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Pediatric obesity prevention: From naïve examination of energy imbalance towards strategies that influence the competition for nutrient resources among tissues

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Abstract

Current pediatric obesity interventions have collectively yielded relatively unsuccessful results. In this Field of Vision, we present plausible physiologic underpinnings fostering ineffectiveness of conventional strategies grounded in requisite induction of negative energy imbalance. Moreover, such recommendations exacerbate the underlying metabolic dysfunction by further limiting metabolic fuel availability, lowering energy expenditure, and increasing hunger (recapitulating the starvation response amid apparent nutritional adequacy) which precede and promote obesity during growth and development. The qualitative aspects of musculoskeletal system (*i.e.*, endocrine response, muscle functional capacity) are likely to improve metabolic function and increase nutrient delivery and utilization. An intricate and complex system including multiple feedback mechanisms operates to homeostatically regulate energy balance and support optimal body composition trajectories and metabolic health, during growth and development. Thus, ignoring the interdependencies of regulatory growth processes initiates a nuanced understanding of energy regulation and thus misguided attempts at preventive strategies. Importantly, these gains are not dependent upon weight-loss, rather we suggest can be achieved through resistance training. Collectively, optimizing musculoskeletal health *via* resistance training elicits augmentation of competitive capacity across systems. Further, substantial gains can be achieved in skeletal muscle mass, strength, and functional capacity through resistance training in a relatively short period of time.

Key words: Childhood obesity; Metabolic control; Energy balance; Resistance training; Effective intervention strategies; Weight loss; Musculoskeletal health

Core tip: As obesity-related recommendations stand today, most are unproven and ineffective. While energy balance is an integral component, the etiology of pediatric obesity is a consequence of adipocytes "out competing" other cell types (*e.g.*, myocytes, osteocytes, hepatocytes) for energy. The cumulative effect of fat storage, energetically less costly is at the expense of optimal development of other tissues. The out-competition, due to hyperplasia and hypertrophy of adipocytes impairs physiologic pathways producing metabolically compromised obese children irreversible with "simple" energy balance paradigms. *Via* the activation of endocrine and paracrine effects of the musculoskeletal system, resistance training may be an effective strategy to improve health independent of initial weight loss. However, forced stress on the system is requisite (*e.g.*, resistance training). Resistance training induces systemic anabolism and enhances nutrient delivery and utilization, which are integral in optimizing metabolic control and body composition during growth and development, and in turn overall lifelong health.

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INTRODUCTION

The presage of pediatric obesity inducing a decline in life expectancy[1,2] has evoked calls for expert committees to direct stakeholders on how to best proceed with comprehensive prevention/intervention platforms. However, despite persistent calls for evidenced based policies, current dietary and physical activity interventions have collectively yielded a fairly unsuccessful paradigm. Herein, we provide a potential explanation for the chasm between the resource allocation to "combat" the pediatric obesity epidemic and improvement in health outcomes. As an exhaustive analysis of all pediatric obesity strategies, to date would be infeasible. Thus, the purpose of this Field of Vision is to highlight the conventional strategies and adoption of recommendations written by "expert committees" for governments or health authorities of the United States[3], United Kingdom[4] and Canada[5], the Institute of Medicine[6] and World Health Organization (WHO)[7] as well as Cochrane reviews[8,9] (largely grounded in inducing negative energy imbalance through increasing physical activity and dietary restriction) as naïve approaches to pediatric obesity prevention.

NAIVE EXAMINATION OF ENERGY IMBALANCE?

Despite endorsements of dietary and physical activity recommendations, the vast majority of interventions to date have had null findings. For example, in 2005, the American Medical Association, the Health Resources and Service Administration, and the Centers for Disease Control and Prevention (CDC) asked representatives from 15 national healthcare organizations to form an expert committee to make recommendations regarding the treatment of childhood and adolescent obesity. The expert committee determined the main foci should include: setting daily eating and activity goals for their overweight or obese children (increased expenditure), increasing consumption of fruits and vegetables (F and V) (modifying intake); minimizing sugary drinks (reduce calories); limiting screen time to $\leqslant$ 2 h (modifying sedentariness); attaining $\geqslant$ 1 h. physical activity (increased expenditure); encouraging primary care providers to more closely monitor these target behaviors and goals, and facilitating more explicit planning by parents to achieve weight loss. Similarly, Obesity Canada, convened a panel of experts to create clinical practice guidelines for Canadian health policy. The Steering Committee and Expert Panels in the United Kingdom and Canada reviewed the literature and several years later published their guidelines, which were very similar to those of the United States[10,11]. Since 2007, all governments in the United Kingdom have had action plans to reduce pediatric obesity prevalence[12]. The WHO globally led the charge indicating that reducing the consumption of high-calorie, energy-dense foods, including sugar-sweetened beverages, increasing the consumption of F and V; and increasing the initiation, duration, and exclusivity of breastfeeding represent comprehensive strategies for reducing pediatric obesity[7]. While we do not argue that these approaches have a reasonable basis with theoretical rationale, empirical evidence supporting implementation of any of the aforementioned for improved health outcomes have not been documented and in some instances proven to be ineffective[13]. Indeed, investigations linking pediatric obesity and early onset metabolic disease has substantiated developmental origins of disease. Despite a vast body of recommendations generated though these working groups, antiquated application of science has led to the promotion of non-evidence based, and sometimes anecdotal application of simple solutions to a complex problem. Furthermore, such unproven, unfiltered and inconsistent messages guiding pediatric weight management strategies persist despite absence of scientific supporting evidence and ultimately have contributed to a culture of confusion and disinterest. We clearly need a much more balanced approach to

discussing energy flux and long-term health. Conversely, very little attention has been devoted to determining those physiological factors characteristic of early life that could be protective to health and contribute to mitigating age-associated morbidities. While physical inactivity and the consequent adverse effects on fat storage and energy metabolism across the life course[14-19], may be more pathologic during development, this critical period also represents a stage in which capitalization on the benefits of body composition may be attained.

FAILURE OF WEIGHT LOSS STRATEGIES

We conjecture that the failure of weight loss strategies to improve health in the pediatric population is grounded in the fundamental assumption that inducing negative imbalances *via* caloric restriction and energy expenditure circumvent excessive fat storage during growth and development. Indeed, energy balance plays a role; however, during growth and development excess fat storage is a consequence of adipocytes "out competing" other cell types (*e.g.,* myocytes, osteocytes, hepatocytes) for energy due to lack of engagement of other cell types in the competition for energy[16-18]. Over the three decades encompassing the pediatric obesity "epidemic", sedentary behaviors have increased drastically, with the vast majority of free time spent by children in light activity or relatively inactive and engaged in limited (if any) moderate to high-intensity activities. During the anabolic growth stage, failure to engage skeletal muscle, as a primary tissue in the regulation of fuel utilization and delivery, in greater than day to day threshold promotes metabolic compromise. In turn, the endocrine and paracrine effects of the musculoskeletal system in which contraction greater than the "typical day to day threshold" is requisite are attenuated, while the endocrine effects of adipose tissue are up-regulated. Dietary restriction, in the absence of muscle contract, further increased sensitivity of adipokines to promote fat storage[18,19]. This conceptualization is strongly supported by extant research, given those increments in fat mass are a function of adiposity, adipocyte number is a primary determinant of obesity, and early pubertal development is a major determinant of adipocyte number and lifelong obesity risk[19]. Thus, modifying diet and/or engaging in low-intensity physical activity programs in which mechanical stress is not requisite, does not generate competitive inclusion of oseto-/myo-cytes. As such, the competitive advantage of adipocytes and ensuing loss of metabolic control due to lack of participation by the musculoskeletal system is nearly impossible to counter. The cumulative effect of nutrient partitioning to adipose at the expense of other tissues in concert with a greater number of adipocytes and impaired glucose and lipid metabolism produce metabolically compromised children predisposed to inactivity, metabolic dysfunction and obesity irrespective of short-term weight loss strategies. In this context, it is naïve to suggest that limiting availability of nutrients without enhancing utilization capacity. According many of the recommendations to date represents a futile process enhancing adipocyte dominance rather than attenuating it, with particular salience during the dynamic metabolic sequalae of critical periods in development (*e.g.,* the pubertal transition).

ABSENCE OF MUSCLE CONTRACTION

Notably, increasing daily activity by children does not merely characterize play, but encompasses an essential component of healthy growth and development. Optimal musculoskeletal development is derived from complex integration of cellular and systemic autocrine, paracrine and endocrine factors that promote the capacity to sustain work. Thus, enhanced musculoskeletal function *via* augmenting metabolic crosstalk has the capacity to improve whole body metabolism including insulin-stimulated glucose uptake, lipolysis, and resting energy expenditure in addition to improving musculoskeletal function and overall health. Substantial evidence in animals and humans highlight the great detriment of physical inactivity. For example, after 4-h of inactivity (tail suspension), a functional decline in lipoprotein lipase (LPL) activity accompanied by decreased skeletal muscle triglyceride clearance, lower HDL and attenuated muscle oxidative capacity with immediate decline in musculoskeletal function has been observed[16-18]. Occupational studies indicate workers who sat most of the day have about twice the rate of cardiovascular disease as those demanding more standing and ambulatory activities[18]. Moreover, human bed rest investigations revealed that one-to-three weeks of bed rest in otherwise healthy, active men had a more profound impact on physical work capacity than did three decades of aging in the same men[15,16]. Within days, decreased muscle activity due to prolonged bed rest decreased skeletal muscle insulin sensitivity, insulin signaling, fitness, leg muscle mass and increased intra-abdominal fat[16] and reduced insulin signaling, altered glucose and lipid metabolism and increased central adiposity even in the absence of weight-loss. We acknowledge that bed rest is an extreme model of inactivity and does not accurately mimic the low levels of physical activity that even most sedentary individuals undergo on a daily basis. However, the minimal 8 h a day of sitting in today's youth in school (not to mention the well-documented low levels of activity in the home environment) may in legitimately represent a degree of such extreme inactivity.

Importantly, the capacity for skeletal muscle to fulfill its essential role in governing glucose and lipid oxidation is largely attributable to stimulation of contractile forces which exceed the day-to-day threshold of skeletal use. Stimulation by contractile forces enhances the synthesis and release of skeletal muscle peptides which participate in a variety of metabolic actions[14,17]. A shift in paradigm is desperately needed.

