact one year later[108]. Life sciences theory affirms infants should never sleep alone, and maternal-infant separation has been shown to increase autonomic arousal[102]. Other co-factors do undoubtedly exist, but for the current paper, supine sleep is identified as a likely contributor to developmental disruption leading to the increase in autism.

Supine sleep does not "cause" autism in and of itself, the model proposes it as one of many external risk factors, operating during a critical period, and requiring underlying vulnerability (genetic susceptibility), analogous to the Triple Risk Model for SIDS. In the model therefore, it is proposed that supine sleep is exerting at least a moderate effect in shifting the curve to the right, thereby increasing the incidence of autism.

DISCUSSION

This hypothesis is consistent with the changing profile of the autism spectrum in the last two decades. The actual numbers of cases with lower IQ and profound developmental disruption has stayed approximately the same[109,110], but the proportion with high functioning and high IQ has increased[48,53]. The first four months are a critical period for socio-emotional development, not IQ. This is also consistent with the observation that many cases are only diagnosed after some years, despite public health efforts at "early diagnosis". The Theory of Mind concept comes with a prolonged "latent" period[103], and when the primary stressor only starts after birth, as opposed to early and midfetal life[72,78], the expression and recognition of autism may be similarly delayed.

Denmark[45] and Japan[110] are countries that have

specifically studied autism in relation to vaccines, demonstrating no effect of the latter. Both however document similar increase in autism incidence (after thimerosal cessation), and in contexts where similar diagnostic criteria have been used consistently. The Danish data is robust, being based on total population inpatient and outpatient psychiatric records, with the population register as denominator. Incidence prior to 1990 was stable, after which there was an increase[45], such an increase may indeed be caused by increased community awareness. Hansen *et al*[111] attribute 60% of increase in Denmark to change in diagnostic criteria in 1994 and inclusion of outpatients in 1995. In Yokohoma Japan, in a defined catchment with dedicated mental health services and standardised tools, reported incidence increased from 40/1000 between 1988 and 1992, to 117.2 for those born in 1996[110]. Robust data also come from the United Kingdom (United Kingdom General Practice Research Database)[112], showing a five-fold increase from 1988 through to 2001, after which "incidence and prevalence rates in 8-year old children reached a plateau… and remained steady through 2010"[52]. This appears to apply also for Israel and Australia, showing a levelling off of the autism increase[52-54], possibly also in the United States since 2001[113], with supine sleep rates remaining stable. This is consistent with the hypothesis presented in that the population dose of supine sleep cannot increase much more (96% in 1996 in the United Kingdom)[42], and the full effect of susceptibility from this one proposed contributory factor is maximised. The hypothesis presented here for autism may equally apply to all or some of social inhibition disorders.

In parallel to autism, SIDS reduction reached a plateau in the United States and elsewhere. Apart from the finite stressor dose effect, another reason for this may be that for both SIDS and autism there are rare underlying genetic susceptibilities. Under the most ideal conditions of low environmental risk factors, both autism and SIDS would therefore still occur, though rarely. Expression of autism and SIDS genes are exacerbated by adverse environments. In autism, supine sleep thereby exerts an epigenetic and developmental mechanism that disrupts the connectome. In SIDS, supine sleep is working as a protective mechanism on already disrupted neural networks. Since supine sleep is a stressor, and is acting at an intermediate level of causation, it is an imperfect intervention, and can only prevent a finite portion of SIDS mortality, hence the plateau. In the absence of new risk factor changes, it is likely that all current increase in autism is secular, as presented for Sweden[28].

Implications and future directions

In presenting this integrated mechanism review as a hypothesis to this readership, the intention is not to make any kind of public health recommendation, this would be premature, and beyond the scope of this paper. The implications are however considerable, and merit urgent attention: A reassessment is warranted[114]. The epidemiological arguments presented should be scrutinised in data sources globally, with respect to sleep position, autism and SIDS. The proposed model identifies some of the complexity involved, in that exacerbating factors over and above supine sleep need to be teased out, as well as protective factors.

The primary contention that supine sleep is a stressor is amenable to testing. Current clinical and physiological studies already provide ample evidence that supine sleep causes autonomic arousal, and other stressor effects, but this finding has been interpreted as healthy. It may be interpreted as harmful if methylation of specific receptors related to autism could be correlated to supine sleep position. A purely epidemiological approach could be to select cohorts that complied or did not comply to supine sleep recommendations, and compare autism rates, first retrospectively, and then perhaps prospectively. Ethically the latter might be possible if the prone cohort had additional protective measures against SIDS. Genome-wide sequencing for methylation, and focusing on methylation of specific genes identified (*e.g.*, for oxytocin receptors), could establish presence or absence of harmful stress. Other measures of stress or allostatic load, and socio-emotional outcome measures, may confirm or refute the hypothesis. The prevalence of SIDS defects and autism genes should be quantified. This may allow a new perspective on the risk benefit ratio in terms of quantifying SIDS decrease against possible autism increase. More research could focus on practical methods to identify neonates with SIDS and autism susceptibility, allowing for differentiated care options.

In conclusion, it is proposed that there may be an association between supine sleep and autism incidence increase. No other potential stressor than supine sleep is known to have been introduced globally in widely separated regions, nor one that matches the temporal patterns described here. The biological rationale proposed is that supine sleep may be a stressor, increasing gene methylation in, and disrupting needed sleep cyclicity for developing socio-emotional neural circuits. As stated above, it would be premature to offer any kind of clinical or parenting advice based on this hypothesis. Rather, the SIDS mechanism proposed and autism model presented should be urgently examined and researched, then the future research agenda may be better directed, toward better care and advice to parents and health departments in order to further decrease SIDS, and reduce autism incidence.

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COMMENTS

Background

Autism has increased since the early 1990's. Sudden infant death syndrome (SIDS) decreased only to level off after supine sleep campaigns in the 1990's. Currently supine sleep for neonates and infants is very strongly encouraged by public health authorities. However, the mechanism whereby supine sleep achieves SIDS reduction is totally unknown. This article suggests that supine sleep achieves SIDS reduction through a stressor mechanism, which will have the unintended side-effect of increasing autistic criteria in sensitive individuals of the population. The relevance of this article is that a re-evaluation of the fields of both SIDS and autism may lead to research that improves outcomes for both.

Research frontiers

Current research into SIDS includes identifying the mechanism of harm from prone sleep; this article suggests such research is fruitless. In terms of autism, a more fruitful direction of research suggested by this study is developmental stress biology.

Innovations and breakthroughs

The major innovative thinking of this article lies in its re-appraisal of prone sleep as the healthy physiological sleep. This can be seen as an application of "rare disease epidemiology". For example, the rare side-effects of vaccines given to the whole population are accepted since the risks of those are greatly outweighed by the benefits. In the case of supine sleep campaigns, the potential risks have not been properly evaluated. Increasing autistic criteria in the population should be regarded as a major risk factor, which requires urgent and accurate quantification in order to properly balance benefit and risk of supine sleep.

Applications

These findings emphasise that for both conditions, rare underlying genetic susceptibility is fundamental, and this will be a fruitful direction of research. The mechanistic model published previously on SIDS, and the model in this article on autism, allow more focused preventive and therapeutic application. In SIDS for example, a cardiorespiratory based physiological screening test is a possibility. In autism, genetic screening could identify a smaller part of the population for which family counselling allowing may result in advice to provide prone sleep, based on "informed choice".

Terminology

The term autism is used for brevity, where the correct terminology is autism spectrum disorder. This is currently best understood as a "connectome" disorder, this term refers to brain networks and their interactions, shared areas of high neural network traffic are referred to as hubs.

Peer-review

The topic is really interesting and the manuscript is clear and well organized.

REFERENCES

1 **Hauck FR**, Tanabe KO. International trends in sudden infant death syndrome: stabilization of rates requires further action. *Pediatrics* 2008; **122**: 660-666 [PMID: 18762537 DOI: 10.1542/peds.2007-0135]

2 **Alm B**, Norvenius SG, Wennergren G, Skjaerven R, Øyen N, Milerad J, Wennborg M, Kjaerbeck J, Helweg-Larsen K, Irgens LM. Changes in the epidemiology of sudden infant death syndrome in Sweden 1973-1996. *Arch Dis Child* 2001; **84**: 24-30 [PMID: 11124779 DOI: 10.1136/adc.84.1.24]

3 **Moon RY**. SIDS and other sleep-related infant deaths: expansion of recommendations for a safe infant sleeping environment. *Pediatrics* 2011; **128**: e1341-e1367 [PMID: 22007003 DOI: 10.1542/peds.2011-2285]

4 **Bergman NJ**. Proposal for mechanisms of protection of supine sleep against sudden infant death syndrome: an integrated mechanism review. *Pediatr Res* 2015; **77**: 10-19 [PMID: 25268147 DOI: 10.1038/pr.2014.140]

5 **Kinney HC**, Thach BT. The sudden infant death syndrome. *N Engl J Med* 2009; **361**: 795-805 [PMID: 19692691 DOI: 10.1056/NEJMra0803836]

6 **Randall BB**, Paterson DS, Haas EA, Broadbelt KG, Duncan JR, Mena OJ, Krous HF, Trachtenberg FL, Kinney HC. Potential asphyxia and brainstem abnormalities in sudden and unexpected death in infants. *Pediatrics* 2013; **132**: e1616-e1625 [PMID: 24218471 DOI: 10.1542/peds.2013-0700]

7 **Sridhar R**, Thach BT, Kelly DH, Henslee JA. Characterization of successful and failed autoresuscitation in human infants, including those dying of SIDS. *Pediatr Pulmonol* 2003; **36**: 113-122 [PMID: 12833490 DOI: 10.1002/ppul.10287]

8 **Dergacheva O**, Griffioen KJ, Neff RA, Mendelowitz D. Respiratory modulation of premotor cardiac vagal neurons in the brainstem. *Respir Physiol Neurobiol* 2010; **174**: 102-110 [PMID: 20452467 DOI: 10.1016/j.resp.2010.05.005]

9 **Linnman C**, Moulton EA, Barmettler G, Becerra L, Borsook D. Neuroimaging of the periaqueductal gray: state of the field. *Neuroimage* 2012; **60**: 505-522 [PMID: 22197740 DOI: 10.1016/j.neuroimage.2011.11.095]

10 **Nishida M**, Pearsall J, Buckner RL, Walker MP. REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cereb Cortex* 2009; **19**: 1158-1166 [PMID: 18832332 DOI: 10.1093/cercor/bhn155]

11 **Kohyama J**, Shimohira M, Itoh M, Fukumizu M, Iwakawa Y. Phasic muscle activity during REM sleep in infancy-normal maturation and contrastive abnormality in SIDS/ALTE and West syndrome. *J Sleep Res* 1993; **2**: 241-249 [PMID: 10607100 DOI: 10.1111/j.1365-2869.1993.tb00095.x]

12 **Kahn A**, Groswasser J, Rebuffat E, Sottiaux M, Blum D, Foerster M, Franco P, Bochner A, Alexander M, Bachy A. Sleep and cardiorespiratory characteristics of infant victims of sudden death: a prospective case-control study. *Sleep* 1992; **15**: 287-292 [PMID: 1519001]

13 **Kinney HC**. Brainstem mechanisms underlying the sudden infant death syndrome: evidence from human pathologic studies. *Dev Psychobiol* 2009; **51**: 223-233 [PMID: 19235901 DOI: 10.1002/dev.20367]

14 **Gross C**, Zhuang X, Stark K, Ramboz S, Oosting R, Kirby L, Santarelli L, Beck S, Hen R. Serotonin1A receptor acts during development to establish normal anxiety-like behaviour in the adult. *Nature* 2002; **416**: 396-400 [PMID: 11919622 DOI: 10.1038/416396a]

15 **Heemstra HE**, van Weely S, Büller HA, Leufkens HG, de Vrueh RL. Translation of rare disease research into orphan drug development: disease matters. *Drug Discov Today* 2009; **14**: 1166-1173 [PMID: 19818412 DOI: 10.1016/j.drudis.2009.09.008]

16 **Biggs WS**. Diagnosis and management of positional head deformity. *Am Fam Physician* 2003; **67**: 1953-1956 [PMID: 12751657]

17 **Majnemer A**, Barr RG. Association between sleep position and early motor development. *J Pediatr* 2006; **149**: 623-629 [PMID: 17095331 DOI: 10.1016/j.jpeds.2006.05.009]

18 **LaSalle JM**. Epigenomic strategies at the interface of genetic and environmental risk factors for autism. *J Hum Genet* 2013; **58**: 396-401 [PMID: 23677056 DOI: 10.1038/jhg.2013.49]

19 **Peirano P**, Algarín C, Uauy R. Sleep-wake states and their regulatory mechanisms throughout early human development. *J Pediatr* 2003; **143**: S70-S79 [PMID: 14597916 DOI: 10.1067/S0022-3476(03)00404-9]

20 **Schore AN**. Effects of a secure attachment relationship on right brain development, affect regulation, and infant mental health. *Infant Ment Health J* 2001; **22**: 7-66 [DOI: 10.1002/1097-0355(200101/04)22:1<7::AID-IMHJ2>3.0.CO;2-N]

21 **Charney DS**. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. *Am J Psychiatry* 2004; **161**: 195-216 [PMID: 14754765 DOI: 10.1176/appi.ajp.161.2.195]

22 **American Psychiatric Association**. Diagnostic and statistical manual of mental disorders - dsm-iv-tr. 5th ed. Arlington: American Psychiatric Publishing, 2013: 1-85

23 **Mbadiwe T**, Millis RM. Epigenetics and autism. *Autism Res Treat* 2013; **2013**: 826156 [PMID: 24151554 DOI: 10.1155/2013/826156]

24 **Baskerville TA**, Douglas AJ. Dopamine and oxytocin interactions underlying behaviors: potential contributions to behavioral disorders. *CNS Neurosci Ther* 2010; **16**: e92-123 [PMID: 20557568 DOI: 10.1111/j.1755-5949.2010.00154.x]

25 **Radulescu E**, Minati L, Ganeshan B, Harrison NA, Gray MA, Beacher FD, Chatwin C, Young RC, Critchley HD. Abnormalities in fronto-striatal connectivity within language networks relate to differences in grey-matter heterogeneity in Asperger syndrome. *Neuroimage Clin* 2013; **2**: 716-726 [PMID: 24179823 DOI: 10.1016/j.nicl.2013.05.010]

26 **Baxter AJ**, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. *Psychol Med* 2015; **45**: 601-613 [PMID: 25108395 DOI: 10.1017/S003329171400172X]

27 **Elsabbagh M**, Divan G, Koh YJ, Kim YS, Kauchali S, Marcín C, Montiel-Nava C, Patel V, Paula CS, Wang C, Yasamy MT, Fombonne E. Global prevalence of autism and other pervasive developmental disorders. *Autism Res* 2012; **5**: 160-179 [PMID: 22495912 DOI: 10.1002/aur.239]

28 **Lundström S**, Reichenberg A, Anckarsäter H, Lichtenstein P, Gillberg C. Autism phenotype versus registered diagnosis in Swedish children: prevalence trends over 10 years in general population samples. *BMJ* 2015; **350**: h1961 [PMID: 25922345 DOI: 10.1136/bmj.h1961]

29 **Pennington ML**, Cullinan D, Southern LB. Defining autism: variability in state education agency definitions of and evaluations for autism spectrum disorders. *Autism Res Treat* 2014; **2014**: 327271 [PMID: 24987527 DOI: 10.1155/2014/327271]

30 **Kulage KM**, Smaldone AM, Cohn EG. How will DSM-5 affect autism diagnosis? A systematic literature review and meta-analysis. *J Autism Dev Disord* 2014; **44**: 1918-1932 [PMID: 24531932 DOI: 10.1007/s10803-014-2065-2]

31 **Maenner MJ**, Rice CE, Arneson CL, Cunniff C, Schieve LA, Carpenter LA, Van Naarden Braun K, Kirby RS, Bakian AV, Durkin MS. Potential impact of DSM-5 criteria on autism spectrum disorder prevalence estimates. *JAMA Psychiatry* 2014; **71**: 292-300 [PMID: 24452504 DOI: 10.1001/jamapsychiatry.2013.3893]

32 **Kim YS**, Fombonne E, Koh YJ, Kim SJ, Cheon KA, Leventhal BL. A comparison of DSM-IV pervasive developmental disorder and DSM-5 autism spectrum disorder prevalence in an epidemiologic sample. *J Am Acad Child Adolesc Psychiatry* 2014; **53**: 500-508 [PMID: 24745950 DOI: 10.1016/j.jaac.2013.12.021]

33 **King BH**, Navot N, Bernier R, Webb SJ. Update on diagnostic classification in autism. *Curr Opin Psychiatry* 2014; **27**: 105-109 [PMID: 24441420 DOI: 10.1097/YCO.0000000000000040]

34 **Huerta M**, Bishop SL, Duncan A, Hus V, Lord C. Application of DSM-5 criteria for autism spectrum disorder to three samples of children with DSM-IV diagnoses of pervasive developmental disorders. *Am J Psychiatry* 2012; **169**: 1056-1064 [PMID: 23032385 DOI: 10.1176/appi.ajp.2012.12020276]

35 **Blumberg SJ**, Bramlett MD, Kogan MD, Schieve LA, Jones JR, Lu MC. Changes in prevalence of parent-reported autism spectrum disorder in school-aged U.S. children: 2007 to 2011-2012. *Natl Health Stat Report* 2013; **(65)**: 1-11, 1 p following 11 [PMID: 24988818]

36 **Kim YS**, Leventhal BL, Koh YJ, Fombonne E, Laska E, Lim EC, Cheon KA, Kim SJ, Kim YK, Lee H, Song DH, Grinker RR. Prevalence of autism spectrum disorders in a total population sample. *Am J Psychiatry* 2011; **168**: 904-912 [PMID: 21558103 DOI: 10.1176/appi.ajp.2011.10101532]

37 **Brugha TS**, McManus S, Bankart J, Scott F, Purdon S, Smith J, Bebbington P, Jenkins R, Meltzer H. Epidemiology of autism spectrum disorders in adults in the community in England. *Arch Gen Psychiatry* 2011; **68**: 459-465 [PMID: 21536975 DOI: 10.1001/archgenpsychiatry.2011.38]

38 **Bishop DV**, Whitehouse AJ, Watt HJ, Line EA. Autism and diagnostic substitution: evidence from a study of adults with a history of developmental language disorder. *Dev Med Child Neurol* 2008; **50**: 341-345 [PMID: 18384386 DOI: 10.1111/j.1469-8749.2008.02057.x]

39 **Shattuck PT**. The contribution of diagnostic substitution to the growing administrative prevalence of autism in US special education. *Pediatrics* 2006; **117**: 1028-1037 [PMID: 16585296 DOI: 10.1542/peds.2005-1516]

40 **Gillberg C**, Fernell E. Autism plus versus autism pure. *J Autism Dev Disord* 2014; **44**: 3274-3276 [PMID: 24958434 DOI: 10.1007/s10803-014-2163-1]

41 **Hrdlicka M**, Dudova I. Controversies in autism: is a broader model of social disorders needed? *Child Adolesc Psychiatry Ment Health* 2013; **7**: 9 [PMID: 23506384 DOI: 10.1186/1753-2000-7-9]

42 **Gilbert R**, Salanti G, Harden M, See S. Infant sleeping position and the sudden infant death syndrome: systematic review of observational studies and historical review of recommendations from 1940 to 2002. *Int J Epidemiol* 2005; **34**: 874-887 [PMID: 15843394 DOI: 10.1093/ije/dyi088]

43 **Bresnahan M**, Li G, Susser E. Hidden in plain sight. *Int J Epidemiol* 2009; **38**: 1172-1174 [PMID: 19797336 DOI: 10.1093/ije/dyp293]

44 **King M**, Bearman P. Diagnostic change and the increased prevalence of autism. *Int J Epidemiol* 2009; **38**: 1224-1234 [PMID: 19737791 DOI: 10.1093/ije/dyp261]

45 **Madsen KM**, Lauritsen MB, Pedersen CB, Thorsen P, Plesner AM, Andersen PH, Mortensen PB. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. *Pediatrics* 2003; **112**: 604-606 [PMID: 12949291 DOI: 10.1542/peds.112.3.604]

46 **Rutter M**. Incidence of autism spectrum disorders: changes over time and their meaning. *Acta Paediatr* 2005; **94**: 2-15 [PMID: 15858952 DOI: 10.1111/j.1651-2227.2005.tb01779.x]

47 **Williams JG**, Higgins JP, Brayne CE. Systematic review of prevalence studies of autism spectrum disorders. *Arch Dis Child* 2006; **91**: 8-15 [PMID: 15863467 DOI: 10.1136/adc.2004.062083]

48 **Keyes KM**, Susser E, Cheslack-Postava K, Fountain C, Liu K, Bearman PS. Cohort effects explain the increase in autism diagnosis among children born from 1992 to 2003 in California. *Int J Epidemiol* 2012; **41**: 495-503 [PMID: 22253308 DOI: 10.1093/ije/dyr193]

49 **Morbidity and Mortality Weekly Report (MMWR)**. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *MMWR Surveill Summ* 2014; **63**: 1-21 [PMID: 24670961]

50 **Schieve LA**, Rice C, Devine O, Maenner MJ, Lee LC, Fitzgerald R, Wingate MS, Schendel D, Pettygrove S, van Naarden Braun K, Durkin M. Have secular changes in perinatal risk factors contributed to the recent autism prevalence increase? Development and application of a mathematical assessment model. *Ann Epidemiol* 2011; **21**: 930-945 [PMID: 22000328 DOI: 10.1016/j.annepidem.2011.08.009]

51 **Atladottir HO**, Gyllenberg D, Langridge A, Sandin S, Hansen SN, Leonard H, Gissler M, Reichenberg A, Schendel DE, Bourke J, Hultman CM, Grice DE, Buxbaum JD, Parner ET. The increasing prevalence of reported diagnoses of childhood psychiatric disorders: a descriptive multinational comparison. *Eur Child Adolesc Psychiatry* 2015; **24**: 173-183 [PMID: 24796725 DOI: 10.1007/s00787-014-0553-8]

52 **Taylor B**, Jick H, Maclaughlin D. Prevalence and incidence rates of autism in the UK: time trend from 2004-2010 in children aged 8 years. *BMJ Open* 2013; **3**: e003219 [PMID: 24131525 DOI:

10.1136/bmjopen-2013-003219]
53 **Nassar N**, Dixon G, Bourke J, Bower C, Glasson E, de Klerk N, Leonard H. Autism spectrum disorders in young children: effect of changes in diagnostic practices. *Int J Epidemiol* 2009; **38**: 1245-1254 [PMID: 19737795 DOI: 10.1093/ije/dyp260]
54 **Senecky Y**, Chodick G, Diamond G, Lobel D, Drachman R, Inbar D. Time trends in reported autistic spectrum disorders in Israel, 1972-2004. *Isr Med Assoc J* 2009; **11**: 30-33 [PMID: 19344009]
55 **Gal G**, Abiri L, Reichenberg A, Gabis L, Gross R. Time trends in reported autism spectrum disorders in Israel, 1986-2005. *J Autism Dev Disord* 2012; **42**: 428-431 [PMID: 21567257 DOI: 10.1007/s10803-011-1252-7]
56 **Boyle CA**, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, Visser S, Kogan MD. Trends in the prevalence of developmental disabilities in US children, 1997-2008. *Pediatrics* 2011; **127**: 1034-1042 [PMID: 21606152 DOI: 10.1542/peds.2010-2989]
57 **Irgens LM**, Markestad T, Baste V, Schreuder P, Skjaerven R, Oyen N. Sleeping position and sudden infant death syndrome in Norway 1967-91. *Arch Dis Child* 1995; **72**: 478-482 [PMID: 7618929 DOI: 10.1136/adc.72.6.478]
58 **Arntzen A**, Samuelsen SO, Daltveit AK, Stoltenberg C. Post-neonatal mortality in Norway 1969-95: a cause-specific analysis. *Int J Epidemiol* 2006; **35**: 1083-1089 [PMID: 16556644 DOI: 10.1093/ije/dyl047]
59 **Isaksen J**, Diseth TH, Schjølberg S, Skjeldal OH. Observed prevalence of autism spectrum disorders in two Norwegian counties. *Eur J Paediatr Neurol* 2012; **16**: 592-598 [PMID: 22342070 DOI: 10.1016/j.ejpn.2012.01.014]
60 **Nilsen RM**, Surén P, Gunnes N, Alsaker ER, Bresnahan M, Hirtz D, Hornig M, Lie KK, Lipkin WI, Reichborn-Kjennerud T, Roth C, Schjølberg S, Smith GD, Susser E, Vollset SE, Øyen AS, Magnus P, Stoltenberg C. Analysis of self-selection bias in a population-based cohort study of autism spectrum disorders. *Paediatr Perinat Epidemiol* 2013; **27**: 553-563 [PMID: 23919580 DOI: 10.1111/ppe.12077]
61 **Surén P**, Bakken IJ, Aase H, Chin R, Gunnes N, Lie KK, Magnus P, Reichborn-Kjennerud T, Schjølberg S, Øyen AS, Stoltenberg C. Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. *Pediatrics* 2012; **130**: e152-e158 [PMID: 22711729 DOI: 10.1542/peds.2011-3217]
62 **McDonald ME**, Paul JF. Timing of increased autistic disorder cumulative incidence. *Environ Sci Technol* 2010; **44**: 2112-2118 [PMID: 20158232 DOI: 10.1021/es902057k]
63 **Sawaguchi T**, Namiki M. Recent trend of the incidence of sudden infant death syndrome in Japan. *Early Hum Dev* 2003; **75** Suppl: S175-S179 [PMID: 14693403 DOI: 10.1016/j.earlhumdev.2003.08.020]
64 **Blaxill MF**. What's going on? The question of time trends in autism. *Public Health Rep* 2004; **119**: 536-551 [PMID: 15504445 DOI: 10.1016/j.phr.2004.09.003]
65 **Willinger M**, Hoffman HJ, Wu KT, Hou JR, Kessler RC, Ward SL, Keens TG, Corwin MJ. Factors associated with the transition to nonprone sleep positions of infants in the United States: the National Infant Sleep Position Study. *JAMA* 1998; **280**: 329-335 [PMID: 9686549 DOI: 10.1001/jama.280.4.329]
66 **Colson ER**, Rybin D, Smith LA, Colton T, Lister G, Corwin MJ. Trends and factors associated with infant sleeping position: the national infant sleep position study, 1993-2007. *Arch Pediatr Adolesc Med* 2009; **163**: 1122-1128 [PMID: 19996049 DOI: 10.1001/archpediatrics.2009.234]
67 **Jung M**, Kosaka H, Saito DN, Ishitobi M, Morita T, Inohara K, Asano M, Arai S, Munesue T, Tomoda A, Wada Y, Sadato N, Okazawa H, Iidaka T. Default mode network in young male adults with autism spectrum disorder: relationship with autism spectrum traits. *Mol Autism* 2014; **5**: 35 [PMID: 24955232 DOI: 10.1186/2040-2392-5-35]
68 **Saito Y**, Suga M, Tochigi M, Abe O, Yahata N, Kawakubo Y, Liu X, Kawamura Y, Sasaki T, Kasai K, Yamasue H. Neural correlate of autistic-like traits and a common allele in the oxytocin receptor gene. *Soc Cogn Affect Neurosci* 2014; **9**: 1443-1450 [PMID: 23946005 DOI: 10.1093/scan/nst136]
69 **Stigler KA**, McDonald BC, Anand A, Saykin AJ, McDougle CJ. Structural and functional magnetic resonance imaging of autism spectrum disorders. *Brain Res* 2011; **1380**: 146-161 [PMID: 21130750 DOI: 10.1016/j.brainres.2010.11.076]
70 **Fakhoury M**. Autistic spectrum disorders: A review of clinical features, theories and diagnosis. *Int J Dev Neurosci* 2015; **43**: 70-77 [PMID: 25862937 DOI: 10.1016/j.ijdevneu.2015.04.003]
71 **Gaugler T**, Klei L, Sanders SJ, Bodea CA, Goldberg AP, Lee AB, Mahajan M, Manaa D, Pawitan Y, Reichert J, Ripke S, Sandin S, Sklar P, Svantesson O, Reichenberg A, Hultman CM, Devlin B, Roeder K, Buxbaum JD. Most genetic risk for autism resides with common variation. *Nat Genet* 2014; **46**: 881-885 [PMID: 25038753 DOI: 10.1038/ng.3039]
72 **Hormozdiari F**, Penn O, Borenstein E, Eichler EE. The discovery of integrated gene networks for autism and related disorders. *Genome Res* 2015; **25**: 142-154 [PMID: 25378250 DOI: 10.1101/gr.178855.114]
73 **Radua J**, El-Hage W, Monté GC, Gohier B, Tropeano M, Phillips ML, Surguladze SA. COMT Val158Met × SLC6A4 5-HTTLPR interaction impacts on gray matter volume of regions supporting emotion processing. *Soc Cogn Affect Neurosci* 2014; **9**: 1232-1238 [PMID: 23748501 DOI: 10.1093/scan/nst089]
74 **Rosti RO**, Sadek AA, Vaux KK, Gleeson JG. The genetic landscape of autism spectrum disorders. *Dev Med Child Neurol* 2014; **56**: 12-18 [PMID: 24116704 DOI: 10.1111/dmcn.12278]
75 **Zielinski BA**, Anderson JS, Froehlich AL, Prigge MB, Nielsen JA, Cooperrider JR, Cariello AN, Fletcher PT, Alexander AL, Lange N, Bigler ED, Lainhart JE. scMRI reveals large-scale brain network abnormalities in autism. *PLoS One* 2012; **7**: e49172 [PMID: 23185305 DOI: 10.1371/journal.pone.0049172]
76 **Crossley NA**, Mechelli A, Scott J, Carletti F, Fox PT, McGuire P, Bullmore ET. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. *Brain* 2014; **137**: 2382-2395 [PMID: 25057133 DOI: 10.1093/brain/awu132]
77 **Goch CJ**, Stieltjes B, Henze R, Hering J, Poustka L, Meinzer HP, Maier-Hein KH. Quantification of changes in language-related brain areas in autism spectrum disorders using large-scale network analysis. *Int J Comput Assist Radiol Surg* 2014; **9**: 357-365 [PMID: 24459035 DOI: 10.1007/s11548-014-0977-0]
78 **Casanova EL**, Casanova MF. Genetics studies indicate that neural induction and early neuronal maturation are disturbed in autism. *Front Cell Neurosci* 2014; **8**: 397 [PMID: 25477785 DOI: 10.3389/fncel.2014.00397]
79 **Ball G**, Boardman JP, Aljabar P, Pandit A, Arichi T, Merchant N, Rueckert D, Edwards AD, Counsell SJ. The influence of preterm birth on the developing thalamocortical connectome. *Cortex* 2013; **49**: 1711-1721 [PMID: 22959979 DOI: 10.1016/j.cortex.2012.07.006]
80 **Guy A**, Seaton SE, Boyle EM, Draper ES, Field DJ, Manktelow BN, Marlow N, Smith LK, Johnson S. Infants born late/moderately preterm are at increased risk for a positive autism screen at 2 years of age. *J Pediatr* 2015; **166**: 269-75.e3 [PMID: 25477165 DOI: 10.1016/j.jpeds.2014.10.053]
81 **Gregory SG**, Anthopolos R, Osgood CE, Grotegut CA, Miranda ML. Association of autism with induced or augmented childbirth in North Carolina Birth Record (1990-1998) and Education Research (1997-2007) databases. *JAMA Pediatr* 2013; **167**: 959-966 [PMID: 23938610 DOI: 10.1001/jamapediatrics.2013.2904]
82 **Polo-Kantola P**, Lampi KM, Hinkka-Yli-Salomäki S, Gissler M, Brown AS, Sourander A. Obstetric risk factors and autism spectrum disorders in Finland. *J Pediatr* 2014; **164**: 358-365 [PMID: 24183209 DOI: 10.1016/j.jpeds.2013.09.044]
83 **Gregory SG**, Connelly JJ, Towers AJ, Johnson J, Biscocho D, Markunas CA, Lintas C, Abramson RK, Wright HH, Ellis P,