SHIFT IN PARADIGM

Enhancing nutrient utilization rather than diminishing nutrient availability (*e.g.,* negative energy balance) can be more readily accepted with improved adherence. Thus, germane to our proposed shift in paradigm, contraction-dependent endocrine effects of skeletal muscle have been shown to improve metabolic parameters and offer a means of improving nutrient delivery and utilization. Importantly, these gains are not dependent upon weight-loss, rather we suggest can be achieved through resistance training. Relative to the commonly prescribed aerobic exercise, resistance exercise: (1) evokes a lower perceived exertion and is more readily accepted among obese individuals; (2) requires less cardiorespiratory capacity in the initial phases (rather short bouts of effort); and (3) activates anabolic processes leading to musculoskeletal hypertrophy. Collectively, optimizing musculoskeletal health elicits augmentation of competitive capacity of myocytes, osteocytes and hepatocytes. Further, substantial gains can be achieved in skeletal muscle mass, strength, and functional capacity through resistance training in a relatively short period of time. While the sense of urgency is now at the pinnacle, evidence of the emergence of the dire health effects caused by inactivity has been steadily mounting for several decades[2,20]. The reduced activity in contemporary youth apparent from the early 1970s to present has substantially altered growth-related outcomes in the pediatric population[21-26]. This is as evidenced by progressive and cumulative increases in height[22,23], body mass[24], bone mass, organ mass, and fat mass/adiposity[25] as well as earlier onset and progression of chronic diseases. As these metabolically compromised children mature and transition through puberty and the adverse effects of physical inactivity manifest[27], the competitive advantage of adipocytes increases, underlying the poor health and well-being prognostication of future generations. To move forward, future research and subsequent recommendations may be most productive if directed away from naïve examination of energy balance and redirected towards intervention/prevention strategies that influence the competition for nutrient resources among tissues.

CONCLUSION

The reliance on conventional strategies for decreasing pediatric obesity prevalence continues despite decades of unequivocal evidence. While, in theory, inducing negative energy imbalance seems logical, targeted efforts have been largely ineffective in sustained weight management and/or improvement in health outcomes. Herein, we explored the chasm between the current recommendations in the pediatric population driving approaches, exposing where lack of science-based direction has led to futility and propose a potential paradigmatic shift away from the adipcentric focus encompassing developmental origins of disease towards capitalizing on the substantive aspects of health during childhood. Cumulatively, work to date has vastly improved our knowledge of the complex nature of pediatric obesity and led to the identification of mechanisms underlying a competitive advantage of adipocytes during growth, however, an effective strategy to promote health outcomes in the contemporary obesogenic environment remains elusive. We contend, the failure of weight (fat) loss strategies in the pediatric population is grounded in a requisite negative energy imbalance for improving health outcomes. While weight management is imperative, we posit that induction of negative energy imbalance should not be the main, and certainly not the only, focus for treatment of the obese child for promotion of metabolic improvement. As such, the persistent dependence on caloric restriction and the prescribed about 60 min per day of aerobic activity has demonstrated that adherence, and consequent long-term weight management and metabolic health improvements are minimal. Thus, to move forward, future research and subsequent recommendations may be most productive if directed away from naïve examination of energy balance and redirected towards intervention/prevention strategies that enhance nutrient partitioning to tissues (*i.e.,* myocytes, hepatocytes, osteocytes, *etc.*). It is well-established that chronic inactivity pathologically elicits adipocyte storage feedback mechanisms (*e.g.,* hyperplastic adiposity, intensified pancreatic β-cell function, impaired skeletal muscle function), increasing the risk of metabolic disease, cardiovascular incidents and some cancers. However, inducing resistance to the musculoskeletal system exerts contractile forces which enhance the synthesis and release of peptides released from muscle, bone and liver which participate in a variety of beneficial metabolic actions, including enhancing glucose uptake and lipid oxidation. Further, nutrient utilization and delivery and in turn, metabolic profile can be improved *via* improving the signaling from other tissues. Importantly, these feed forward metabolic actions can be achieved even in the absence of weight-loss, and without negative energy imbalance.

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REVIEW

Single-incision pediatric endosurgery in newborns and infants

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Abstract

This study focuses on the successful application of single-incision pediatric endosurgery in the treatment of congenital anomalies and acquired diseases in neonates and infants. The purpose of this scientific review consists in highlighting the spectrum, indications, applicability, and effectiveness of single-port endosurgery in children during the first 3 postnatal months.

Key words: Laparoscopy; Neonates; Infants; Single-incision laparoscopic surgery; Single-incision pediatric endosurgery

Core tip: Consequently, reports on a successful use of single-incision endosurgical technique in the treatment of congenital malformations and diseases in neonates and infants are still not numerous and often sporadic. Advanced skills and a high technical demand, along with the lack of specialized surgical equipment are factors limiting the popularity and availability of single-incision pediatric endosurgery (SIPES) for pediatric surgery in first 3 mo of life. However, the current body of evidence shows that a SIPES is indeed applicable in infants with outcome comparable to that of standard laparoscopy, and that it results in minimal post-operative surgical trauma and superb cosmesis.

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INTRODUCTION

The success of minimally invasive surgery resulted

in significant changes of operative techniques that are mutually beneficial for the patient as well as the surgeon. The reduction of postoperative discomfort, quicker recovery, and improved cosmetic results became ubiquitously known advantages of laparoscopic surgery. Laparoscopy and thoracoscopy have further evolved with the purpose of making the operation virtually scarless. The first single-incision endosurgical intervention was a tubal ligation performed by Wheeless[1] in 1969. In the early nineteen nineties, Pelosi *et al*[2] described the first single-incision laparoscopic appendectomy. A few years later, the first transumbilical endoscopic appendectomy was performed in a child[3]. Single-site laparoscopic surgery developed in parallel to the idea of performing endoscopic surgery entirely *via* natural orifices [so-called natural orifice transluminal endoscopic surgery (NOTES)] and appeared as an alternative to conventional, multi-port laparoscopy. NOTES involves extensive investment in expensive specialized equipment, and involves the risk of intra-abdominal infection due to access into the abdominal cavity *via* a usually colonized hollow viscus. To solve this problem, surgeons began using a natural embryonic orifice - the umbilicus - as a "door" to the abdominal cavity, giving rise to the development of single-incision endosurgery. Just a few years ago, single-port surgery has been limited to routine operations, including appendectomy and cholecystectomy. Later, a variety of innovative methods were developed on the basis of complex endosurgical procedures that include nephrectomy, splenectomy, adrenalectomy and intestinal resection and subsequent intracorporeal anastomoses[4-7]. In children, the procedure was coined single-incision pediatric endosurgery or single-incision pediatric endosurgery (SIPES). SIPES is an alternative to triangulated multiport laparoscopy in the surgical therapy of a spectrum of entities. Despite an extensive use of single-incision endosurgery in adult patients, the implementation of this type of surgery for treating children was somewhat slower. A possible explanation is that pediatric minimally invasive techniques have historically lacked behind those of adults. Size-appropriate laparoscopic instrumentation for infants and children has been produced only by select companies due to the smaller potential market share and profit margins.

TERMINOLOGY AND DEFINITION

Currently, single-incision endosurgery is defined as minimally invasive surgery performed *via* a single incision in the abdomen, chest, or retroperitoneal space (Figure 1). Many terms have been used to describe this approach: The term Single-incision laparoscopic surgery (SILS™) is quite prevalent, but has been trademarked by a large device company. To avoid any conflicts of interest, we generally avoid it. One-port umbilical surgery[8], transumbilical endoscopic surgery[9], embryonic natural orifice transumbilical endoscopic surgery[10] have been proposed. Other abbreviations are single-port access (SPA), laparoendoscopic single-site, single laparoscopic-incision transumbilical surgery. Nevertheless, many pediatric surgeons prefer of the abbreviation SIPES[11,12] since this term comprises all laparoscopy, thoracoscopy, and retroperitoneoscopy performed in children by means of a single incision. It also is a clear statement that this type of surgery indeed is performed in children, and that device companies should make an effort to develop size-appropriate equipment for this special application.

Single-port endosurgery was employed in infants much later than in older children. This lag appeared due to misconceptions of surgeons concerning the fact that miniature but visible scars left after conventional pediatric laparoscopy, were perfectly acceptable for patients as well as for their parents. However, scars grow proportionally along with the individual, so that even small scars in infancy may translate into larger ones visible later in life. Moreover, some surgeons were very concerned about compromised maneuverability of endosurgical instruments in a small abdomen of neonates and infants. Despite this concern, pediatric surgeons explored surgical procedures in which SIPES may provide advantages superior to those of multiport access in infants. Soon enough, gastrostomy in children placed *via* a single access was proposed and compared favorably with the three-port technique[13].

Several pediatric surgical centers that use modern laparoscopy showed interest in SIPES and promptly expanded surgical indications for it. Over the last decade, this technique was applied for many new indications (Table 1). Despite the growing popularity of SIPES, it is still not widely used in the newborn and infant population[14-27]. Ponsky *et al*[28], in one of their first scientific reviews, rejected in the strongest terms a capability to perform single-port surgery in children in the first three months of life. The number of scientific publications on the application of SIPES in this age group remains small and mostly devoted to a narrow circle of diseases where single-port surgery has demonstrated its effectiveness. A recent systematic review[29] analyzed all publications of the National Library of Medicine and National Institutes of Health on the website http://www.ncbi.nlm.nih.gov.pubmed, appeared before March 2012 and related to single-incision endosurgery in children. The study identified only 99 neonates among the 4212 pediatric patients. Children in the first month of life mostly underwent operations for congenital pyloric stenosis, Hirschsprung disease, ovarian cysts, inguinal hernias and ventriculoperitoneal shunt placements.