Langford CF, Worley G, Delong GR, Murphy SK, Cuccaro ML, Persico A, Pericak-Vance MA. Genomic and epigenetic evidence for oxytocin receptor deficiency in autism. *BMC Med* 2009; **7**: 62 [PMID: 19845972 DOI: 10.1186/1741-7015-7-62]

84 **LoParo D**, Waldman ID. The oxytocin receptor gene (OXTR) is associated with autism spectrum disorder: a meta-analysis. *Mol Psychiatry* 2015; **20**: 640-646 [PMID: 25092245 DOI: 10.1038/mp.2014.77]

85 **Olza Fernández I**, Marín Gabriel M, Malalana Martínez A, Fernández-Cañadas Morillo A, López Sánchez F, Costarelli V. Newborn feeding behaviour depressed by intrapartum oxytocin: a pilot study. *Acta Paediatr* 2012; **101**: 749-754 [PMID: 22452314 DOI: 10.1111/j.1651-2227.2012.02668.x]

86 **McEwen BS**, Gianaros PJ. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Ann N Y Acad Sci* 2010; **1186**: 190-222 [PMID: 20201874 DOI: 10.1111/j.1749-6632.2009.05331.x]

87 **Ko WR**, Huang JY, Chiang YC, Nfor ON, Ko PC, Jan SR, Lung CC, Chang HC, Lin LY, Liaw YP. Risk of autistic disorder after exposure to general anaesthesia and surgery: a nationwide, retrospective matched cohort study. *Eur J Anaesthesiol* 2015; **32**: 303-310 [PMID: 25101714 DOI: 10.1097/EJA.0000000000000130]

88 **Shonkoff JP**, Garner AS. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics* 2012; **129**: e232-e246 [PMID: 22201156 DOI: 10.1542/peds.2011-2663]

89 **Kumsta R**, Hummel E, Chen FS, Heinrichs M. Epigenetic regulation of the oxytocin receptor gene: implications for behavioral neuroscience. *Front Neurosci* 2013; **7**: 83 [PMID: 23734094 DOI: 10.3389/fnins.2013.00083]

90 **McGowan PO**, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, Turecki G, Meaney MJ. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 2009; **12**: 342-348 [PMID: 19234457 DOI: 10.1038/nn.2270]

91 **Idring S**, Magnusson C, Lundberg M, Ek M, Rai D, Svensson AC, Dalman C, Karlsson H, Lee BK. Parental age and the risk of autism spectrum disorders: findings from a Swedish population-based cohort. *Int J Epidemiol* 2014; **43**: 107-115 [PMID: 24408971 DOI: 10.1093/ije/dyt262]

92 **Uvnäs-Moberg K**. Neuroendocrinology of the mother-child interaction. *Trends Endocrinol Metab* 1996; **7**: 126-131 [PMID: 18406738 DOI: 10.1016/1043-2760(96)00036-7]

93 **Gettler LT**, McKenna JJ. Evolutionary perspectives on mother-infant sleep proximity and breastfeeding in a laboratory setting. *Am J Phys Anthropol* 2011; **144**: 454-462 [PMID: 21302271 DOI: 10.1002/ajpa.21426]

94 **Lyall K**, Schmidt RJ, Hertz-Picciotto I. Maternal lifestyle and environmental risk factors for autism spectrum disorders. *Int J Epidemiol* 2014; **43**: 443-464 [PMID: 24518932 DOI: 10.1093/ije/dyt282]

95 **Jones EJ**, Gliga T, Bedford R, Charman T, Johnson MH. Developmental pathways to autism: a review of prospective studies of infants at risk. *Neurosci Biobehav Rev* 2014; **39**: 1-33 [PMID: 24361967 DOI: 10.1016/j.neubiorev.2013.12.001]

96 **Canitano R**. New experimental treatments for core social domain in autism spectrum disorders. *Front Pediatr* 2014; **2**: 61 [PMID: 24999471 DOI: 10.3389/fped.2014.00061]

97 **Wang D**, Szyf M, Benkelfat C, Provençal N, Turecki G, Caramaschi D, Côté SM, Vitaro F, Tremblay RE, Booij L. Peripheral SLC6A4 DNA methylation is associated with in vivo measures of human brain serotonin synthesis and childhood physical aggression. *PLoS One* 2012; **7**: e39501 [PMID: 22745770 DOI: 10.1371/journal.pone.0039501]

98 **Jack A**, Connelly JJ, Morris JP. DNA methylation of the oxytocin receptor gene predicts neural response to ambiguous social stimuli. *Front Hum Neurosci* 2012; **6**: 280 [PMID: 23087634 DOI: 10.3389/fnhum.2012.00280]

99 **Hochberg Z**, Feil R, Constancia M, Fraga M, Junien C, Carel JC, Boileau P, Le Bouc Y, Deal CL, Lillycrop K, Scharfmann R, Sheppard A, Skinner M, Szyf M, Waterland RA, Waxman DJ, Whitelaw E, Ong K, Albertsson-Wikland K. Child health, developmental plasticity, and epigenetic programming. *Endocr Rev* 2011; **32**: 159-224 [PMID: 20971919 DOI: 10.1210/er.2009-0039]

100 **Walker CK**, Krakowiak P, Baker A, Hansen RL, Ozonoff S, Hertz-Picciotto I. Preeclampsia, placental insufficiency, and autism spectrum disorder or developmental delay. *JAMA Pediatr* 2015; **169**: 154-162 [PMID: 25485869 DOI: 10.1001/jamapediatrics.2014.2645]

101 **Born J**, Wagner U. Sleep, hormones, and memory. *Obstet Gynecol Clin North Am* 2009; **36**: 809-829, x [PMID: 19944302 DOI: 10.1016/j.ogc.2009.10.001]

102 **Morgan BE**, Horn AR, Bergman NJ. Should neonates sleep alone? *Biol Psychiatry* 2011; **70**: 817-825 [PMID: 21802659 DOI: 10.1016/j.biopsych.2011.06.018]

103 **Kana RK**, Libero LE, Hu CP, Deshpande HD, Colburn JS. Functional brain networks and white matter underlying theory-of-mind in autism. *Soc Cogn Affect Neurosci* 2014; **9**: 98-105 [PMID: 22977198 DOI: 10.1093/scan/nss106]

104 **Parker KJ**, Garner JP, Libove RA, Hyde SA, Hornbeak KB, Carson DS, Liao CP, Phillips JM, Hallmayer JF, Hardan AY. Plasma oxytocin concentrations and OXTR polymorphisms predict social impairments in children with and without autism spectrum disorder. *Proc Natl Acad Sci USA* 2014; **111**: 12258-12263 [PMID: 25092315 DOI: 10.1073/pnas.1402236111]

105 **Feldman R**. Oxytocin and social affiliation in humans. *Horm Behav* 2012; **61**: 380-391 [PMID: 22285934 DOI: 10.1016/j.yhbeh.2012.01.008]

106 **Olza-Fernández I**, Marín Gabriel MA, Gil-Sanchez A, Garcia-Segura LM, Arevalo MA. Neuroendocrinology of childbirth and mother-child attachment: the basis of an etiopathogenic model of perinatal neurobiological disorders. *Front Neuroendocrinol* 2014; **35**: 459-472 [PMID: 24704390 DOI: 10.1016/j.yfrne.2014.03.007]

107 **Bigelow AE**, Littlejohn M, Bergman N, McDonald C. The relation between early mother-infant skin to skin contact and later maternal sensitivity in South African mothers of low birth weight infants. *Infant Ment Health J* 2010; **31**: 358-377 [DOI: 10.1002/imhj.20260]

108 **Bystrova K**, Ivanova V, Edhborg M, Matthiesen AS, Ransjö-Arvidson AB, Mukhamedrakhimov R, Uvnäs-Moberg K, Widström AM. Early contact versus separation: effects on mother-infant interaction one year later. *Birth* 2009; **36**: 97-109 [PMID: 19489802 DOI: 10.1111/j.1523-536X.2009.00307.x]

109 **Parner ET**, Thorsen P, Dixon G, de Klerk N, Leonard H, Nassar N, Bourke J, Bower C, Glasson EJ. A comparison of autism prevalence trends in Denmark and Western Australia. *J Autism Dev Disord* 2011; **41**: 1601-1608 [PMID: 21311963 DOI: 10.1007/s10803-011-1186-0]

110 **Honda H**, Shimizu Y, Rutter M. No effect of MMR withdrawal on the incidence of autism: a total population study. *J Child Psychol Psychiatry* 2005; **46**: 572-579 [PMID: 15877763 DOI: 10.1111/j.1469-7610.2005.01425.x]

111 **Hansen SN**, Schendel DE, Parner ET. Explaining the increase in the prevalence of autism spectrum disorders: the proportion attributable to changes in reporting practices. *JAMA Pediatr* 2015; **169**: 56-62 [PMID: 25365033 DOI: 10.1001/jamapediatrics.2014.1893]

112 **Smeeth L**, Cook C, Fombonne PE, Heavey L, Rodrigues LC, Smith PG, Hall AJ. Rate of first recorded diagnosis of autism and other pervasive developmental disorders in United Kingdom general practice, 1988 to 2001. *BMC Med* 2004; **2**: 39 [PMID: 15535890 DOI: 10.1186/1741-7015-2-39]

113 **Rosenberg RE**, Daniels AM, Law JK, Law PA, Kaufmann WE. Trends in autism spectrum disorder diagnoses: 1994-2007. *J Autism Dev Disord* 2009; **39**: 1099-1111 [PMID: 19294498 DOI: 10.1007/s10803-009-0723-6]

114 **Pelligra R**, Doman G, Leisman G. A reassessment of the SIDS Back to Sleep Campaign. *ScientificWorldJournal* 2005; **5**: 550-557 [PMID: 16075152 DOI: 10.1100/tsw.2005.71]

115 **Inbar Z**, Meibar R, Shehada S, Irena V, Rubin L, Rishpon S. "Back to sleep": parents compliance with the recommendation on the most appropriate sleeping position of infants, Haifa District, Israel, 2001. *Prev Med* 2005; **40**: 765-768 [PMID: 15850877 DOI: 10.1016/

j.ypmed.2004.09.020]
116 **Tauman R**, Reisner SH, Amitai Y, Wasser J, Nehama H, Sivan Y. Sleep position in Israeli Jewish infants following the "back to sleep" campaign. *Isr Med Assoc J* 2004; **6**: 540-545 [PMID: 15373312]

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ORIGINAL ARTICLE

Observational Study

Solitary rectal ulcer syndrome: Is it really a rare condition in children?

Seyed Mohsen Dehghani, Maryam Bahmanyar, Bita Geramizadeh, Anahita Alizadeh, Mahmood Haghighat

Seyed Mohsen Dehghani, Maryam Bahmanyar, Bita Geramizadeh, Anahita Alizadeh, Mahmood Haghighat, Department of Pediatric Gastroenterology, Gastroenterohepatology Research Center, Shiraz Transplant Research Center, Nemazee Teaching Hospital, School of Medicine, Shiraz University of Medical Sciences, Shiraz 71937-11351, Iran

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Correspondence to: Seyed Mohsen Dehghani, MD, Professor, Department of Pediatric Gastroenterology, Gastroenterohepatology Research Center, Shiraz Transplant Research Center, Nemazee Teaching Hospital, School of Medicine, Shiraz University of Medical Sciences, Shiraz 71937-11351, Iran. dehghanism@sums.ac.ir
Telephone: +98-71-36125849
Fax: +98-71-36474298

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Abstract

AIM: To evaluate the clinicopathologic characteristics of the children with solitary rectal ulcer.

METHODS: Fifty-five children with a confirmed diagnosis of solitary rectal ulcer were studied in a period of 11 years from March 2003 to March 2014. All data were collected from the patients, their parents and medical records in the hospital.

RESULTS: From 55 studied patients, 41 were male (74.5%) and 14 female (25.5%). The mean age of the patients was 10.4 ± 3.7 years and the average time period from the beginning of symptoms to diagnosis of solitary rectal ulcer was 15.5 ± 11.2 mo. The most common clinical symptoms in our patients were rectal bleeding (n = 54, 98.2%) and straining during defecation or forceful defecation (n = 50, 90.9%). Other symptoms were as follows respectively: Sense of incomplete evacuation (n = 34, 61.8%), mucorrhea (n = 29, 52.7%), constipation (n = 14, 25.4%), tenesmus and cramping (n = 10, 18.2%), diarrhea (n = 9, 16.4%), and rectal pain (n = 5, 9.1%). The colonoscopic examination revealed 67.3% ulcer, 12.7% polypoid lesions, 10.9% erythema, 7.3% both polypoid lesions and ulcer, and 1.8% normal. Most of the lesions were in the rectosigmoid area at a distance of 4-6 cm from the anal margin. Finally, 69.8% of the patients recovered successfully with conservative, medical and surgical management.

CONCLUSION: The study revealed that solitary rectal ulcer is not so uncommon despite what was seen in previous studies. As the most common symptom was rectal bleeding, clinicians and pathologists should be familiar with this disorder and common symptoms in order to prevent its complications with early diagnosis.

Key words: Rectal bleeding; Children; Solitary ulcer; Colonoscopy; Forceful defecation

Core tip: What is known? (1) solitary rectal ulcer is considered a rare condition in children; (2) there is a small number of case report and small case series in pediatric age group in the literature; and (3) this disorder has not been well known in children, so, their symptoms can be confused with other more common diseases. What is new? (1) this study reveals that solitary rectal ulcer is not so uncommon in children; (2) to the best of our knowledge it is the largest pediatric series in the world; and (3) high index of suspicious is needed to think about and diagnosis of this disorder.

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INTRODUCTION

Solitary rectal ulcer has been defined as an infrequent but benign disorder of rectal and sigmoid region which is diagnosed on the basis of clinical symptom and histologic findings[1,2]. Although solitary rectal ulcer is a relatively common disorder in adults, it has been reported as a rare disease in children, so it can be misdiagnosed and troublesome in pediatric cases[3].

The exact cause is not known, but several causes such as trauma, rectal prolapse, ischemia, behavioral disorders such as excessive straining during defecation and rectal manipulation, sexual abuse and disharmony of the pelvic floor muscles during defection may be involved. Patients with this disorder exhibit a range of symptoms; however, a small number of patients can be asymptomatic[2,4-6].

The clinical symptoms in children are similar to adults, but since this disorder has not been well known in children, their symptoms can be confused with more common diseases. For instance, the obstructive symptoms can be viewed by parents as constipation, rectal bleeding may be related to the anal fissure or causes such as juvenile polyps or tenesmus and also rectal bleeding, may be incorrectly diagnosed as inflammatory bowel disease[3].

Colonoscopic findings are not specific and can be similar to other disorders of the rectal and anal area[2]. The histological study of solitary rectal ulcer has a distinct diagnostic appearance including thickening of the mucosal layer with disrupting crypts structure, infiltration of the lamina propria with fibroblasts, muscle and collagen fibers that lead to hypertrophied and disrupted muscularis mucosa which look like fibromuscular obliteration. Diagnosis of solitary rectal ulcer is usually based on the clinical history and histopathological changes from the rectal biopsy.

Before treatment, it is very important to differentiate solitary rectal ulcer from other disorders of the rectum including cancer, Crohn's disease, granulomatous diseases like lymphogranuloma venereum using laboratory facilities[7].

Many treatments have been tried so far, but there is no strong evidence for their effects[7]. It seems that the medical and surgical treatments are not very effective due to the high incidence of recurrence[8].

The first step of treatment is conservative therapy including dietary fiber, fluid intake, behavioral adaptation and use of laxative, which has not been proven to have long term benefits[2,5].

Enema with sucralfate can cover the wounds and act as a protection against harmful substances to heal the wound. Injection of sclerosing agents into the submucosa or rectal space has been useful for the treatment of rectal prolapse in some cases, but the benefits of long term uses need further investigation[5].

Most patients with solitary rectal ulcer have a satisfactory prognosis with treatments such as behavior change in their childhood. Follow up of these patients is necessary in order to improve and sustain treatment method to prevent morbidity and recurrences which lead to the disease progresses to adulthood[3]. The aim of this study was to assess the children diagnosed with solitary rectal ulcer in Southern Iran.

MATERIALS AND METHODS

All of the children including 55 (14 females and 41 males) with final diagnosis of solitary rectal ulcer in Pediatric Gastroenterology Section of Nemazee Hospital affiliated to Shiraz University of Medical Sciences from March 2003 to March 2014 were studied.

The diagnosis of solitary rectal ulcer in our patients was based on the clinical history, colonoscopic and histopathological findings of rectosigmoid biopsies.

The colonoscopies were done under general anesthesia and biopsies were taken from normal and abnormal looking mucosa and all lesions of the rectum and sigmoid colon in all patients. Histopathologic evaluation of all biopsy samples was done by a gastrointestinal pathologist (BG).

After confirming the diagnosis, their information including age and sex, clinical presenting symptoms, colonoscopic and histopathologic findings and also therapeutic modalities and responses to their treatment were retrieved from their registered medical records

and also by phone calls. All of the information obtained from patients' records was registered into the designed collecting data forms; then the analysis of data, was performed according to their age and sex, presenting symptoms, colonoscopic and histopathologic findings and treatment outcome.

This study was approved by the Research Ethics Committee of Shiraz University of Medical Sciences and informed consent was obtained from all the parents or legal guardians.

RESULTS

In these 11 years, 55 children with the final diagnosis of solitary rectal ulcer were evaluated. The mean age of the onset of symptoms in the patients was 9.2 ± 3.4 years. The mean age of the patients at diagnosis was 10.4 ± 3.7 years. The average time from the onset of symptoms to final diagnosis was 15.5 ± 11.2 mo. The youngest and oldest patients at the onset of symptoms were 1.5 and 17 years, respectively. From 55 patients, 14 were female (25.5%) and 41 male (74.5%).

The first clinical finding in all patients except one was rectal bleeding. One patient presented with a history of passing of mucoid stool and had no history of rectal bleeding during the illness.

The most common presenting clinical symptoms of the patients was rectal bleeding (n = 54; 98.2%) and then straining during defecation or forceful defecation (n = 50; 90.9%). Sense of incomplete evacuation was reported in 34 patients (61.8%) and 29 cases had a history of passing mucoid stool (52.7%). Change of bowel habits was seen in some patients as 14 patients were suffering from constipation (25.4%) and 9 patients had a history of diarrhea (16.4%). Although abdominal pain is not an obvious symptom of the disease, 18.2% of the patients were suffering from this problem. Three patients (5.4%) had a history of anal manipulation with fingers, 1 had a history of sexual abuse, and 4 patients (7.3%) had a history of rectal prolapse and the sensation of a mass during defecation.

The colonoscopic studies of 55 patients as recorded in their charts were examined. Colonoscopy was normal in 1 of the patients and showed no specific findings (1.8%). Colonoscopy of 37 patients showed ulcers (67.3%). Among the ulcers, 3 were superficial (8.1%), 1 was circumferential (2.7%), 1 was reported as linear (2.7%), and 1 of them was clean based (2.7%). The others (83.8%) were white based ulcers with erythematous borders and exudates. Seven patients had polypoid lesions (12.7%) which were pedunculated in 3 patients (42.8%). Four patients had both ulcers and polypoid lesions (7.3%). Colonoscopy of 6 patients only showed erythema (10.9%) and there was no obvious ulcer. In colonoscopy of 37 patients only one lesion was seen (67.3%), 7 patients had two lesions (12.7%) and 10 patients showed more than two lesions (18.2%).

The ulcers were registered with different sizes. Most of them were 5-15 mm in diameter.

Table 1 Different treatment protocol and response rate in children with solitary rectal ulcer

Treatment protocol	Number	Percent
Conservative treatment	11	21.6%
Asacol suppositories	23	45.1%
Sucralfate enema	9	17.6%
Alcohole injection	2	3.9%
Methylprednisolone injection	1	1.9%
Rectopexy	5	9.8%

All of the ulcers were localized in the rectosigmoid region. The distance of most of them from the anal margin was 4 to 6 cm, but it was about 13 cm in one of the patients and 20 cm in another one.

The histology findings of patients included ulcer, granulation tissue, inflammation, increasing collagen bands and fibrosis in lamina propria, and sometimes elongation of the crypts, fibrosis, reduction in goblet cells and hyperplastic changes.

The therapeutic information of 51 patients was provided from their reports and by phone calls. Different treatments were offered for different patients based on the severity of the symptoms. Conservative measures including avoidance from excessive straining during defecation, use of high fiber diets and fluids, and use of laxatives (if they had constipation) were recommended to all patients. Eleven patients (21.6%) became completely symptom free with only recommended conservative treatments. In 23 patients (45.1%) who had not responded to the conservative treatments, the use of Asacol suppository was recommended. Nine patients (17.6%) were treated with Sucralfate enema.

The alcohol injection was carried out for 2 patients (3.9%) who had rectal prolapse. Methylprednisolone was injected around the lesion in 1 of the patients. Five patients (9.8%) with persistent solitary rectal ulcer and rectal prolapse were finally treated with laparoscopic ventral rectopexy (Table 1).

From 55 patients, 43 were followed by medical reports and also with phone calls. Thirty patients (69.8%) showed a significant improvement during the follow-up and their symptoms disappeared. Most of these patients (28 patients) had responded to the conservative treatments, Asacol suppositories, and Sucralfate enema and 2 patients were treated with rectopexy. Thirteen patients had still their symptoms (30.2%) at the time of the study.

DISCUSSION

Solitary rectal ulcer is an unusual and uncommon disorder of rectosigmoid region which is mostly seen and reported in adults and is less common in children. This disorder is diagnosed with clinical findings, colonoscopy findings and histology changes[2].

In this study, 55 children with the final diagnosis of solitary rectal ulcer were evaluated in 11 years, and to the best of our knowledge it is the largest pediatric

series in the world.

Most of the patients (74.5%) were male in this study which is similar to other studies and reports on the children with solitary rectal ulcer. In the study by Perito *et al*[9], 9 out of 15 patients were male. Five of 6 children were male in Urganci *et al*[8] study and 9 out of 12 patients were also male in Dehghani *et al*[10] study, but in Blackburn *et al*[3] study, from 8 affected children, 4 were female and 4 were male. However, this predominance in males is only in the pediatric age group and the prevalence of disorder between male and female is the same in adults. It has been even mentioned in some articles that it has more prevalence in the women; so that, from 68 studied patients in Madigan and Morson[7]'s study, 33 were male and 35 were female.