APPLICATION OF SIPES IN SMALL BABIES

Consequently, reports on a successful use of single-incision endosurgical technique in the treatment of congenital malformations and diseases in neonates and infants are still not numerous and often sporadic. We have limited data on possible areas of application

Table 1 Indications for single-incision pediatric endosurgery

Indication	Year introduced	Comments
Inguinal herniorrhaphy[14]	2006	No intraoperative complications. Recurrence rate 0.73% in 711 children
Pyeloplasty[15]	2007	One small anastomotic leak that closed spontaneously occurred in 16 cases
Meckel diverticulectomy[16]	2008	Single-incision approach was faster than multitrocar laparoscopy
Nephrectomy[17,18]	2009, 2010	Independent case reports, technically feasible
Splenectomy[19,20]	2009, 2010	Extraction of the spleen facilitated by a larger single incision compared to standard laparoscopic surgery
Pyloromyotomy[11,12]	2010, 2011	Crossing instruments and stabilizing the antrum rather than the duodenum associated with fewer complications
Orchidopexy[21]	2010	Case report, feasible
Morgagni diaphragmatic hernia repair[22]	2010	Case report, intracorporal knot tying challenging
Fundoplication[23]	2011	SIPES intracorporal suturing is technically demanding. Several alternative techniques available
Hepaticojejunostomy[24]	2012	One bile leak early in the series of 19 patients. Two conversions to multiport laparoscopy. Operative time, length of stay, other outcome parameters same as conventional laparoscopy
Ventriculoperitoneal shunt placement[25]	2011	Successful placement of the distal shunt limb in a series of 5 patients
Total colectomy[26,27]	2011, 2012	Results similar to those after open and multiport laparoscopic surgery

SIPES: Single-incision pediatric endosurgery.

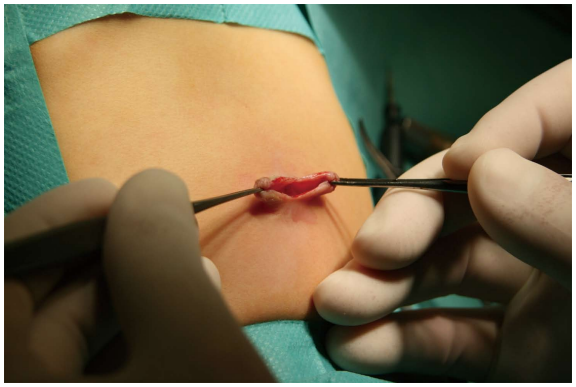

Figure 1 Creation of single umbilical incision.

of SIPES and weak evidence of its prevalence among infant populations.

Inguinal herniorrhaphy

Over the last decade single-port techniques for laparoscopic inguinal hernia repair were developed. Currently, the literature contains a limited number of reports on single-port laparoscopic surgery in neonates and infants with inguinal hernia[19,30-32].

A variety of SIPES procedures has been described, mostly including atransperitoneal dissection and percutaneous ligature without direct manipulation. Methods including LPEC[33], SEAL[34] and PIRS[35] perform the extraperitoneal ligation of the hernia sac under laparoscopic vision devoid of additional ports. These methods have specific drawbacks, however. For instance, the LPEC method (Laparoscopic Percutaneous Extraperitoneal Closure) as described by some authors requires the use of special LPEC-needle, which is not approved surgery in premature and low birth weight children. Other authors have described the use of a spinal (Touhy) needle for the dissection, an item that is widely available in most hospitals[36,37].

While using the PIRS method (percutaneous internal ring suturing), closure of the internal inguinal ringis incomplete, since the parts of the peritoneum over the spermatic cord and spermatic vessels are generally spared. Theoretically, the rate of recurrence and hydrocele formation may therefore be higher after these interventions. The SEAL method implies type of extraperitoneal hernia repair in babies without the need for special devices. In this technique a large-diameter needle is driven around the internal inguinal ring, throught the skin at another location, and in a retrograde fashion through the initial skin incision (Figure 2). SEAL allows a complete peritoneal hernia sac closure, possibly decreasing the risk of hydrocele formation[36]. Currently, there are only a few comparative studies of single-port and multi-port laparoscopic methods for pediatric inguinal hernia repair[37,38]. The Russian study[37] shows that periopioperative results of single-port herniorrhaphy are similar to those of the multi-port approach. The Indian study[38] compared results of the two discussed methods of endoscopic treatment of inguinal hernias and found superiority of the single-port laparoscopic method in the form of reduced operation time (15 min *vs* 25 min in cases of unilateral localization). This study, however, confers grave limitations in that the control group and the intervention group were subjected to different techniques of herniorrhaphy - extracorporeal and intracorporeal, respectively. This may explain the lack of superiority of the single-port approach. Both studies demonstrate the one main advantage of single-incision laparoscopic method - the impeccable cosmesis, dut to the hidden scar in the navel.

Pyloromyotomy

The first single-port pyloromyotomy without a use of special equipment or instruments was performed in Birmingham, Alabama[11]. The operation was completed through multiple puncture holes in the abdominal fascia

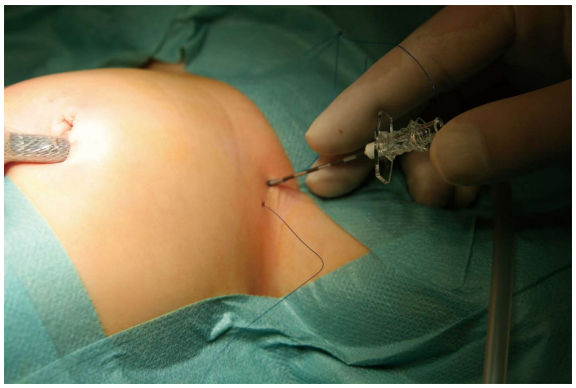

Figure 2 Position of the endoscope and Tuohy needle during subcutaneous endoscopically assisted ligation inguinal herniorrhaphy.

after the umbilical skin incision was stretched. Perforation of gastric mucosa occurred in 3.2% of cases, and SIPES was converted into a three-port laparoscopy in 4.7% of cases. As a result, the authors assumed that SIPES pyloromyotomy is feasible, but a demonstration of its safety is still under an investigation due to a high number of perforations. Since presenting their initial results, the group has changed to a cross-technique single-incision pyloromyotomy, with no further mucosal perforations so far[12]. Another group of patients[39] contained 12 patients who underwent a SIPES pyloromyotomy. That comparative study found no significant difference in operative time or length of hospitalization, as well as an uncomplicated postoperative course in the SIPES group.

Nephrectomy

A single-port laparoscopic approach for nephrectomy is not widely used in newborns and infants. Primarily, this is due to the fact that the majority of pediatric surgeons are satisfied with the cosmetic results of the multi-port endoscopic techniques. Another explanation of this phenomenon is the lack of technology and practical skills to implement SIPES in small babies. Park *et al*[17] and Johnson *et al*[40] were the first, who reported on single-incision nephrectomy in children. Publications regarding this method of nephrectomy in infants are considerably rare and limited by low case numbers[41-44]. These case series, which included 4 to 11 pediatric patients, demonstrated the possibility of removing a kidney laparoscopically through a single incision. The lowest average weight and age of patients in these scientific reports was 10.6 kg and 12 mo, respectively[44].

Nissen fundoplication

The largest series of truly single-incision laparoscopic fundoplications in children was published in 2011 and consisted of 3 infants[23]. Despite the limited number of patients and the inconsistent techniques employed, this study highlights many important aspects, challenges, and solutions of SIPES Nissen fundoplication. For one, the dissection phase of the operation is easily accomplished, whereas the reconstruction part can be quite difficult. Suturing with instruments in parallel alignment turned out to be the most complex task of the operation. The authors concluded that the so-called "Magic Wand technique" was the quickest way of tying the knots. Liver retraction during single-incision laparoscopic fundoplication is problematic. In this series, a dynamic grasper was used to hold the liver away when necessary in some cases. In the remainder, a 2-mm trocarless instrument (Mini-Lap Technologies Inc., Dobbs Ferry, NY) was passed under the liver and anchored in the diaphragm above the hiatus, suspending the liver on its shaft. At this time, the advantages of performing SIPES over conventional laparoscopic Nissen fundoplication are mainly cosmetic in nature. The benefit of virtually scarless surgery in neurologically impaired children who also require a gastrostomy is at least debatable.

Ovarian cystectomy

The relative proximity of the ovaries of newborn to the umbilical region became the object of attention of surgeons practicing single-port endoscopic techniques[45-50]. This approach allowed the surgeons to extract and resect pathological ovarian tissue through one incision made in the umbilical ring. The use of such technical innovations as transparietal aspiration and subsequent extraction of the cyst through a single but larger umbilical incision, provide the surgeon with a quick and comfortable means to remove pathological tissue from the ovaries. Ovarian cystectomy is the most common SIPES procedure reported and has been performed in patients in infancy. Prospective studies are required to demonstrate SIPES benefits in pediatric gynecology.

Other procedures

Only one report demonstrates the use of SIPES for endorectal pull-through for Hirschsprung disease in infants[51]. Though the procedure is technically complex, as it turned out, it can be safely performed with good postoperative results and without complications. Later, publications appeared on individual cases of duodenal web resection in patients with duodenal atresia[52], and resection of a NEC stricture in a premature infant[53].

ACCESS DEVICES

In the beginning of the SIPES era, there was a lack of proper tools to provide access to the abdominal cavity in infants. Enthusiastic pediatric surgeons looked for new methods and put innovative ideas into life. Originally, as an alternative to currently known port systems, they used homemade devices[17,54]. The use of surgical gloves (Glove port), introduced through, was one of the examples. Every finger of the glove was used for a individual laparoscopic tools[55]. The increasing demand for an optimal platform for SPA has led to a large number of inventions of multichannel devices such as

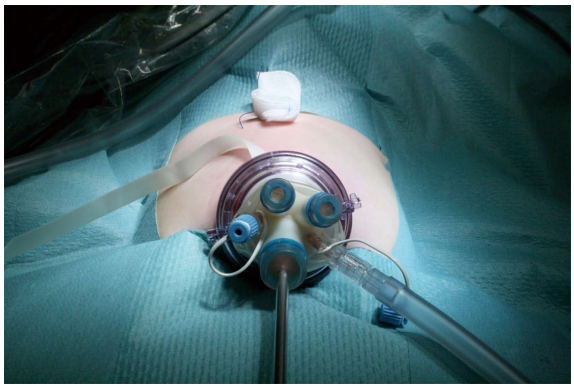

Figure 3 Placement TriPort single-port device (Advanced Surgical Concepts, Olympus, Japan) into abdominal cavity.