In this study, the youngest and oldest patients were 1.5 and 17 years at the onset of the symptoms. The mean ± SD of the patients was 10.4 ± 3.7 years and the average of time from the beginning of symptoms to diagnosis of solitary rectal ulcer was 15.5 ± 11.2 mo, these results are similar to Blackburn *et al*[3] study in which the mean age of children was 9.87 years and the average time from the onset of the symptoms to diagnosis was 1.73 years. In Urganci *et al*[8] study, the average of time from the onset of symptoms to the diagnosis of disease was reported as 4.7 years; this is longer than this study. In Suresh *et al*[11] study, the age of the youngest patient studied was 1.5 years which is similar to this study.

In this research, the first presenting symptom in most patients was rectal bleeding (98.2%) and then excessive straining during defecation (90.9%). Other problems in order of their prevalence included the sense of incomplete evacuations, mucoid stools, constipation, abdominal pain and tenesmus, diarrhea, and rectal pain. In the study by Suresh *et al*[11] the most common clinical finding of the patients have also been reported as rectal bleeding which has been seen in all 22 patients, but it is expressed that need for blood transfusions in this disorder is low. In another study by Madigan and Morson, the most common clinical symptoms were bleeding from the anus (91%), then mucorrhea, rectal pain, diarrhea and lower abdominal pain[7]. In another study by Blackburn *et al*[3] all of the patients had the history of straining on defecation and 7 of 8 patients had rectal bleeding history. Other symptoms in order of frequency were sense of incomplete evacuation, tenesmus, mucus excretion, constipation, diarrhea and manipulation of the anus for defecation, respectively[3]. According to this study and other related studies, it seems that rectal bleeding is the most common symptom; other less common symptoms were mucorrhea and straining during defecation which can be easily obtained from the patient's history.

The main causes of this disorder are still unknown. In previous studies, it has been concluded that several factors lead to this disorder. In most of the previous studies, it has been stated that the main mechanism of this disorder is mostly excessive straining during defecation which leads to increased intra-abdominal pressure which in turn causes protrusion of the anterior wall of the rectum into the anal canal and puborectalis muscle contraction and continuation of this state leads to trapping the mucus membrane of the anterior wall of the rectum, edema and hyperemia and finally hypoperfusion, ischemia and ulceration[12]. In the present study, more than 90% of patients had excessive straining during defecation which can confirm this problem. In addition to these, 3 patients had the history of anal manipulation with fingers, 1 had the history of sexual abuse and 4 patients had the history of rectal prolapse and sensation of a mass during defecation which is considered as causes of this disorder due to mucosal trauma.

De la Rubia *et al*[1] have reported ischemia as the etiology of this disorder because of the lack of trauma in the studied patients and histologic changes in the course of the disease and have suggested that continuous contraction of the puborectalis muscle during defecation can cause hyperemia, edema, necrosis and ulcer in the mucous membrane of the rectum. Womack *et al*[13] also concluded that the combination of rectal prolapsed and high pressure during defecation cause instability between intra-abdominal pressure and into the rectum which leads to ruptured submucosal vessels and mucosal necrosis[13]. In Dehghani *et al*[10] study, traditional way of defecation has been proposed as the cause of solitary rectal ulcer, which leads to protrusion of the anterior wall of the rectum into the anal canal and then hyperemia, edema and ulcer.

Therefore, according to these studies and the results of the present study, it can be concluded that the combination of high rectal pressure during defecation, the hidden prolapse and insufficient contraction of the puborectalis muscle in addition to trauma which cause direct damages, leads to hyperemia, ischemia, and finally ulceration of the rectal wall and the traditional way of defecation in our geographic region in Iran, can intensify these factors; it is the reason for high prevalence of this disease. It has been recommended that defecography and anorectal manometry should be performed in all children with solitary rectal ulcer to define the primary pathophysiological abnormality and to select the most appropriate treatment protocol. These evaluations were not performed in this work.

In the present study, the most common findings in the colonoscopic examination of the patients were ulcer (67.3%), polypoid lesions (12.7%), and mucosal redness and erythema (10.9%). Four patients had both ulcer and polypoid lesions (7.3%) and 1 colonoscopy failed to show any specific finding (1.8%). Most of the patients had one lesion (67.3%) and the size of many ulcers was 5-15 mm and most of them were in 4-6 cm of the anal margin. There were one ulcer in 13 cm and the other one in 20 cm of the anal margin. In the study by Madigan *et al*[7], most of the patients had one ulcer (70%). The size of most of the ulcers was about 2 cm

and their distance from the anus was between 3 and 15 cm, but most of them were in 7-10 cm of the anal margin. It is stated in this study that there is one stage of disease in which there is no ulcer and it can be seen at the local inflammation of the rectum[7]. It seems that there were some patients in this stage that did not show any specific findings in colonoscopy or only showed redness and inflammation. In the study by Dehghani *et al*[10] 11 out of 12 patients had between 1 to 4 superficial ulcers which was in 7 cm of rectosigmoid area and only 1 patient had polypoid lesion. In the study by Perito *et al*[9] it is mentioned that the lesions of patients are mostly at the end part of rectum and in 10 cm of the anal margin. From 10 registered colonoscopy report, there were redness and inflammation in 8 patients and there was polypoid lesions in 4 of them.

According to the studies conducted so far, it seems that polypoid lesions are rare in the pediatric age group and most of the lesions are ulcers, erythema and inflammation; this has been reported in previous studies[14].

All of the patients evaluated in this study, were initially treated with conservative treatments, recommendation to avoid straining during defecation and also dietary changes. Only the patients who did not respond to this method were treated with Sucralfate enema, Asacol suppository and also methylprednisolone injection around the lesion and finally 5 patients who did not also respond to these treatments, were treated with laparoscopic ventral rectopexy. During the follow-up, the symptoms of 69.8% of patients were recovered. Only 2 of these non-responsive patients were treated with rectopexy and the others with conservative treatments and use of Sucralfate enema and Asacol suppository.

In the study by Dehghani *et al*[10] conservative treatments, and behavioral and dietary changes were recommended as the preliminary treatment. In that study, 58.3% of the patients (7 out of 12 patients) had the complete recovery of symptoms after treatment with Sucralfate enema and concluded that this is a suitable treatment for children. One of their patients responded to Salicylate enema, 1 to corticosteroid enema, 2 to corticosteroid injection and 1 of the patients were finally treated with rectopexy[10].

In the study by Martín de Carpi *et al*[15] which was conducted on 3 affected patients, 2 patients were treated with budesonide enema and 1 patient with only a dietary change. The symptom of all the 3 patients was recovered. In the study by Blackburn *et al*[3] changing the behavior and encouraging children not to strain on defecation were recommended and the stool softeners were only used for the patients who had rigid stool; improvement was seen in all patients except for a patient who was not able to cooperate due to autism. This study indicated that most of the patients responded to behavioral change methods like biofeedback therapy[3]. In another study by Urganci *et al*[8] the patient's treatment began with Mesalazine enema, Sucralfate and steroid enema.

These and other similar studies reveal that a comprehensive study has not been conducted so far to determine the best therapeutic procedures, so determining suitable treatment requires more and more complete examinations. But it seems that the treatment method without complications like trying to change diets and bowel habits is the best treatment in children; also, it is better to consider medical treatment and use of laxatives and enema with different substances as the second line of treatment[2,9].

There are also different studies about the medical management in the children and most of the surgical cases have been conducted in patients with polypoid lesions or rectal prolapse and patients who were still symptomatic after trying several medical treatment[14,16,17].

Bonnard *et al*[17] have published the first successful rectopexy with laparoscopic method in a 12-year-old child who became asymptomatic in the next follow up and his colonoscopy became normal. In Godbole *et al*[16] study, polypoid lesions and hidden rectal prolapse were diagnosed in the examinations for 1 of the 2 studied patients. Polypectomy through the anus and then ablation of the remained granulation were performed for this patient. The second patient had a large prolapse and was treated with rectopexy and the symptoms of both patients were recovered in the next follow-ups.

According to this and other similar studies, it seems that this disorder is not so rare in children in spite of what had been said about its rarity before and the reason of its low reporting is low familiarity of physicians with this disorder and its similarity with other common diseases of the anal canal and rectosigmoid. Therefore, the physicians should be aware of this disorder and thus prevent the late diagnosis of the disease and prevent its long term complications.

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COMMENTS

Background

Solitary rectal ulcer is defined as an infrequent but benign disorder of rectal and sigmoid colon which is diagnosed on the basis of clinical symptoms and histologic findings. The clinical symptoms in children are similar to adults, but since this disorder has not been well known in children, their symptoms can be confused with more common diseases of the rectum and sigmoid. It is very important to differentiate solitary rectal ulcer from other disorders of the rectum and sigmoid before starting treatment. Follow-up of these patients is necessary

in order to improve and sustain treatment method to prevent morbidity and recurrences which lead to the disease progresses to adulthood.

Research frontiers

Solitary rectal ulcer is diagnosed as a cause of rectal bleeding in children in Pediatric Gastroenterology Section of Nemazee Hospital affiliated to Shiraz University of Medical Sciences and its frequency become increasing during the last years. However, there are very few English language literatures sources from Iran and other countries concerning the diagnosis and treatments of solitary rectal ulcer in children. The research hotspot is to introduce these real things happening to this population and to help other peers understand these backgrounds and trends in Iran.

Innovations and breakthroughs

In recent years, the number of children with rectal bleeding who diagnosed as of solitary rectal ulcer has been increasing in Shiraz, Iran. The present study represents the largest pediatric series of solitary rectal ulcer in the world. On the other hand, the current data also suggested that this disorder is not so rare in children in spite of what had been said about its rarity before and the reason of its low reporting is low familiarity of physicians with this disorder and its similarity with other common diseases of the rectosigmoid. Therefore, the physicians should be aware of this disorder and thus prevent the late diagnosis of the disease and prevent its long term complications.

Applications

The data in this study suggested that solitary rectal ulcer is not so rare in children and conservative and medical management for solitary rectal ulcer could yield relatively favorable outcomes. Furthermore, this study also provided readers with important information regarding the clinical and colonoscopic findings in these patients.

Terminology

Solitary rectal ulcer is a benign and chronic disorder well known in young adults and less in children. It is often related to prolonged excessive straining or abnormal defecation and clinically presents as rectal bleeding, copious mucus discharge, feeling of incomplete defecation, and rarely rectal prolapse. Solitary rectal ulcer is diagnosed based on clinical symptoms and endoscopic and histological findings. The current treatments are suboptimal.

Peer-review

Available papers concerning pediatric solitary rectal ulcer are scarce. The authors in this study analyzed the characteristics and outcomes of children with solitary rectal ulcer based on a large single-center series. This study showed that solitary rectal ulcer is not so rare in children. The results were interesting and provided important information concerning the background and trends of various treatments for solitary rectal ulcer in children.

REFERENCES

1 **De la Rubia L**, Ruiz Villaespesa A, Cebrero M, Garcia de Frias E. Solitary rectal ulcer syndrome in a child. *J Pediatr* 1993; **122**: 733-736 [PMID: 8496752 DOI: 10.1016/S0022-3476(06)80016-8]

2 **Zhu QC**, Shen RR, Qin HL, Wang Y. Solitary rectal ulcer syndrome: clinical features, pathophysiology, diagnosis and treatment strategies. *World J Gastroenterol* 2014; **20**: 738-744 [PMID: 24574747 DOI: 10.3748/wjg.v20.i3.738]

3 **Blackburn C**, McDermott M, Bourke B. Clinical presentation of and outcome for solitary rectal ulcer syndrome in children. *J Pediatr Gastroenterol Nutr* 2012; **54**: 263-265 [PMID: 22266488 DOI: 10.1097/MPG.0b013e31823014c0]

4 **Dehghani SM**, Malekpour A, Haghighat M. Solitary rectal ulcer syndrome in children: a literature review. *World J Gastroenterol* 2012; **18**: 6541-6545 [PMID: 23236227 DOI: 10.3748/wjg.v18.i45.6541]

5 **Keshtgar AS**. Solitary rectal ulcer syndrome in children. *Eur J Gastroenterol Hepatol* 2008; **20**: 89-92 [PMID: 18188026 DOI: 10.1097/MEG.0b013e3282f402c1]

6 **Vaizey CJ**, Roy AJ, Kamm MA. Prospective evaluation of the treatment of solitary rectal ulcer syndrome with biofeedback. *Gut* 1997; **41**: 817-820 [PMID: 9462216 DOI: 10.1136/gut.41.6.817]

7 **Madigan MR**, Morson BC. Solitary ulcer of the rectum. *Gut* 1969; **10**: 871-881 [PMID: 5358578 DOI: 10.1136/gut.10.11.871]

8 **Urgancı N**, Kalyoncu D, Eken KG. Solitary rectal ulcer syndrome in children: a report of six cases. *Gut Liver* 2013; **7**: 752-755 [PMID: 24312719 DOI: 10.5009/gnl.2013.7.6.752]

9 **Perito ER**, Mileti E, Dalal DH, Cho SJ, Ferrell LD, McCracken M, Heyman MB. Solitary rectal ulcer syndrome in children and adolescents. *J Pediatr Gastroenterol Nutr* 2012; **54**: 266-270 [PMID: 22094902 DOI: 10.1097/MPG.0b013e318240bba5]

10 **Dehghani SM**, Haghighat M, Imanieh MH, Geramizadeh B. Solitary rectal ulcer syndrome in children: a prospective study of cases from southern Iran. *Eur J Gastroenterol Hepatol* 2008; **20**: 93-95 [PMID: 18188027 DOI: 10.1097/MEG.0b013e3282f1cbb6]

11 **Suresh N**, Ganesh R, Sathiyasekaran M. Solitary rectal ulcer syndrome: a case series. *Indian Pediatr* 2010; **47**: 1059-1061 [PMID: 20453265 DOI: 10.1007/s13312-010-0177-0]

12 **Ertem D**, Acar Y, Karaa EK, Pehlivanoglu E. A rare and often unrecognized cause of hematochezia and tenesmus in childhood: solitary rectal ulcer syndrome. *Pediatrics* 2002; **110**: e79 [PMID: 12456946 DOI: 10.1542/peds.110.6.e79]

13 **Womack NR**, Williams NS, Holmfield JH, Morrison JF. Pressure and prolapse--the cause of solitary rectal ulceration. *Gut* 1987; **28**: 1228-1233 [PMID: 3678951 DOI: 10.1136/gut.28.10.1228]

14 **Saadah OI**, Al-Hubayshi MS, Ghanem AT. Solitary rectal ulcer syndrome presenting as polypoid mass lesions in a young girl. *World J Gastrointest Oncol* 2010; **2**: 332-334 [PMID: 21160895 DOI: 10.4251/wjgo.v2.i8.332]

15 **Martín de Carpi J**, Vilar P, Varea V. Solitary rectal ulcer syndrome in childhood: a rare, benign, and probably misdiagnosed cause of rectal bleeding. Report of three cases. *Dis Colon Rectum* 2007; **50**: 534-539 [PMID: 17080282 DOI: 10.1007/s10350-006-0720-1]

16 **Godbole P**, Botterill I, Newell SJ, Sagar PM, Stringer MD. Solitary rectal ulcer syndrome in children. *J R Coll Surg Edinb* 2000; **45**: 411-414 [PMID: 11153436]

17 **Bonnard A**, Mougenot JP, Ferkdadji L, Huot O, Aigrain Y, De Lagausie P. Laparoscopic rectopexy for solitary ulcer of rectum syndrome in a child. *Surg Endosc* 2003; **17**: 1156-1157 [PMID: 12728388 DOI: 10.1007/s00464-002-4285-3]

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ORIGINAL ARTICLE

Prospective Study

Factors affecting breastfeeding duration in Greece: What is important?

Evangelia-Filothei Tavoulari, Vassiliki Benetou, Petros V Vlastarakos, Theodora Psaltopoulou, George Chrousos, George Kreatsas, Alexandros Gryparis, Athena Linos

Evangelia-Filothei Tavoulari, Vassiliki Benetou, Theodora Psaltopoulou, Alexandros Gryparis, Athena Linos, Department of Hygiene, Epidemiology and Medical Statistics, University of Athens, 11527 Goudi, Athens, Greece

Petros V Vlastarakos, ENT Department, MITERA Paediatric Infirmary, 15123 Marousi, Athens, Greece

George Chrousos, 1st Department of Pediatrics, University of Athens, "Aghia Sophia" Children's Hospital, 11527 Athens, Greece

George Kreatsas, 2nd OBG Department, Aretaieion University Hospital, 11528 Athens, Greece

Author contributions: Tavoulari EF conducted the research, participated in the interpretation of data, and wrote the article; Benetou V participated in study design and in the interpretation of data, and wrote the article; Vlastarakos PV participated in the interpretation of data, and wrote the article; Psaltopoulou T participated in the interpretation of data, and critically reviewed the article; Chrousos G and Linos A participated in study design and critically reviewed the article; Kreatsas G provided the setting and patients for the study, participated in study design, and critically reviewed the article; Gryparis A prepared the statistical analysis of data, and critically reviewed the article; all authors read and approved the final manuscript.

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Correspondence to: Dr. Evangelia-Filothei Tavoulari, Department of Hygiene, Epidemiology and Medical Statistics, University of Athens, 75 Mikras Asias Str., 11527 Goudi, Athens, Greece. tavoularieva@yahoo.gr
Telephone: +30-210-8577976

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Abstract

AIM: To investigate factors associated with breastfeeding duration (BD) in a sample of mothers living in Greece.

METHODS: Four hundred and twenty-eight mothers (438 infants) were initially recruited in a tertiary University Hospital. Monthly telephone interviews (1665 in total) using a structured questionnaire (one for each infant) were conducted until the sixth postpartum

month. Cox regression analysis was used to assess factors influencing any BD.

RESULTS: Any breastfeeding rates in the first, third, and sixth month of the infant's life reached 87.5%, 57.0% and 38.75%, respectively. In the multivariate analysis, maternal smoking in the lactation period [hazard-ratio (HR) = 4.20] and psychological status (HR = 1.72), and the introduction of a pacifier (HR = 2.08), were inversely associated, while higher maternal education ($HR_{university/college\ vs\ primary/high\ school}$ = 0.53, $HR_{master's\ vs\ primary/high\ school}$ = 0.20), and being an immigrant (HR = 0.35) were positively associated with BD.

CONCLUSION: Public health interventions should focus on campaigns against smoking during lactation, target women of lower educational status, and endorse the delayed introduction of pacifiers.

Key words: Breastfeeding; Exclusive; Formula feeding; Duration; Greece

Core tip: This was a prospective study investigating the factors which are associated with breastfeeding duration (BD) in a sample of mothers living in Greece. Maternal smoking during lactation, the respective psychological status, and the introduction of a pacifier, were inversely associated, while higher maternal education and maternal immigrant status positively associated with BD. Public health interventions should focus on campaigns against smoking during lactation, target women of lower educational status, and endorse the delayed introduction of pacifiers.

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INTRODUCTION

Breastfeeding is the natural way to feed infants and young children ensuring optimal growth and development[1-5], while exclusive breastfeeding is recommended for the first six months of life[5]. Nevertheless, breastfeeding is not fully protected and supported as expected, and a number of important international public health initiatives were endorsed by the World Health Organization and United Nations International Children's Emergency Fund in order to protect and support breastfeeding[6-8].

Although some slight improvements have been recorded in breastfeeding rates during the last decade, they continue to fall short of global recommendations, and many mothers, who initially chose to breastfeed, shift to formula-feeding, and finally cease breastfeeding[9-12].

A variety of factors influence and determine breastfeeding initiation and duration, including personal and socio-cultural characteristics of the mother, the child and the family, aspects of the health care system, public health and social policies, as well as advertising and promotion of alternative feeding methods[13]. Some of these factors, such as maternal education and employment, may act on the opposite direction in different populations[11]. The identification of the determinants that influence breastfeeding duration (BD) across countries may provide useful information, which could be used to improve breastfeeding rates at national levels and worldwide.

The aim of the present study is to investigate the factors which are associated with BD in a sample of mothers living in Greece, a typical Southern European country, and explore further how modifiable these factors are.

MATERIALS AND METHODS

Study population and data collection at baseline

Four hundred and twenty-eight mothers, who had given birth to 438 live infants, were recruited in the maternity ward of a tertiary University Hospital between February and December 2009. The hospital provides gynaecological and maternity services to women residing in the Prefecture of Attica, where the capital of Greece, Athens is located, and monitoring of high-risk pregnancies at a nationwide level.

The study design and characteristics of the study population have been described in more detail elsewhere[14]. In brief, during the aforementioned 10-mo period, women, who had delivered a child and were permanent inhabitants of Greece with basic understanding of the Greek language, were approached by the first author after 24 h from delivery, and asked to participate in the study. The mothers were expected to be in good condition to withstand an interview at that time, taking also into account that the average nationwide in-patient stay in the maternity ward is four days.

The study protocol was approved by the Ethics Committee of the Medical School of University of Athens. All participants were asked to sign an informed consent form before being enrolled in the study.

At recruitment, baseline information about medical, lactation-related, and socio-demographic characteristics was collected through a structured baseline questionnaire, by means of an interview conducted by the first author. The baseline questionnaire consisted of five sections: (1) a section associated with the lactation status of the specific newborn/s (seven items); (2) a section associated with the gestation/childbirth of the specific newborn/s (eight items); (3) a section related

to the past medical/gynaecological history of the mother (two items); (4) a section for general information (three items); and (5) socio-economic characteristics (12 items).

The selection of the variables included in each section was based on prior knowledge derived from respective studies which had investigated a similar research hypothesis, as well as on our intention to explore further the respective parameters in the Greek setting. The questionnaire included both open-ended and closed questions and the baseline interviews typically lasted for about 30 min. Pre-pregnancy body weight and height were self-reported.

Data collection during follow-up

Telephone interviews for the collection of information about the duration of breastfeeding and/or alternative feeding methods were conducted by the first author with the use of an itemized follow-up questionnaire. The respective phone calls were made every month during the first six months following the child's birth. In total, 1665 interviews took place within a 14-mo period. The first interview wave involved 400 infants yielding a participation rate of 91.3%.

The follow-up questionnaire, consisting of closed-ended questions, collected information which was grouped in the following sections: (1) topics relating to the infant (number of items 5); (2) issues associated with the mother (number of items 7); (3) approaches of health professionals (number of items 1); and (4) alterations influenced by social/economic factors (number of items 4). The duration of the follow-up interview was approximately 15 min.

Infant feeding definitions

Exclusive breastfeeding comprised of giving breastmilk (or expressed breastmilk) only to the infant, precluding the use of any other liquid or solid food, except vitamin syrups/drops, medication, or mineral supplements. Formula-fed babies were given liquid food from a bottle with a nipple/teat, while no breastmilk was provided[15]. Any other combination of breastmilk with formula and/or additional liquids, or the administration of food and food-based fluids (such as weaning foods) was classified as partial breastfeeding[16].

A mother was considered to be continuing either exclusive or partial breastfeeding when she replied positively to the respective question, during the follow-up phone call.

Statistical analysis

Initial analysis included descriptive statistics. Categorical variables are presented as relative and absolute frequencies. The main variable of interest was BD (exclusive and partial together, henceforth referred as any breastfeeding). BD is a quantitative variable demonstrating right censoring. We employed Cox proportional hazard models to explore the parameters which were associated with any BD, after ascertaining that the respective prerequisite assumptions were met. Univariate models were initially run, in order to detect any potential association between BD (in weeks) and each of the covariates of interest. Potential confounding was addressed with the use of multivariate models. The final multivariate model included all covariates demonstrating a *P* value of less than 0.1 in the univariate analysis, as well as, a small set of covariates inserted in the model based on prior knowledge from the pertinent literature. These covariates comprised the age of the mother, the pre-pregnancy body mass index (BMI), and the employment status. Maternal age was additionally tested for correlation with the period of active lactation by applying Spearman's correlation coefficient. Pre-pregnancy BMI was calculated by dividing the weight of the mother (in kilogram) by the square height (in meters).

Available data were processed by using the IBM SPSS Statistics 21.0. Statistical importance was accepted at a level of 0.05 and lower.

Table 1 Main socio-demographic characteristics of the mothers at recruitment

Characteristics	% (*n*)
Maternal age	
Mean (SD)[1]	32.0 (4.7)
Country of origin	
Greece	71.0 (304)
Other	29.0 (124)
Marital status[2]	
Married	96.2 (403)
Not married	3.8 (16)
Educational status	
Primary school	1.8 (8)
Secondary/high school	37.0 (158)
University/college	54.4 (233)
Postgraduate studies	6.8 (29)
Employment status[3]	
Employed	73.4 (311)
Public sector	18.6 (79)
Private sector	45.1 (191)
Self-employed	7.8 (33)
Other	1.9 (8)
Domestically occupied	20.5 (87)
Unemployed	6.1 (26)

[1]In years; [2]Missing cases $n = 9$; [3]Missing cases $n = 4$. *n*: Absolute numbers.

RESULTS

Approximately 70% of recruited mothers had Greek nationality, while the mean age was 32 years (min 19, max 44) (Table 1). A high percentage of the mothers were university or college graduates (54.4%) and employed (73.4%). The vast majority of mothers were also married. The mean maternal BMI was 23.4 kg/m^2 at the beginning of gestation and 28.6 kg/m^2 before delivery. Almost one third of the mothers (30.8%) were smokers before pregnancy. Previous breastfeeding

Table 2 Characteristics of the infant population at recruitment

Characteristics	% (*n*)
Gender	
Female	45.7 (200)
Male	54.3 (238)
Birth weight	
Mean (SD)[1]	3215 (493)
Delivery mode	
Vaginal delivery	49.0 (218)
Caesarean section	51.0 (220)
Multiplicity	
Singletons	95.4 (418)
Twins	4.6 (20)
Prematurity (< 37 wk)	
No	91.0 (399)
Yes	9.0 (39)
Newborn health problems[2]	
No	80.5 (350)
Yes	19.5 (86)

[1]In grams; [2]Missing cases *n* = 2. *n*: Absolute numbers.

Table 3 Partial and exclusive breastfeeding rates during the follow-up period by postpartum month

Postpartum month	Partial breastfeeding *n*[1] (%)	Exclusive breastfeeding *n* (%)
1	175 (43.75)	174 (43.50)
2	125 (31.25)	154 (38.50)
3	92 (23.00)	136 (34.00)
4	75 (18.75)	118 (29.50)
5	58 (14.50)	106 (26.50)
6	57 (14.25)	98 (24.50)

[1]Absolute numbers.

experience was reported in 44.5% of women, whilst the present birth was the first in 50.0% of recruited mothers.

With regard to baseline characteristics related to the infant (Table 2), the percentage of babies being delivered *via* caesarean section was remarkably high (51.0% of all deliveries), although in most cases the reason was a previous caesarean. The majority of infants were full-term (91.0%), had normal birth weight (94.0%), and were born without any health problem (80.5%). A far as the maternity hospital practices were concerned, rooming-in was implemented in 47.0% of newborns and breastfeeding was encouraged by health professionals and/or family in 89.7% of them.

Any breastfeeding initiation rate was high (92.1%), while almost half of the mothers (44.4%) practiced exclusively breastfeeding. Any breastfeeding rates were 87.5% for the first, 57.0% for the third and 38.8% for the sixth postpartum month. Exclusive breastfeeding at the first, third and six month reached 43.5%, 34.0% and 24.5%, respectively (Table 3). The percentages of formula-feeding were 12.5%, 36.5% and 57.3%, for the aforementioned monthly periods, respectively. With respect to BD, the mean duration was 15.3 (± 8.6, min 1 and max 24) wk.