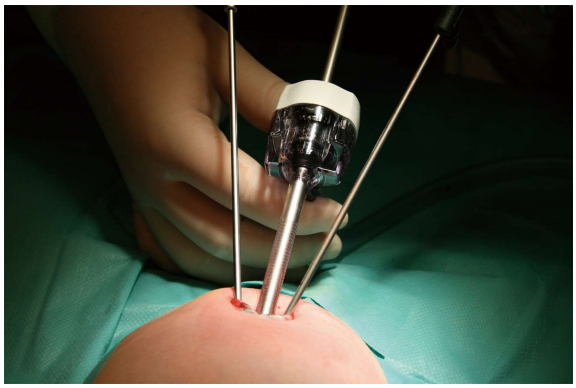

Figure 4 Installation of laparoscopic instruments through fascial wounds without a use of trocars.

the X-Cone, S-Cone and EndoCone (Karl Storz GmbH, Germany), KeyPort (Richard Wolf GmbH, Germany), TriPort and QuadPort (Advanced Surgical Concepts, Olympus, Japan), SILS-port (Covidien Inc., Switzerland), Uni-X (Pnavel Systems, United States), AirSeal (SurgiQuest, United States), GelPort (Applied Medical, United States). However, none are particularly suitable in newborns or infants. The idea of an introducing multiple instruments through a single device was appreciated by specialists dealing with a single-port surgery[56-61]. However, a generally large size of the multiport systems, which may require a 2-3 cm fascial incision, often restricts a use in small children. Rothenberg *et al*[62] reported on a use of a special device for the performing of SIPES cholecystectomy. The technique of S. Rothenberg involved the use of an operating laparoscope with an accessory channel through which was introduced a single working tool. However, such devices for the performing of SIPES also did not gain widespread popularity in children, mostly due to their large diameter. The only exception to the above-mentioned multichannel systems are those that rely on a ringed "sleeve" such as the TriPort or QuadPort devices (Advanced Surgical Concepts, Olympus, Japan), or the GelPoint (Applied Medical, United States), which require only a 1.5 cm fascial incision, feasible even in neonates

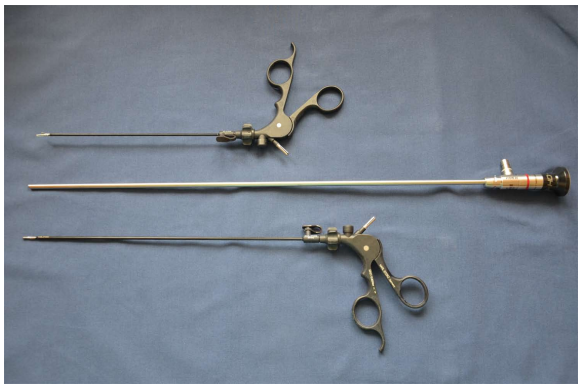

Figure 5 Laparoscopic instruments for single-incision pediatric endosurgery - a 5 mm endoscope with a length of 45 cm and 3 mm instruments with different lengths (20 and 30 cm).

(Figure 3). Soon after the invention of multiport devices, the access to the abdominal cavity was achieved using several three to five millimeter trocars introduced individual, closely-spaced umbilical access points. That is the technique commonly used nowadays in young patients (Figure 4). When a working space is limited, for instance in infants, laparoscopic instruments are installed directly through the fascia without a use of trocars[63]. As expected, the leak of carbon dioxide became more significant using this technique[64]. However, an increased risk of postoperative umbilical hernias as a result of the "Swiss cheese" effect resulting from placing multiple trocars through the fascia in one are was not confirmed in studies[65-68].

Having considered the technical aspects of single-port technique, there are some peculiarities for its application in young children. Some authors found that the majority of SIPES operations in infants, in fact, could be done without the use of expensive proprietary multi-port systems. Placement of separate laparoscopic trocars through a single-incision provides good ergonomics and excellent cosmetic results, at no additional costs necessary for the purchase of multi-port systems[69]. Furthermore, long telescopes, instruments with a different working length (Figure 5), transparietal stitches, and a crossed manipulation system allows surgeons to perform surgical maneuvers and to avoid a collision of instruments, were all beneficial.

INSTRUMENTS AND TECHNIQUES OF MANIPULATION

Just as there are no special devices for umbilical access made specifically for small children, the available selection of instruments for SIPES in small children is limited. The lack of triangulation of instruments is a major hurdle to SIPES. To overcome these inconveniences, Hansen E made a point of using different length graspers, separating the working hands along the Z-axis. This avoids collision of the surgeon's hands and instrument handles that result from employing the

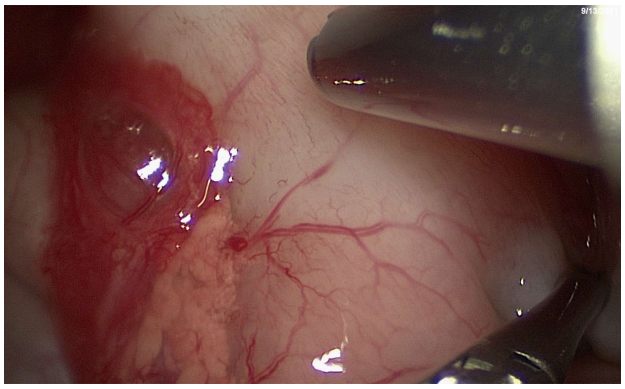

Figure 6 The technique of the "cross-handed" manipulation (cross instrumentation) during pyloromyotomy.

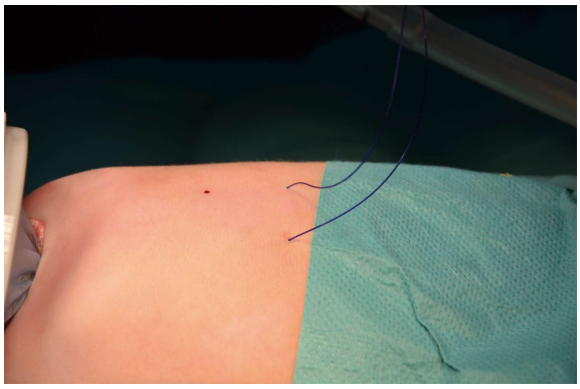

Figure 7 Transparietal stich sutured around the ligamentum teres hepatis.

usual, nonbent laparoscopic devices[64]. New instruments with a flexible distal part, or a so-called "reticulation", have an advantage in terms of their ability to avoid collision[70]. Unfortunately, the use of these modern devices is limited, since their cost is high, and application in small children is precluded by their large size.

The technique of the "cross-handed" manipulation (cross-instrumentation), proposed by Hansen *et al*[64] in 2011, gained popularity in young children due to an absence of special instruments (Figure 6). Also, to ensure the retraction of internal organs, some surgeons place an additional 2 mm diameter grasper through the abdominal wall (MiniLap, Stryker, United States)[71]. Whether this is still "single" incision laparoscopy is open to debate. A group from Argentina, led by Padilla *et al*[26], designed and manufactured mini alligator-graspers connected to a strong magnet. They were placed into the abdominal cavity at the beginning of the case, placed on the tissue to be retracted, and managed from the outside by an external sterile magnet on the surgical field. These magnet-graspers can retract abdominal organs and thereby augment the working space.

Together with above-mentioned devices for retraction, many surgeons also have started to apply transparietal stitches to fix internal organs. There are several types of such stitches described, and they are especially applicable in neonates and infants. Some of them are sutured around the ligamentum teres hepatis (Figure 7) to elevate the liver and provide access to the pylorus or to the gastroesophageal junction[64]. Others bite the seromuscular layer of hollow organs and are intended to stabilize the stomach, parts of intestine, gallbladder[63,72]. Finally, telescopes underwent further evolution. Many surgeons use laparoscopes with a length of 45-50 cm. This allows better visualization and spatial separation between the surgeon and the assistant[28].

TISSUE DIVISION

Modern minimally invasive surgery relies on innovative means of a tissue dissection. These comprise the traditional mechanical and physical ways using "cold" steel instruments along with the more advanced types of energy - high frequency, ultrasound, laser. The application of an endoscopic knife or scissors has limited application for neonates and infants and usually is employed for standard procedures - pyloromyotomy, pyeloplasty, duodenal anastomosis[11,12,73,74].

An ideal dissector and coagulator for patients of all ages does not exist. Application of a certain type of energy may be effective in adults and older children, but it may be dangerous or undesirable in small babies. Advanced energy cutting tools either use monopolar or bipolar coagulation. Monopolar tissue dissection is more commonly used in infants, because the energy of a monopolar source is sufficient enough for the delicate dissection of small diameter vessels. A 3 mm diameter monopolar hook is an ideal dissection device in an infant. Bipolar coagulation has the advantage that the current flows only through the target tissue and not the entire body of the patient. However, it is usually delivered through a clamp, mostly of 5 mm diameter or more.

In infants, tissue dissection is mostly achieved by the "pull and coagulate" principle[66]. It entails the combination of traction and countertraction of the tissue placed between two endoscopic clamps. One often, an atraumatic clamp such as the "duckbill" is employed. In the authors experience, the tissue is fixed and held with the left hand. The right hand grasps an endoscopic Kelly- or Maryland-type grasper connected to the monopolar electrosurgical source, and is used to dissect and coagulate the tissues of the patient under traction. This setup minimizes the time necessary for dissection of the tissues, and provides complete control over bleeding. In case of an intraoperative hemorrhage, having two clamps simultaneously in the abdomen allows the surgeon to stop it immediately by mechanical compression and to coagulate it with the monopolar clamp without changing tools.

The limits of bipolar dissection and coagulation in children of the first three months of life are surgical interventions requiring extensive tissue dissection, operations on parenchymal organs, and those procedures

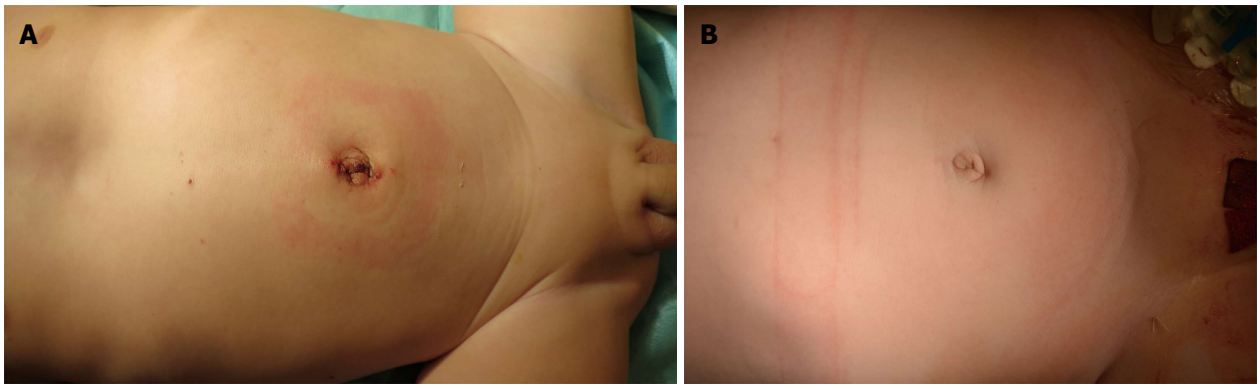

Figure 8 Cosmetic result. A: Cosmetic result after 7 d from a single-incision laparoscopic right nephrectomy; B: Cosmetic result after 1 mo from a single-incision laparoscopic right nephrectomy (same patient).

with a need of alloying vessels of big diameter - short gastric vessels, renal and suprarenal arteries and veins. The ultrasound dissector (Harmonic scalpel, Ethicon, United States) and BiClamp technology (ERBE, Germany) are the energy resources usually used for performing SIPES in infants. These devices simplify dissection of tissue planes and reduce the lateral thermal damage on adjacent tissues[28,75]. The unique design of the BiClamp allows very exact manipulations in the limited spaces of an infant body. The other benefit of this tool is the possibility of resterilization.