Table 4 Reasons for breastfeeding cessation in the postpartum period as reported by mothers (percentages only refer to mothers who have stopped breastfeeding)

Reason for breastfeeding cessation	Percentage of mothers (%)
Not enough milk	48.5
Other[1]	29.3
Other medical reason[2]	13.5
Return to work	4.2
Sore/traumatized nipples	2.4
Mastitis	1.5
Obstructed mammary ducts	0.6

[1]Includes fatigue, ablactation, general breastfeeding problems; [2]Includes health problems of the infant, maternal health problems, medications received by the mother.

Commonly reported problems which led to breastfeeding discontinuation are shown in Table 4. Almost half of the mothers (48.5%), who stopped breastfeeding, reported that the main reason for the cessation of breastfeeding was the production of inadequate milk volume. In addition, a noteworthy percentage of mothers reported "other" (29.3%) (*i.e.*, fatigue, ablactation, general breastfeeding problems), or "other medical" (13.5%) (*i.e.*, health problems of the infant, maternal health problems, medications received by the mother) reasons for breastfeeding cessation.

Exclusive breastfeeding percentage is also presented, as it evolves during the follow-up period, when the monthly samples of the interviewed mothers are examined individually (*i.e.*, a given sample of mothers who continue to breastfeed is compared to the previous or the next interview). The progress of exclusive breastfeeding for each monthly sample is depicted in Figure 1. The percentage of exclusively breastfed babies in the overall population of breastfed babies of each monthly interview was, hence, noted. Exclusive breastfeeding practice, when studied under this approach, demonstrated an increasing trend throughout follow-up, up until the fifth postpartum month (saturation period), after which the respective rates started to fall (Figure 1).

Table 5 presents the fully adjusted Cox regression-derived hazard ratios for any BD by specific characteristics of the mother or the infant. Mothers who smoked during the follow-up period were 4.2 times more likely (95%CI: 2.57-6.89) to stop breastfeeding earlier within the first 6 mo after delivery, compared to women who did not smoke during follow-up ($P < 0.001$). On the other hand, maternal smoking before pregnancy was not associated with any BD ($P = 0.124$) in the multivariate analysis, in contrast to the results of the univariate analysis, where it was found to be inversely associated (HR = 2.16, 95%CI: 1.67-2.80) (data not shown).

The nationality of the mother was found to be important, as immigrant mothers had 0.35 times (95%CI: 0.21-0.58) less chance for earlier breastfeeding discontinuation in comparison with Greek

Table 5 Adjusted hazard ratios and 95%CI for any breastfeeding duration

Characteristic	HR	95%CI	*P* value
Maternal age (per year)	1.01	0.97 to 1.05	*P* = 0.779
BMI before pregnancy (per kg/m^2)	1.01	0.97 to 1.05	*P* = 0.600
Maternal educational status			
High school graduate or lower	1.00		
University/college education	0.53	0.37 to 0.76	*P* = 0.001
Postgraduate degree	0.20	0.09 to 0.43	*P* < 0.001
Maternal employment status			
Unemployed/domestically occupied	1.00		*P* = 0.213
Employed	0.76	0.50 to 1.17	
Maternal nationality			
Greek	1.00		
Immigrant	0.35	0.21 to 0.38	*P* < 0.001
Smoking before pregnancy			
No	1.00		
Yes	0.49	0.20 to 1.22	*P* = 0.124
Smoking during follow-up			
No	1.00		
Yes	4.20	2.57 to 6.89	*P* < 0.001
Maternal psychological problems			
No	1.00		
Yes	1.72	1.23 to 2.41	*P* = 0.002
Previous breastfeeding experience			
No	1.00		*P* = 0.069
Yes	0.69	0.46 to 1.03	
Breastfeeding encouragement			
No	1.00		
Yes	0.98	0.60 to 1.58	*P* = 0.916
Multiparity			
Singleton	1.00		
Twins	1.83	0.89 to 3.74	*P* = 0.099
Prematurity			
Full-term	1.00		*P* = 0.088
Premature	1.65	0.93 to 2.93	
Pacifier introduction			
No	1.00		
Yes	2.08	1.40 to 3.08	*P* < 0.001

mothers (*P* < 0.001).

A similar trend was observed regarding the maternal educational status. In addition to having a postgraduate study degree (*P* < 0.001), which had also been identified as important in the univariate analysis, increased duration of any breastfeeding was also found to be more likely among university/college graduates, compared to mandatory education and high school graduates (*P* = 0.001). Indeed, having a university/college diploma was associated with a lower risk of earlier breastfeeding cessation (HR = 0.53, 95%CI: 0.37-0.76), and having a postgraduate study degree with an even lower risk of earlier weaning (HR = 0.20, 95%CI: 0.09-0.43), compared with mandatory or high school education.

The psychological status of the mother, reflecting the prevalence of related psychological problems postpartum (including swinging mood, easy change of disposition, bad disposition, anxiety, and easy crying), was inversely associated with the duration of any breastfeeding (*P* = 0.002). The presence of such problems carried a 1.72 (95%CI: 1.23-2.41) times higher risk of earlier breastfeeding cessation.

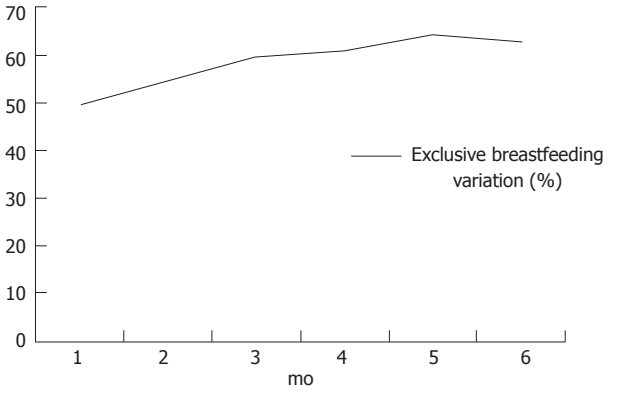

Figure 1 Exclusive breastfeeding evolvement during the postpartum period (monthly samples).

Finally, the use of a pacifier was found to affect any BD in a negative manner (*P* < 0.001, HR = 2.08, 95%CI: 1.40-3.08), a result also observed in the univariate analysis (HR = 2.87, 95%CI: 2.05-4.00).

Previous breastfeeding experience and lack of home support, immigrant status of the father, and low birth weight/prematurity, or multiplicity of the newborns, although found significant in the univariate analysis, did not remain significant in the final multivariate model. In addition, maternal age was neither associated with the duration of breastfeeding in the univariate analysis (*P* = 0.689), nor was it correlated with the period of active lactation after applying Spearman's correlation coefficient (ρ = 0.013, *P* = 0.783).

DISCUSSION

The present study sample comprising mothers, who were recruited in a maternity ward of a tertiary University Hospital, indicated that maternal smoking during the postpartum period was associated with higher risk for the cessation of any breastfeeding, whereas maternal education and immigrant status were positively associated with increased duration of any breastfeeding. The adverse maternal psychological status and the introduction of a pacifier affected the continuation of any breastfeeding in a negative manner.

The initiation of any breastfeeding among the interviewed mothers was high, with almost half of them practicing exclusive breastfeeding. Any breastfeeding rates gradually declined during the follow-up period, reaching 38.75% at the sixth postpartum month, while exclusive breastfeeding exhibited a similar trend and was practiced by the one quarter of the study sample at the sixth postpartum month.

It is interesting to note however, that if we examine each monthly sample of interviewed mothers separately as they evolve during the follow-up period, the progress of exclusive breastfeeding rate for each sample demonstrates an increasing trend throughout the follow-up period, up until the fifth postpartum month (saturation period), after which the respective

rates started to fall (Figure 1). That means, in effect, that every month until the fifth postpartum month, the proportion of exclusively breastfed babies in the remaining population increased. In other words, more babies who were partially breastfeeding stop being breastfed, compared to their exclusively breastfed counterparts, from the first until the fifth postpartum month (Table 3). This, in turn, might suggest that promoting exclusive breastfeeding may be a good strategy to avoid early weaning.

Exclusive and any BD rates were also reported in previous Greek studies, but the respective percentages were lower[17-19]. The lack of breastfeeding-friendly hospital practices has been consistently identified as detrimental for BD[18,19]. However, Bakoula *et al*[18] concluded that women in Greece seemed capable of overcoming formula supplementation in the hospital environment and could revert to exclusive breastfeeding at home. Hence, it can be postulated that mothers, who choose to continue breastfeeding in this study, possess the determination to overcome the related obstacles. The finding that any BD was not affected by previous information about breastfeeding, maternal employment status, or paid leave of absence, may, therefore, not be unrelated.

It should also be mentioned that the majority of mothers in the present study (48.5%) reported that the main reason for the cessation of breastfeeding was the production of inadequate milk volume. This belief is erroneous from a scientific point of view, as various studies have determined that less than 5% mothers do not seem able to meet the goals regarding the appropriate weight gain of their infant, because of inadequate milk production[20-23]. Thus, the length of BD may further increase, if mothers receive appropriate guidance from health professionals[24].

Drawing on the factors, which positively influenced the continuation of any breastfeeding, higher educational level of the mother was positively associated with BD. University/college graduates had about half the risk of premature weaning during the first six months, compared to mandatory education and high school graduates, whereas Master degree holders less than one fifth of that risk. Similar findings were reported by Flacking *et al*[25] in a prospective population-based cohort study in Sweden. Mothers of term infants with mandatory or upper secondary education in that study had more than twice the risk of premature discontinuation of breastfeeding within the first six postpartum months, compared with mothers of higher educational level. It should be mentioned that the educational level measured in the present analysis was the level of formal education, rather than education about breastfeeding. Further research might discern which aspects of maternal education play the most important role in breastfeeding, and such information may be used in school educational programs.

Immigrant mothers were also more likely to demonstrate increased duration of any breastfeeding. This finding has been previously reported in multi-cultural societies (*i.e.*, United States, United Kingdom), in which lower breastfeeding rates were consistently associated with acculturation[26-29]. It is possible that the association identified in this study, reflects the fact that immigrant mothers in Southern Europe come from families and communities, where breastfeeding is by far the predominant infant feeding method[30]. Moreover, even in societies with multi-cultural backgrounds there seems to be a stark contrast in of breastfeeding by ethnicity[26,27], which, in turn, suggests that different public health approaches need to be adopted in order to increase BD. In contrast, paternal immigrant status was not found to be significant in this study.

Focusing on the factors which adversely affected the continuation of any breastfeeding, smoking during follow-up was found to be important. In particular, mothers who reverted to regular smoking after delivery had a fourfold risk of stopping breastfeeding earlier within the first 6 postpartum months, compared to women who did not smoke. An early weaning risk of similar magnitude was also reported by Rattner *et al*[31] in a secondary analysis of data from a randomized controlled trial involving 228 women, who had stopped smoking before pregnancy, but reverted to daily smoking thereafter. In contrast, in a retrospective questionnaire-based national survey of a random sample of 24438 Norwegian women, Haug *et al*[32] reported that women who did not smoke were twice as likely to continue to breastfeed at 6 mo, compared with women who smoked. In addition, the adjusted odds ratio for breastfeeding continuation of more than 6 mo in women who had stopped smoking in pregnancy was 3.7 in the study of Giglia *et al*[33]. Further to the potential biological mechanisms associated with smoking and lactation[34-36], women who smoke may wean prematurely because of being unsure whether it is still safe to breastfeed. These women may be reluctant to seek the advice of health professionals, or even help for breastfeeding problems, as they could be wary of their reactions[37].

The adverse psychological status of the mother during the first postpartum month proved significant and affected the duration of any breastfeeding in a negative manner. The related postpartum problems which were examined included swinging mood, easy change of disposition, bad disposition, anxiety, and easy crying. As a whole the appearance of such problems postpartum carried a 1.72 times higher risk of earlier breastfeeding cessation. Hence, not only true depression, but also other forms of postnatal distress seem to influence the duration of breastfeeding, and timely identification and intimate knowledge of these factors could assist in recognizing women at risk for early weaning, and constructing programs capable of increasing the length of BD. The importance of psychological factors in predicting BD was also stressed in the study of O'Brien *et al*[38].

The introduction of a pacifier was found to negatively affect the duration of any breastfeeding. Similar

results were reported by Howard *et al*[39], who had associated the introduction of a pacifier by the sixth week with a significant decline in BD, in a prospective cohort study of 265 breastfeeding mother-infant dyads. However, the duration of breastfeeding up to 3 mo was not affected by the early introduction of a pacifier in that study. In addition, Scott *et al*[40], in a prospective study of 587 Australian mothers, found that the introduction of a pacifier after 10 wk did not significantly affect the duration of breastfeeding, whilst its use in the first 10 wk increased the risk for the cessation of full breastfeeding by 6 mo and overall breastfeeding by 12 mo. It has been suggested that the decreases in BD associated with pacifier use may be a consequence of less frequent breastfeeding among women who introduce pacifiers to their infants[27]. The reasons for introducing a pacifier in the first place need to be determined. There is also a need to determine whether breastfeeding problems associated with the use of pacifiers precede or follow their introduction. In the former case women need to be advised on how to prevent, identify, and manage breastfeeding problems, as a means of reducing the need for the use of pacifiers. In the latter case, however, women need to be discouraged from introducing pacifiers in order to reduce the risk of breastfeeding problems, and increase the duration of breastfeeding[28].

Limitations

The present study was conducted in a single-centre setting, which may result to the study sample not being strictly representative of the Greek population. Nevertheless, the study population was recruited in the maternity ward of a tertiary University hospital, which is not only serving the Prefecture of Attica, but also accepting referrals of high-risk pregnancies from the entire Greek territory. Hence, the validity of the associations found between BD and various factors under study is not likely to have been affected.

In conclusion, the results of the present study revealed the importance of maternal education and immigrant status regarding the duration of any breastfeeding. In addition, maternal smoking during lactation, as well as the use of a pacifier, were inversely associated with the duration of any breastfeeding. Post-partum psychological status was also found to be inversely associated with any BD in this study sample.

Public health interventions in order to protect, support and promote breastfeeding should include campaigns against smoking during lactation, as a means of increasing BD, as well as, endorsing the delayed introduction of pacifiers. Interventions should also focus on women of low educational status, which obviously consist a high risk group for early breastfeeding cessation.

Findings of this study could also prove useful for comparing factors which are responsible for BD across countries, and providing information that could be used as a tool for the promotion of practices and programs that encourage breastfeeding.

It is becoming increasingly important that public health authorities and health professionals need to identify the factors that influence BD across countries, and aim at creating socio-cultural and economic settings that encourage the continuation of breastfeeding.

COMMENTS

Background

Breastfeeding is the natural way to feed infants and young children ensuring optimal growth and development, while exclusive breastfeeding is recommended for the first six months of life. Although some slight improvements have been recorded in breastfeeding rates during the last decade, they continue to fall short of global recommendations, and many mothers, who initially chose to breastfeed, shift to formula-feeding, and finally cease breastfeeding. A variety of factors influence and determine breastfeeding initiation and duration, including characteristics of the mother, the child and the family, aspects of the health care system, public health and social policies, advertising and promotion of alternative feeding methods. The identification of the determinants that influence breastfeeding duration (BD) across countries may provide useful information, which could be used to improve breastfeeding rates at national levels and worldwide.

Research frontiers

Maternal smoking during the postpartum period is associated with higher risk for earlier breastfeeding discontinuation, as also the adverse maternal psychological status and the early introduction of a pacifier to the infant. Maternal education and immigrant status, on the other hand, are positively associated with increased BD.

Innovations and breakthroughs

In the present study, the authors additionally examined each monthly sample of interviewed mothers separately, as they evolved during the follow-up period. The progress of exclusive breastfeeding rate for each sample demonstrated an increasing trend throughout the follow-up period, up until the fifth postpartum month (saturation period), after which the respective rates started to fall. That means, in effect, that every month until the fifth postpartum month, the proportion of exclusively breastfed babies in the remaining population increased. In other words, more babies who were partially breastfeeding stop being breastfed, compared to their exclusively breastfed counterparts, from the first until the fifth postpartum month. This, in turn, might suggest that promoting exclusive breastfeeding may be a good strategy to avoid early weaning.

Applications

Public health interventions in order to protect, support and promote breastfeeding should include campaigns against smoking during lactation, as a means of increasing BD, as well as, endorsing the delayed introduction of pacifiers. Interventions should also focus on women of low educational status, which obviously consist a high risk group for early breastfeeding cessation. Findings of this study could also prove useful for comparing factors which are responsible for BD across countries, and providing information that could be used as a tool for the promotion of practices and programs that encourage breastfeeding.

Peer-review

In this paper, authors investigated factors associated with BD in a sample of mothers living in Greece. The results of the present study revealed the importance of maternal education and immigrant status regarding the duration of any breastfeeding. Furthermore, authors also found that maternal smoking during lactation and the use of a pacifier, were inversely associated with the duration of any breastfeeding. This is a well written and well conducted study.

REFERENCES

1 **Binns C**, Lee M, Low WY. The Long-Term Public Health Benefits of Breastfeeding. *Asia Pac J Public Health* 2016; **28**: 7-14 [PMID:

26792873 DOI: 10.1177/1010539515624964]
2 **Victora CG**, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, Murch S, Sankar MJ, Walker N, Rollins NC. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 2016; **387**: 475-490 [PMID: 26869575 DOI: 10.1016/S0140-6736(15)01024-7]
3 **Davanzo R**, Romagnoli C, Corsello G. Position Statement on Breastfeeding from the Italian Pediatric Societies. *Ital J Pediatr* 2015; **41**: 80 [PMID: 26498033 DOI: 10.1186/s13052-015-0191-x]
4 **Section on Breastfeeding**. Breastfeeding and the use of human milk. *Pediatrics* 2012; **129**: e827-e841 [PMID: 22371471 DOI: 10.1542/peds.2011-3552]
5 **WHO/UNICEF**. Global strategy for infant and young child feeding. Geneva: Switzerland, 2003
6 **World Health Assembly**. International Code of Marketing of Breastmilk Substitutes. Geneva: WHO, 1981
7 **WHO/UNICEF**. Innocenti declaration on the protection, promotion, and support of breastfeeding. In: Breastfeeding in the 1990's: A global initiative meeting in Florence, Italy and New York. Geneva: Switzerland, 1990
8 **WHO/UNICEF**. Baby-Friendly Hospital Initiative and program manual. Geneva: Switzerland, 1992
9 **Radzyminski S**, Callister LC. Mother's Beliefs, Attitudes, and Decision Making Related to Infant Feeding Choices. *J Perinat Educ* 2016; **25**: 18-28 [PMID: 26848247 DOI: 10.1891/1058-1243.25.1.18]
10 **Daly A**, Pollard CM, Phillips M, Binns CW. Benefits, barriers and enablers of breastfeeding: factor analysis of population perceptions in Western Australia. *PLoS One* 2014; **9**: e88204 [PMID: 24516612 DOI: 10.1371/journal.pone.0088204]
11 **Cattaneo A**, Burmaz T, Arendt M, Nilsson I, Mikiel-Kostyra K, Kondrate I, Communal MJ, Massart C, Chapin E, Fallon M. Protection, promotion and support of breast-feeding in Europe: progress from 2002 to 2007. *Public Health Nutr* 2010; **13**: 751-759 [PMID: 19860992 DOI: 10.1017/S1368980009991844]
12 **Hannula L**, Kaunonen M, Tarkka MT. A systematic review of professional support interventions for breastfeeding. *J Clin Nurs* 2008; **17**: 1132-1143 [PMID: 18416790 DOI: 10.1111/j.1365-2702.2007.02239.x]
13 **Peters E**, Wehkamp KH, Felberbaum RE, Krüger D, Linder R. Breastfeeding duration is determined by only a few factors. *Eur J Public Health* 2006; **16**: 162-167 [PMID: 16207725 DOI: 10.1093/eurpub/cki199]
14 **Tavoulari EF**, Benetou V, Vlastarakos PV, Andriopoulou E, Kreatsas G, Linos A. Factors affecting breast-feeding initiation in Greece: What is important? *Midwifery* 2015; **31**: 323-331 [PMID: 25467601 DOI: 10.1016/j.midw.2014.10.006]
15 **World Health Organization**. Division of child health and development. Indicators for assessing breastfeeding practices. Reprinted report of an informal meeting. Geneva, Switzerland, 1991
16 **UNICEF UK**. How to implement baby friendly standards. A guide for maternity settings. UK, London, 2011
17 **Vassilaki M**, Chatzi L, Bagkeris E, Papadopoulou E, Karachaliou M, Koutis A, Philalithis A, Kogevinas M. Smoking and caesarean deliveries: major negative predictors for breastfeeding in the mother-child cohort in Crete, Greece (Rhea study). *Matern Child Nutr* 2014; **10**: 335-346 [PMID: 22642318 DOI: 10.1111/j.1740-8709.2012.00420.x]
18 **Bakoula C**, Nicolaidou P, Veltsista A, Prezerakou A, Moustaki M, Kavadias G, Lazaris D, Fretzayas A, Krikos X, Karpathios T, Matsaniotis N. Does exclusive breastfeeding increase after hospital discharge? A Greek study. *J Hum Lact* 2007; **23**: 165-173; quiz 174-178 [PMID: 17478869 DOI: 10.1177/0890334407300384]
19 **Theofilogiannakou M**, Skouroliakou M, Gounaris A, Panagiotakos D, Markantonis SL. Breast-feeding in Athens, Greece: factors associated with its initiation and duration. *J Pediatr Gastroenterol Nutr* 2006; **43**: 379-384 [PMID: 16954963 DOI: 10.1097/01.mpg.0000228104.97078.bb]
20 **Khanal V**, da Cruz JL, Karkee R, Lee AH. Factors associated with exclusive breastfeeding in Timor-Leste: findings from Demographic and Health Survey 2009-2010. *Nutrients* 2014; **6**: 1691-1700 [PMID: 24756151 DOI: 10.3390/nu6041691]
21 **Yarnoff BO**, Allaire BT, Detzel P. Associations between Infant Feeding Practices and Length, Weight, and Disease in Developing Countries. *Front Pediatr* 2013; **1**: 21 [PMID: 24400267 DOI: 10.3389/fped.2013.00021]
22 **Dewey KG**, Heinig MJ, Nommsen LA, Lönnerdal B. Adequacy of energy intake among breast-fed infants in the DARLING study: relationships to growth velocity, morbidity, and activity levels. Davis Area Research on Lactation, Infant Nutrition and Growth. *J Pediatr* 1991; **119**: 538-547 [PMID: 1919883 DOI: 10.1016/S0022-3476(05)82401-1]
23 **Neville MC**, Keller R, Seacat J, Lutes V, Neifert M, Casey C, Allen J, Archer P. Studies in human lactation: milk volumes in lactating women during the onset of lactation and full lactation. *Am J Clin Nutr* 1988; **48**: 1375-1386 [PMID: 3202087]
24 **Li R**, Fein SB, Chen J, Grummer-Strawn LM. Why mothers stop breastfeeding: mothers' self-reported reasons for stopping during the first year. *Pediatrics* 2008; **122** Suppl 2: S69-S76 [PMID: 18829834 DOI: 10.1542/peds.2008-1315i]
25 **Flacking R**, Nyqvist KH, Ewald U. Effects of socioeconomic status on breastfeeding duration in mothers of preterm and term infants. *Eur J Public Health* 2007; **17**: 579-584 [PMID: 17392294 DOI: 10.1093/eurpub/ckm019]
26 **Singh GK**, Kogan MD, Dee DL. Nativity/immigrant status, race/ethnicity, and socioeconomic determinants of breastfeeding initiation and duration in the United States, 2003. *Pediatrics* 2007; **119** Suppl 1: S38-S46 [PMID: 17272583 DOI: 10.1542/peds.2006-2089G]
27 **Kelly YJ**, Watt RG, Nazroo JY. Racial/ethnic differences in breastfeeding initiation and continuation in the United kingdom and comparison with findings in the United States. *Pediatrics* 2006; **118**: e1428-e1435 [PMID: 17079543 DOI: 10.1542/peds.2006-0714]
28 **Merewood A**. Race, ethnicity, and breastfeeding. *Pediatrics* 2006; **118**: 1742-1743 [PMID: 17015568 DOI: 10.1542/peds.2006-2161]
29 **Gibson-Davis CM**, Brooks-Gunn J. Couples' immigration status and ethnicity as determinants of breastfeeding. *Am J Public Health* 2006; **96**: 641-646 [PMID: 16507724 DOI: 10.2105/AJPH.2005.064840]
30 **Tavoulari EF**, Benetou V, Vlastarakos PV, Kreatsas G, Linos A. Immigrant status as important determinant of breastfeeding practice in southern Europe. *Cent Eur J Public Health* 2015; **23**: 39-44 [PMID: 26036097 DOI: 10.21101/cejph.a4092]
31 **Ratner PA**, Johnson JL, Bottorff JL. Smoking relapse and early weaning among postpartum women: is there an association? *Birth* 1999; **26**: 76-82 [PMID: 10687570 DOI: 10.1046/j.1523-536x.1999.00076.x]
32 **Haug K**, Irgens LM, Baste V, Markestad T, Skjaerven R, Schreuder P. Secular trends in breastfeeding and parental smoking. *Acta Paediatr* 1998; **87**: 1023-1027 [PMID: 9825966 DOI: 10.1111/j.1651-2227.1998.tb01407.x]
33 **Giglia RC**, Binns CW, Alfonso HS. Which women stop smoking during pregnancy and the effect on breastfeeding duration. *BMC Public Health* 2006; **6**: 195 [PMID: 16869976 DOI: 10.1186/1471-2458-6-195]
34 **Hopkinson JM**, Schanler RJ, Fraley JK, Garza C. Milk production by mothers of premature infants: influence of cigarette smoking. *Pediatrics* 1992; **90**: 934-938 [PMID: 1437437]
35 **Vio F**, Salazar G, Infante C. Smoking during pregnancy and lactation and its effects on breast-milk volume. *Am J Clin Nutr* 1991; **54**: 1011-1016 [PMID: 1957815]
36 **Andersen AN**, Schiøler V. Influence of breast-feeding pattern on pituitary-ovarian axis of women in an industrialized community. *Am J Obstet Gynecol* 1982; **143**: 673-677 [PMID: 6807095 DOI: 10.1016/0002-9378(82)90113-2]
37 **Amir LH**. Smoking status of breastfeeding women. *Acta Paediatr* 1999; **88**: 1412-1413 [PMID: 10626534 DOI: 10.1111/j.1651-2227.1999.tb01063.x]
38 **O'Brien M**, Buikstra E, Hegney D. The influence of psychological factors on breastfeeding duration. *J Adv Nurs* 2008; **63**: 397-408

[PMID: 18727767 DOI: 10.1111/j.1365-2648.2008.04722.x]

39 **Howard CR**, Howard FM, Lanphear B, deBlieck EA, Eberly S, Lawrence RA. The effects of early pacifier use on breastfeeding duration. *Pediatrics* 1999; **103**: E33 [PMID: 10049989 DOI: 10.1542/peds.103.3.e33]

40 **Scott JA**, Binns CW, Oddy WH, Graham KI. Predictors of breastfeeding duration: evidence from a cohort study. *Pediatrics* 2006; **117**: e646-e655 [PMID: 16585281 DOI: 10.1542/peds.2005-1991]

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