SUTURING

Suturing in parallel alignment turns out to be extremely challenging. Different SIPES approaches for intracorporal suturing have been[23]. In the "Magic Wand technique", the needle is grasped by the tip and used as an angulation device that helps wrap the suture around the tip of the counterinstrument. Extracorporeal knot tying is an attractive alternative for those that want to avoid the difficulties of intracorporal suturing in parallel. The "Spaghetti technique" can be performed using just one instrument, which grasps the suture close to, but not quite at the needle. The surgeon then twists the instrument around its axis so that the suture wraps around the shaft like around a fork loading up on spaghetti. After the wrapping, the instrument opens and grasps the free suture end, pulling it through the loops while the other instrument provides countertraction. Automatic suturing devices such as the Ti-knot (LSI Solutions, New York, United States) secure the suture by a metal clamp.

ADVANTAGES OF SIPES

Disputes over SIPES still exist and mainly focus on the fact that many surgical interventions are much more difficult to perform through a single access site[24,69]. Also, it has not been shown so far that single-port techniques are safer or more effective than standard laparoscopy. In addition, the aesthetic advantage has not been evaluated objectively and the "improved cosmetic result" remains a subjective outcome.

There is no doubt that a better cosmesis is the primary advantage of SIPES, which uses the umbilicus as a "keyhole" to hide the postoperative scar (Figure 8). An umbilical incision is also valuable since it can easily be converted into a multiport laparoscopy or into an extended umbilical incision, for example, for "hybrid" operations that combine principles of laparoscopic and open surgery.

Currently, there is no clear advantage of SIPES over the other methods due to a weak level of evidences in most publications, except for reports on single-port appendectomy and cholecystectomy. There are odd bits of information concerning the children of older age groups, which are discrepant.

POSTOPERATIVE PAIN

Initially, Chandler *et al*[76] reported on a decrease in the need for intravenous drugs after SIPES appendectomy in comparison with conventional multiport laparoscopy performed on 110 children. However, in 2011 St Peter *et al*[77] found the opposite - patients require more analgesia during their hospital stay after a single-port appendectomy in comparison to those who underwent conventional laparoscopic appendectomy. The postoperative length of children's hospital stay after the cholecystectomy was equal to that of a standard single-port laparoscopy[78]. However, a recent study of patients, who underwent single-incision endosurgical cholecystectomy, showed that they had a lower level of postoperative pain and required less analgesics than patients that underwent a multiport endoscopy. The same study also showed a reduction of the length of hospital stay[79].

As soon as special equipment is required, SIPES becomes less profitable. Some of the special instruments and proprietary multi-ports significantly increase expenses of these operations. Though experienced surgeons have used conventional laparoscopic instruments for SIPES, and have comparable results with

regard to operative time, it must be noted that the learning curve of these techniques is quite long and requires at least 40 cases to reach a plateau[80,81].

A definitive advantage of SIPES *vs* conventional laparoscopic surgery becomes apparent when ablative procedures are performed. It is much easier to extract a large Spleen or even a gallbladder full of stones through a single 2 cm incision than it is to do it through a 5 or even 10 mm trocar site. The other advantage is that a finger can be inserted through the larger single umbilical access site, allowing the surgeon to obtain tactile information, something impossible through several 3, 5, or even 10 mm incisions. Therefore, SIPES may be an ideal technique for ablative and oncologic indications.

COMPLICATIONS AND CONVERSIONS

Rare complications after application SIPES in neonates and infants have been reported in the literature, including intestinal perforation, trauma of adjacent organs, and wound infection[64]. In the first series of single-port pyloromyotomy, the complication rate was 6%, including perforations of the pyloric mucosa and duodenal mucosa. Although the perforations were immediately recognized, repaired, and the patients suffered no postoperative sequelae, the relatively high perforation rates prompted the authors to change their technique to the cross-technique instead.

Initial reports also raised concern over an increasing risk of wound infections after SIPES. However, later studies showed a decrease of the wound infection rate, corresponding to increased experience in handling tissues around the navel. Studies have shown that the wound infection rate (2.3%) did not differ from that of the conventional laparoscopic procedures[77]. Another concern is the possibility that a large umbilical incision may theoretically increase the risk of postoperative umbilical hernia. However, cases of this complication were not found in the existing literature.

There is no consensus in the literature concerning the definition of "conversion" in SIPES. Analyzing the available publications, it has been defined as[28,68]: (1) a need to use one or more additional ports to complete single-port procedure; or (2) a switch to the open surgery. Conversion to conventional laparoscopy or placement of additional trocarss should not be considered a failure of SIPES. A surgeon must not endanger the patient safety, must use sane judgment, and add ports as necessary. Ponsky *et al*[28] reported their experience of more than 70 cases of SIPES in children. They reported on an acceptable level of conversions to standard laparoscopy and few perioperative complications. In other studies, including that of older children, SIPES results were similar to those of conventional laparoscopic procedures, with a conversion rate of 2%-11%[63,68,76,82-84].

CONCLUSION

General interest in the umbilical ring as a "keyhole" for single-incision access to the abdominal cavity organs, has promoted the development of modern endoscopic surgery towards the development of a "stealth" techniques, those that leave no visible scar behind. We believe that SIPES, despite its initial success, still has huge obstacles to overcome in order to be recognized as a universal, standard surgical approach in children in the first 3 mo of life. Modern laparoscopic instruments of a small diameter with multidirectional reticulation and abilities to move in several planes may soon let pediatric surgeons perform complex laparoscopic procedures more efficiently. With their introduction, the limited triangulation and reduced degrees of freedom will no longer be a problem. Moreover, in the near future one could expect the introduction of single-incision port devices that are more appropriate for small children. Advanced skills and a high technical demand, along with the lack of specialized surgical equipment are factors limiting the popularity and availability of SIPES for pediatric surgery in first 3 mo of life. However, the current body of evidence shows that a SIPES is indeed applicable in infants with outcome comparable to that of standard laparoscopy, and that it results in minimal post-operative surgical trauma and superb cosmesis.

Summarizing our review, we conclude that: (1) The current experience with SIPES in children in first 3 mo of life shows good outcomes, few complications, and a low conversion rate; (2) Special costly proprietary devices and instruments are not required to perform SIPES; (3) Most surgeons perform these procedures with conventional laparoscopic instruments, standard energy devices, and some have improvised to build their own low-cost access ports; (4) Superb postoperative long-term cosmesis is the biggest advantage of the SIPES, although there is no objective evaluation of this in the literature so far studies comparing the cosmetic outcome should be performed in the future; and (5) Most endoscopic surgeons that practice SIPES believe that it is an evolutionary continuation of traditional laparoscopy. However, the prospective controlled studies must be performed to determine the real advantages of this novel approach.

Although we have made every effort to include all relevant studies in our review on SIPES in the newborn and infant, it must be remembered that published data on the subject at this time is insufficient to perform a formal meta-analysis. Most publications at this time are case series or retrospective analyses. A well-defined control group is mostly absent. Therefore, formal scientific scrutiny of SIPES techniques in infants at this time is limited. We encourage pediatric surgeons to prospectively evaluate their results with SIPES interventions in the future.

Despite these recognized limitations, our review highlights the immense creative potential of pediatric surgeons in search for less invasive methods, which might eventually develop and turn SIPES into a preferred method for endosurgical operations in infants and children.

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REVIEW

Congenital and childhood myotonic dystrophy: Current aspects of disease and future directions

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Abstract

Myotonic dystrophy type 1 (DM1) is multisystem disease arising from mutant CTG expansion in the non-translating region of the dystrophia myotonica protein kinase gene. While DM1 is the most common adult muscular dystrophy, with a worldwide prevalence of one in eight thousand, age of onset varies from before birth to adulthood. There is a broad spectrum of clinical severity, ranging from mild to severe, which correlates with number of DNA repeats. Importantly, the early clinical manifestations and management in congenital and childhood DM1 differ from classic adult DM1. In neonates and children, DM1 predominantly affects muscle strength, cognition, respiratory, central nervous and gastrointestinal systems. Sleep disorders are often under recognised yet a significant morbidity. No effective disease modifying treatment is currently available and neonates and children with DM1 may experience severe physical and intellectual disability, which may be life limiting in the most severe forms. Management is currently supportive, incorporating regular surveillance and treatment of manifestations. Novel therapies, which target the gene and the pathogenic mechanism of abnormal splicing are emerging. Genetic counselling is critical in this autosomal dominant genetic disease with variable penetrance and potential maternal anticipation, as is assisting with family planning and undertaking cascade testing to instigate health surveillance in affected family members. This review incorporates discussion of the clinical manifestations and management of congenital and childhood DM1, with a particular focus on hypersomnolence and sleep disorders. In addition, the molecular genetics, mechanisms of disease pathogenesis and development of novel treatment strategies in DM1 will be summarised.

Key words: Clinical manifestations; Myotonic dystrophy type 1; Childhood myotonic dystrophy; Congenital myotonic dystrophy; Natural history; Management

Core tip: Type 1 myotonic dystrophy is an often undetected neuromuscular disease in paediatric patients with variable clinical manifestations and burden of disease. We review the current understandings of disease pathogenesis, symptoms and management in congenital and childhood myotonic dystrophy with a particular focus on hypersomnolence and sleep disorders. Future directions should target standardised care and regular surveillance, understanding pathophysiology and new treatment strategies.

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INTRODUCTION

Myotonic dystrophy type 1 (DM1) is a multisystem genetic disease that affects skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous systems (CNS) caused by expansion of a CTG trinucleotide repeat in the non-coding region of the dystrophia myotonica gene (*DMPK)*. The phenotype is variable and encompasses a broad spectrum of severity from mild to severe. It is the most common adult muscular dystrophy, with an estimated worldwide prevalence of one in eight thousand, but age of onset varies from prenatal to adulthood. While the clinical manifestations and natural history of DM1 in adulthood are well established, the manifestations and management of DM1 in children warrants further evaluation. Multidisciplinary care including proactive respiratory care and nutrition optimisation have seen changes in the natural history of a number of neuromuscular disorders[1-3]. It is critical to develop a better and focused understanding of the unique issues encountered in the management of DM1 in paediatrics and neonatology to optimise outcomes and develop standards of care. Accordingly, this review will summarise the current understandings of congenital and childhood DM1, with a particular focus on sleep and hypersomnolence.

CLINICAL CLASSIFICATION AND NATURAL HISTORY

There are five clinical phenotypes of DM1 that generally correlate with CTG repeat size (Table 1), including premutation, mild adult DM, classical adult DM, childhood-onset DM and congenital DM.

Congenital myotonic dystrophy (CDM) is characterised by severe hypotonia and weakness at birth, often with respiratory insufficiency. The incidence of CDM is up to 1 in 47619 live births[4] and the mortality in the neonatal period may be 30%-40%[5].

Childhood-onset DM is initially clinically apparent between ages 1-10, however diagnosis may occur later, and predominantly affects muscle strength, cognition, respiratory, central nervous and gastrointestinal systems (Table 2). Juvenile DM is apparent between 10-20 years, however onset may be vague and manifestations overlap between childhood and classic DM. Patients with childhood and juvenile DM survive into adulthood, however the natural history remains to be fully determined, with recent advances in supportive care. Adult type problems arise in later life. Severe CDM demonstrates a unique "biphasic" course, whereby neonatal symptoms improve or stabilise in surviving neonates, before adult-type symptoms present in later life[6]. Echenne and Bassez[5] also observe a "continuum", where CDM survivors and childhood-onset/juvenile types develop the same clinical picture before eventually showing classical adult-onset manifestations. Consequently developing standards of care focusing on the neonatal and childhood periods of DM1 in addition to adult DM are needed. In addition, developing guidelines on transitioning to adult medical care for patients with congenital and childhood DM is necessary.

CLINICAL MANIFESTATIONS OF DM1 IN NEONATES AND CHILDREN

Neonatal period in CDM

Polyhydramnios, reduced foetal movements and preterm delivery often complicate CDM gestation[7]. Classically, neonates are born with hypotonia and immobility, bilateral talipes, contractures, arthrogryposis, facial dysmorphia (carp mouth, ptosis, long neck and face, temporal muscle atrophy), hyporeflexia, a weak cry, sucking and respiratory difficulties. Cases of premature (less than 36 wk gestation) and small for gestational age DM1 babies have also been reported[6]. The presence of respiratory distress is sometimes used to distinguish between mild and severe CDM[8]. Respiratory difficulties were present in about 50% of neonates (Wallgren-Petterson, Bushby, Mellies, and Simonds, 2004) and are the main cause of neonatal mortality which ranges between thirty and forty percent[9].

Musculoskeletal manifestations

Muscle weakness in DM1 is typically distal but may be proximal, the latter indicating a poorer prognosis[10]. Following initial improvement in the neonatal period, the natural history of progressive muscle weakness is variable. While strength is typically stable until adolescence with gradual deterioration subsequently evident, rarely rapid increasing weakness may occur in young adults[8,11]. Complications of muscle weakness may include scoliosis and contractures, particularly at the tendo-achiles producing foot deformity and toe walking. Bulbar muscle weakness may also produce

Table 1 Myotonic dystrophy type 1 clinical phenotypes

Phenotype	Clinical characteristics	CTG repeat length	Age of onset (yr)
Premutation	Not applicable	38-49	Not applicable
Mild/late onset adult	Mild myotonia Cataracts	50-100	20 to 70
Classical adult	Myotonia Muscle weakness Cataracts Conduction defects Insulin resistance Respiratory failure	50-1000	10 to 30 (median 20 to 25)
Childhood onset	Facial weakness Cognitive defects Psychosocial issues Incontinence	> 800	1-10
Congenital	Hypotonia Respiratory distress Cognitive defects Motor and developmental delay Feeding difficulties	> 1000	Birth

swallowing difficulties, speech and language difficulties, separate to cognitive impairment and may initiate consideration of DM1. In contrast to adult DM1, severe myotonia is not common in children but is present to some extent in most children by age 10 years[11-13]. The worsening facial dysmorphia and "carp" mouth appearance seen in CDM neonates is not a feature at birth for childhood-onset cases[12]. These patients may experience facial weakness but to a lesser severity.

Sleep disturbances

Sleep disorders are a significant complaint in both adult and childhood DM1 (Table 3) and may adversely affect learning, memory, high-level cognitive processing and physical functioning, thereby exacerbating psychomotor and cognitive delays in DM1[14,15]. Consequently, understanding sleep pathophysiology and assessment approaches are important in determining management in DM1. Normal sleep is maintained through CNS regulation of breathing and sleep-wake cycles and respiratory muscle integrity.

CNS disturbances in DM1 can affect sleep through central deregulation of breathing whilst sleeping, resulting in hypoventilation and subsequent sleep fragmentation, producing excessive Daytime Sleepiness (EDS)[16]. EDS in DM1 is characterised by persistent sleepiness, more likely during situations requiring less attention, and is not improved by naps and has been reported in approximately 50% of children with DM1[17]. It occurs concurrently and may be attributed to other sleep disorders including sleep apnoea, periodic limb movement disorders (PLMs) and rapid eye movement (REM) sleep dysregulation. Neuronal loss and gliosis in the reticular activating system and brainstem may underlie central deregulation of ventilation[18,19]. Immunoendocrine causes with abnormal levels of growth hormone, cortisol and cytokinesin DM1 may also affect sleep control[20,21]. MRI studies indicate white matter changes are evident; however, the changes do not correlate with severity of EDS[22].

Sleep disordered breathing (SDB) can arise from obstructive causes (apnoeas - airway hypotonia or tonsillar hypertrophy) or central ventilator dysfunction in DM1. Muscle weakness can contribute to obstructive sleep disorders. Apnoea-Hypnoea indices are raised in adult DM1 patients[23]. This causes nocturnal hypoxemia and hypoventilation, subsequent sleep fragmentation and EDS[24,25]. EDS and apnoeas, however have been noted to occur independently, and correction of hypoventilation does not always improve EDS[16]. Sympathetic hyperactivity associated with cardiac conduction disturbances are suspected to be linked to PLMs[26]. Thus conduction deficits seen in DM1 could in part explain sleep fragmentation and subsequent EDS by increasing the occurrence of PLMs.

Cognitive impairment

Cognitive impairment is one of the most common manifestations and challenging management aspects of childhood DM1. This may be the presenting characteristic in children, ranging from mild to moderate intellectual impairment. Overall, both groups have lower than average IQ. CDM patients are more severely affected and full-scale IQ ranges from 40-80, with a mean below 70[12]. Childhood-onset patients have a wider range from 42 to 114 and a mean of about 70-80[27-29]. It is highly possible that patients' IQ is underestimated however, due to the false impressions given by apathy and reduced facial expression commonly seen in DM1. Cognitive impairment correlates with severity of muscle weakness, size of CTG repeat and maternal transmission[27,28].

Psychosocial function

Approximately half of children with DM1 have at least one DSM-IV psychiatric diagnosis[27], with internalising disorders (phobia, depression, anxiety) and attention deficit hyperactivity disorders being common. Avoidant personality types, apathy and autistic features may also be evident[30,31]. Brain imaging of (CT, MRI) CDM and JDM patients often reveal ventricular dilatation, cortical atrophy, and hypoplasia of the corpus callosum, and hyper-intense white matter in cortical regions seem to be specific to CDM[32]. While not evident during paediatric management, these may relate to subsequent development of dementia, and are important considerations in further understanding pathogenic mechanisms of neuro-degeneration.

Respiratory

Respiratory manifestations, related to inspiratory and expiratory muscle weakness, are a major feature of CDM and remain important in childhood. These include sleep breathing disorders, recurrent infections, weak cough

Table 2 Summary of the clinical manifestations in congenital and childhood-onset/juvenile myotonic dystrophy type 1

System	Congenital (CDM)	Childhood-onset/juvenile onset
Prenatal	Polyhydramnios	Not applicable
	Reduced foetal movements	
	Preterm delivery	
Muscular	Hypotonia at birth	Facial dysmorphia (may be subtle)
	Talipes	Generalised muscle weakness
	Contractures	Myotonia, usually after 1st decade
	Scoliosis, lordosis, kyphosis	Muscle atrophy
	Arthrogryposis	Brisk reflexes
	Characteristic facial dysmorphia	Mild talipes and contractures Motor delay
	Hyporeflexia	
	Generalised muscle weakness (distal > proximal)	
	Muscle atrophy	
	Motor delay	
Vision	Visual impairment	Visual impairment
	Strabismus	Strabismus
	Reduced visual acuity	Reduced visual acuity
	Lens pathology	Lens pathology
Respiratory	Respiratory distress at birth	Recurrent infections (weak cough)
	Raised right hemi-diaphragm	Sleep apnoea and sleep disordered breathing
	Pulmonary hypoplasia	
	Bronchopulmonary dysplasia	
	Aspiration pneumonia	
	Sleep apnoea and sleep disordered breathing	
	Pneumothorax	
	Recurrent infections	
	Impaired central respiratory control	
Gastrointestinal and feeding	Sucking difficulties from birth	Recurrent abdominal pain
	Gastroparesis	
	Gastroesophageal reflux and aspiration	
	Constipation	
	Recurrent diarrhoea	
	Faecal incontinence	
	Anal dilatation	
	Persistent abdominal pain	
CNS	Increased sensitivity to anaesthesia	Hypersomnolence and fatigue
	Neuroendocrine disturbance	Periodic limb movements
	Psychiatric disorders (ADHD, anxiety, depression)	Psychiatric disorders
	Autism	Autism
	Hypersomnolence and fatigue	
Cognitive function	Lower IQ	Lower IQ
	Full scale ranges between 40-80	Full scale ranges from 42 to 114
	Mean less than 70	Mean between 70 and 80
Cardiac	Conduction disturbances	Conduction disturbances
	Structural abnormality, valve defects (most commonly mitral)	Structural abnormality, valve defects (More common in older patients)
Endocrine	Testicular atrophy	Testicular atrophy
	Hormone abnormalities: growth hormone, hypothyroidism (late teens)	Later onset: hormone abnormalities
Hearing	Recurrent otitis media	Recurrent otitis media (less common)
Oral health	Dental caries, plaque, gingivitis decay/trauma	Dental caries, plaque, gingivitis decay/trauma
Speech and language	Nasal voice and dysarthria	Speech delay
	Speech delay	Nasal voice and dysarthria
Life expectancy	30%-40% death rate within neonatal period	Mortality similar to adult-onset
	Mean life expectancy: 45 yr	Mean life expectancy: approximately 60 yr

CDM: Congenital myotonic dystrophy; ADHD: Attention-deficit/hyperactivity disorder; CNS: Central nervous system; IQ: Intelligence quotient.

and aspiration pneumonia[8,12,33]. It is also important to appreciate DM1 patients have hypersensitivity to anaesthesia, which arises from respiratory muscle compromise and central dysregulation of breathing[34]. Separately, obesity may adversely affect pulmonary function and sleep-disordered breathing in adults with DM1, although this remains to be defined in paediatric DM1 patients. Cognitivive impairment may affect an individual's ability to reliability undertake conventional respiratory function tests. Consequently sniff nasal inspiratory pressure (SNIP), which correlates with pulmonary function, may provide an easier and more accurate measurement[35].

Gastrointestinal symptoms

Gastrointestinal complaints often predate diagnosis of DM1 and significantly contribute to morbidity. Previous studies have determined that forty per cent of

Table 3 Sleep disorders in myotonic dystrophy type 1 that contribute to hypersomnolence

Sleep disorder	Description and components
Excessive daytime sleepiness	Greater susceptibility to falling asleep, especially when in situations requiring less attention Naps are long, frequent and unrefreshing
Long night time sleep	Sleep often does not feel sufficient or restorative Sleep fragmentation and frequent arousals
Sleep related breathing disorders	Sleep apnoea or hypopnoea: Obstructive and/or central Hypercapnoea and hypoxemia in both day and night time
RLS and PLM	RLS refers to the urge to move limbs while both awake and asleep, while PLM refers to uncontrolled limb movements during sleep. Both commonly co-exist
REM sleep dysregulation	Abnormal periods of SOREMPs during MSLTs Increased density and frequency of REM sleep nocturnally

RLS: Restless leg syndrome; PLM: Periodic limb movements; SOREMPs: Sleep-onset REM periods; MSLTs: Multiple sleep latency tests; REM: Rapid eye movement.

children and young adults regularly experience faecal incontinence, with twenty per cent stating this was their worst symptom[36]. Up to a third may also report constipation and irregular bowel habits[37]. Recurrent or persistent diffuse abdominal pain are common[38]. In both adults and children, dysphagia, gastroesophageal reflux and choking have been observed[4,39,40]. Dyspeptic symptoms of nausea, vomiting, and early satiety may be attributed to delayed gastric emptying. Lower tract problems also include faecal incontinence, episodic and recurrent diarrhoea, with significant social implications[37,39].

There are multiple factors that cause the gastrointestinal disturbances, including reduced peristalsis and secondary bacterial overgrowth. The latter is a mechanism of diarrhoea which may be overcome with antibiotics[41,42]. Delayed gastric emptying may also be related to gut hormone abnormalities guiding future management strategies[43,44].

Other systems

Many key features of adult "classic" DM are not evident in childhood, including cataracts, significant cardiac disorders and diabetes mellitus. Even so, lens pathology may be evident in 41% of patients, and may be predictive of future cataract development[45]. Conduction disturbances observed on electrocardiography are not uncommon in children, however they do not often present symptomatically with dyspnoea, palpitations or syncope. Valve abnormalities have also been observed, but again, are not clinically significant. Hypothyroidism, hypogonadism, growth hormone imbalance and androgen insensitivity have been observed but are rare[8,46]. In contrast, testicular atrophy and infertility are common amongst CDM males. Females with severe CDM patients may experience very irregular periods and prolonged episodes of amenorrhoea[46].

CURRENT TREATMENT AND MANAGEMENT

Management of childhood DM1 is currently adapted from approaches to adult myotonic dystrophy. A multidisciplinary team approach is critical in providing supportive care to manage manifestations, reduce complications, optimise function and undertake health surveillance (Table 4). This includes involvement of genetic counsellors, nurses, educators, physiotherapists, speech therapists, occupational therapists, social workers, and dieticians in addition to medical specialists. Standards of care for other rare neuromuscular disorders, for example spinal muscular atrophy and Duchenne Muscular Dystrophy, have been established and are easily accessible to health care professionals and patients[1-3]. Advances in the management of respiratory impairment and nutrition have seen an evolution in the natural history of these disorders[47]. The multisystemic nature of DM1 brings about similar complex care, yet the unique cognitive and psychological manifestations of DM1 may limit ongoing engagement with medical services. Patients may present ad hoc to clinicians unfamiliar with DM1. Consequently creating standards of care, encompassing the specific needs of children with DM1 and anticipating transition to adult services, for best practice is critical. Further these need to be accessible and practical to primary care physicians and converted into individual health care plans.

In severe CDM, neonatal intensive care is often required to provide respiratory support. Chest radiography may demonstrate diaphragm elevation, prompting additional management of pulmonary hypoplasia. Nutrition and feeding may require enteral supplementation. Oesophageal function should be evaluated with barium studies and speech pathology assessments to consider aspiration. Cerebral ultrasounds or head CT may be undertaken for concurrent birth related hypoxia or cerebral haemorrhage. Splinting of talipes is also commenced[48].

Recognising cognitive impairment and psychiatric/psychological manifestations are critical in guiding overall management and planning appropriate educational support. Formal cognitive testing and psychological assessments are essential. Special education is common and previous studies have revealed that more than two thirds of DM1 children have repeated a grade at

Table 4 Current management strategies in congenital and childhood myotonic dystrophy type 1

Clinical problem	Management strategies
Muscle weakness	
General	Exercise and physical therapy
	Possible drug therapy (DHEA, IGF-1, BP3, Creatinine use has shown possible benefits but this is not routinely done)
Talipes, foot drop, osteopenia, contractures	Orthopaedic surgery (*e.g.*, tendon transfer, if required)
	Mobility aids
	Physiotherapy, ankle foot orthoses, splints
(Scoliosis, kyphosis)	Optimise vitamin D and calcium
	Physiotherapy, stretches and splints
Speech (dysarthria)	Orthopaedic surgery
Swallowing/feeding	Speech therapy
	Speech therapy
	Modification of food consistency
	Physiotherapy to enhance swallowing
Myotonia	Occupational therapy – adaptive devices
	Drug therapy (Mexiletine, anti-epileptics, amino acids, antidepressants)
Respiratory	
Chest wall weakness and respiratory function	Regular surveillance screening with a symptom checklist including:
	Orthopnoea, dyspnoea with ADLs, sleep disturbances, morning headaches, apnoea, reduced cognition, EDS, fatigue, recent chest infections
	Respiratory function tests including
	Regular forced vital capacity, FEV1, pulse oximetry and peak expiratory cough flow
	Elective monitoring also includes mean inspiratory and expiratory pressures, and arterial blood gas analysis
	Imaging may include chest radiography or ultrasound for detection of motion abnormalities and thinning of diaphragm
	Nocturnal non-invasive ventilation: BiPAP or CPAP (in more obstructive cases)
Weak cough	CDM: Intubation and ventilation during neonatal period
Greater	Physiotherapy incorporating airway clearing techniques, manual assisted cough and postural drainage of secretions
Susceptibility to infections/recurrent infections	Antibiotics for management of acute infections
	Prophylactic vaccinations
	Respiratory physician consultation
	Prophylactic antibiotics
Cardiac	
Conduction disorders	Annual surveillance with ECG and echocardiography
	Holter monitoring
	Pacemaker or defibrillator insertion if indicated
Sleep	
Sleep related breathing disorders	Respiratory function testing
	Overnight pulse oximetry
	Polysomnography
	Non-invasive ventilation
Upper airway obstruction/apnoea	Total tonsillectomy or adenoidectomy may be beneficial
Periodic limb movements	Assessment of serum iron and ferritin
	Consider dopaminergic agents
Excessive daytime somnolence	Thorough assessment (questionnaires, actigraphy)
	Drug therapy/psychostimulants (Modafanil)
Hearing	Regular assessment
	Antibiotics for otitis media
	Grommets for recurrent otitis media
Gastrointestinal	
Nutrition	Monitoring growth
	Assessment of micronutrients (*e.g.*, iron and vitamin D) and supplementation as needed
	Dietician consultation
Irritable bowel syndrome type symptoms	Antibiotics to counteract bacterial overgrowth
Diarrhoea	Antibiotics (erythromycin)
	Drug therapy (cholestyramine)
Constipation	Stool softeners
	Laxatives/stimulating agents
	Regular toileting routine assisted by bulking agents and laxatives
Faecal incontinence	Cholestyramine
(Anal dilatation)	Colostomy (last resort)
Abdominal Pain	Pain medication (NSAIDs)
	Cholestyramine
Anaesthesia	

Hypersensitivity with risk of respiratory depression	Detailed anaesthetic work up and assessment that may include ultrasound examination of gastric volume for risk of aspiration Establish airway: modified rapid induction, tracheal tube/supra-glottic device
Increased risk of intraoperative myotonia	Avoid opioid infusions and intravenous administrations Consider local anaesthetia as an alternative (Caudal, spinal and epidural) Extensive post-operative monitoring and support Paracetamol and NSAIDs
Poor oral health	Regular dental hygiene Regular visits to general and specialist dental clinics Good home care techniques: cleaning, plaque removal
Vision	Early and regular screening Prevention of amblyopia Early correction of hyperopia and astigmatism
Psychological	
Cognitive deficits and mental retardation	Cognitive assessment Planning of appropriate education environment and support
Neuropsychiatric comorbidities (Attention deficit, personality disorders)	Psychotherapy, social skills training Drug therapy (*e.g.*, stimulants for ADHD)
Social issues	Specialised school or special arrangements

DHEA: Dehydroepiandrosterone; IGF: Insulin-like growth factor; EDS: Excessive daytime sleepiness; BiPAP: Bi-level positive airway pressure; CPAP: Continuous positive airway pressure; CDM: Congenital myotonic dystrophy; NSAIDs: Non-steroidal anti-inflammatory drugs; BP3: Binding protein 3; ADL: Activities of daily living; FEV1: Forced expiratory volume in 1 s; ECG: Electrocardiogram; NSAIDS: Non-steroidal inflammatory drugs; ADHD: Attention deficit hyperactivity disorder.

school[27]. Anticipating economic and vocational support are critical, with unemployment common in young adults. Taken together, special education, psychotherapy, social and vocational skills training should be utilised to maximise functionality. Stimulant medication may be prescribed for management of attention deficit hyperactivity disorder, a common comorbidity, with attention to screening for cardiac rhythm disorders.

Muscle weakness is rarely progressive in childhood; however physiotherapy, occupational therapy and orthopaedic surgery are important to limit and manage complications (contractures, pain and scoliosis) and maximise function. This includes regular assessments of strength, range of motion and function. Stretches, orthoses and assistive devices may be utilised. Tendo-achilles lengthening and scoliosis surgery may be indicated. Even though exercise therapy is commonly used, studies have shown neither benefit nor harm[49]. A Cochrane review published in 2006[50] found limited evidence supporting drugs for myotonia. Agents analysed included sodium channel blockers (such as procainamide and mexiletine), calcium channel blockers (nifedipine), benzodiazepines (diazepam), taurine and tricyclic antidepressants (clomipramine and imipramine). A more recent study has found that mexiletine is effective and well tolerated for improving debilitating grip myotonia in adults[51]. Facial weakness worsens with age and swallowing dysfunction may be assisted with diet modification and speech pathology. Speech therapy will also assist in language development. In addition facial weakness and an open mouth posture may cause more plaque, gingivitis and caries such that more frequent brushing, dental hygiene and regular dental reviews are important[52].

Regular surveillance for respiratory and cardiac complications is important in childhood. The most recent European Neuromuscular Centre workshop (ENMC) for chronic respiratory disease in DM1 describes consensus recommendations for assessment, management and follow-up based on current evidence and clinician experience[53]. Interviews with patient and carer should include a checklist for symptoms of orthopnoea, dyspnoea while performing activities of daily living, sleep disturbances, morning headaches, apnoea, reduced cognition, EDS, fatigue and chest infections since last review to identify and quantify respiratory insufficiency[53]. Accompanying tests should include respiratory function testing, pulse oximetry and polysomnography (Table 4). Management should include routine vaccination for pertussis, pneumococcus and influenza in preventing respiratory infections. Airway clearance techniques are beneficial in management of weak cough. Respiratory support is more commonly indicated in neonates than in childhood. Non-invasive ventilation may improve quality of life when there is hypoventilation or apnoea, however clinicians still debate its efficacy and further studies will clarify utility[53]. While Bi-level positive airway pressure (BiPAP) use is first line, continuous positive airway pressure (CPAP) should be used when there is a predominantly obstructive component in respiratory insufficiency. CPAP use should be accompanied with careful monitoring of blood gases[53]. Importantly, there may be a possible relation between apnoea and dysrhythmia[54] such that cardiac monitoring should accompany appropriate respiratory management when spontaneous apnoea is present[53].

Routine electrocardiography and echocardiogram should be performed and Holter monitoring may be undertaken if clinically indicated to assess for arrhythmia. Cardiac interventions, such as pacing or implanted defibrillator, are more likely to be needed closer to adulthood.

Recurrent and persistent otitis media is common

in CDM[12] and should be referred to ear, nose and throat (ENT) specialists for assessment of hearing and management. Likewise, gastrointestinal problems are an important management issue. Supportive therapies such as stool softeners/bulking agents, laxatives, antibiotics for bacterial growth, and pain medication are useful. Some drug therapies have also proven effective in remediating symptoms (Table 4). Bile acid sequestrator agents, such as cholestyramine, have been noted to reduce diarrhoea, incontinence and abdominal pain[33].

Genetic counselling is crucial in understanding the nature and inheritance pattern of DM1[55]. Multiple family members are commonly affected, and early counselling allows for surveillance and early intervention in these individuals as well as family planning with foetus risk assignment depending on parental disease. Genetic anticipation, the occurrence of decreasing age of onset and increasing severity in successive generations related to expansion of CTG repeats during meiosis, is an important consideration in genetic counselling. Notably, women have a higher risk of CDM offspring and risk factors include length of triplet repeats, symptoms during pregnancy and severity of their clinical presentation. Previous studies vary in estimation of CDM risk related to maternal CTG repeat length, rendering specific risk assessments difficult. Maternal alleles longer than 300 repeats have been demonstrated to have a 59% risk of CDM, compared with a 10% risk when CTG repeats are less than 300[56]. Different studies have found a maternal CTG length greater than 100 may have a 63% risk of CDM[57,58]. Anticipation with paternal inheritance is also possible and risk factors include onset less than aged 30 years and previous CDM pregnancies[59,60]. A parent may be identified with DM1 following diagnosis in their child and is of significance in planning of health care for the family.

Management of sleep disturbances

Sleep disturbances have been shown to be linked to greater psychosocial issues, depressive symptoms and lower quality of life[16,61,62]. Further, it is a condition faced in both adult and paediatric populations; hence early management is highly beneficial. Current management involves a thorough assessment and quantification of the sleep problem with appropriate tests. This includes polysomnography, lung function, and subjective questionnaires to assess daytime sleepiness, quality of life assessments and monitoring activity and rest cycles through non-invasive actigraphy. If a SDB is suspected, supportive ventilation with CPAP, BiPAP, sero-ventilation can improve arterial blood gases and prolong survival but may not always alleviate EDS[62]. Use of psychostimulants remains debated. A Cochrane review[63] found that evidence was inconclusive to support psychostimulant use in hypersomnia, but subjective clinician experience and other studies have found modafinil to be beneficial for EDS[64,65]. The American Academy of Sleep Medicine recognises modafinil as a therapeutic option for EDS in adult DM1, and states the current dosing recommendation as 200 mg once daily for treatment of EDS in narcolepsy[66]. There are limited clinical trials and safety information for modafinil use in children, hence modafinil is not approved by regulatory bodies for use in young children. Further studies in this group are needed to determine safety and efficacy.

GENETICS AND PATHOGENESIS OF DM1

DM1 has autosomal dominant inheritance and penetrance is variable (Figure 1). It is caused by a CTG repeat expansion of the non-coding DNA segment on the *DMPK* gene on chromosome 19q13.3. In unaffected individuals, the *DMPK* gene segment is highly polymorphic and can range from 5-27 copies[67]. There can be greater than 2000 CTG repeats in DM1[68]. Larger repeats correlate with greater symptom severity and earlier age of onset (Figure 2). One study demonstrated that in severe congenital DM1, 44% had more than 4.5 kb (up to 2000 repeats), however the largest repeat was not conditional for congenital disease[69].

DM1 demonstrates anticipation, as the CTG repeat expansion in *DMPK* may increase and become unstable with each generation. Even though amplification occurs regardless of the parental sex, offspring repeat size seems to increase more in paternally transmitted cases when the father has smaller repeats[70], but instability is greater when the mother has an expansion of more than 0.5 kb[71]. Many studies have also found occasional contractions in repeat size and variants to the repeats, but it has yet to be established if variants or interruptions in the repeats alters pathogenesis[72,73]. A sound understanding is especially important in management with regard to family planning. Adequate counselling of women who are considering pregnancy is crucial and foetal risk of disease should be assessed based on parental repeat size and presence of siblings with DM1 as mentioned before[59].

MOLECULAR PATHOGENESIS

The molecular pathogenesis of DM1 is mediated by toxic RNA with disruption of splicing of pre-mRNA transcripts including CUG binding protein (CUG-BP) and Musclebind-like protein (MBNL) (Figure 3). The CTG DNA expansion produces transcription of mutant (CUG) RNA repeats which bind to splice-regulating proteins producing aggregation and formation of ribonuclear inclusions[74,75]. Deregulated alternative splicing of pre-mRNAs has been attributed to abnormal levels of splice-regulating proteins. MBNL and CUG-BP are the two main proteins indicated[76], and the RNA toxicity mediated process is commonly known as "spliceopathy". It is uncertain as to how many other RNA-binding proteins/splice-regulating proteins are involved in DM1 pathogenesis.

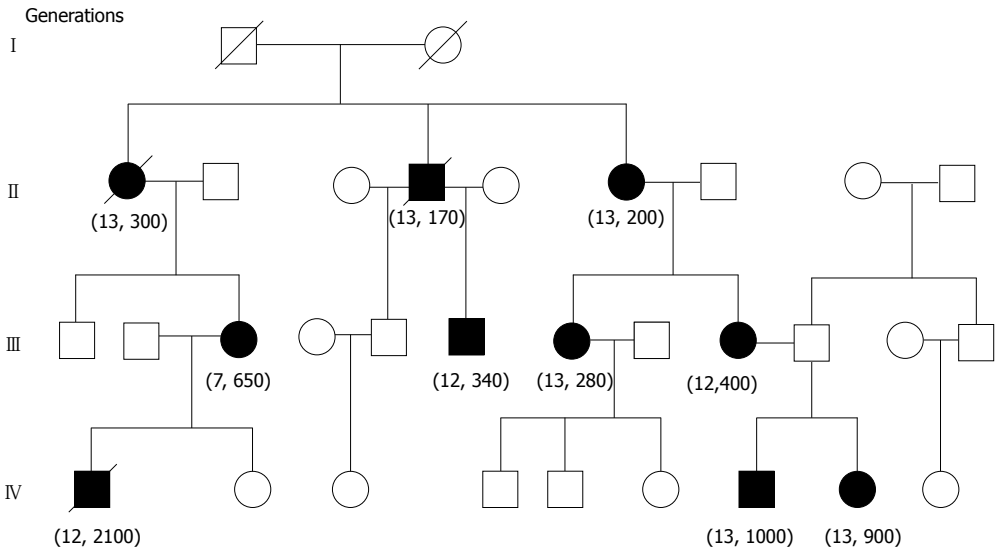

Figure 1 Genogram of family with myotonic dystrophy type 1 illustrating autosomal dominant inheritance. The numbers in brackets indicate the number of CTG triplet repeats in the 3' untranslated portion of the *DMPK* gene of affected individuals. Square = male; Circle = female; Black symbol = DM1 affected individuals; Strikethrough symbol = deceased.

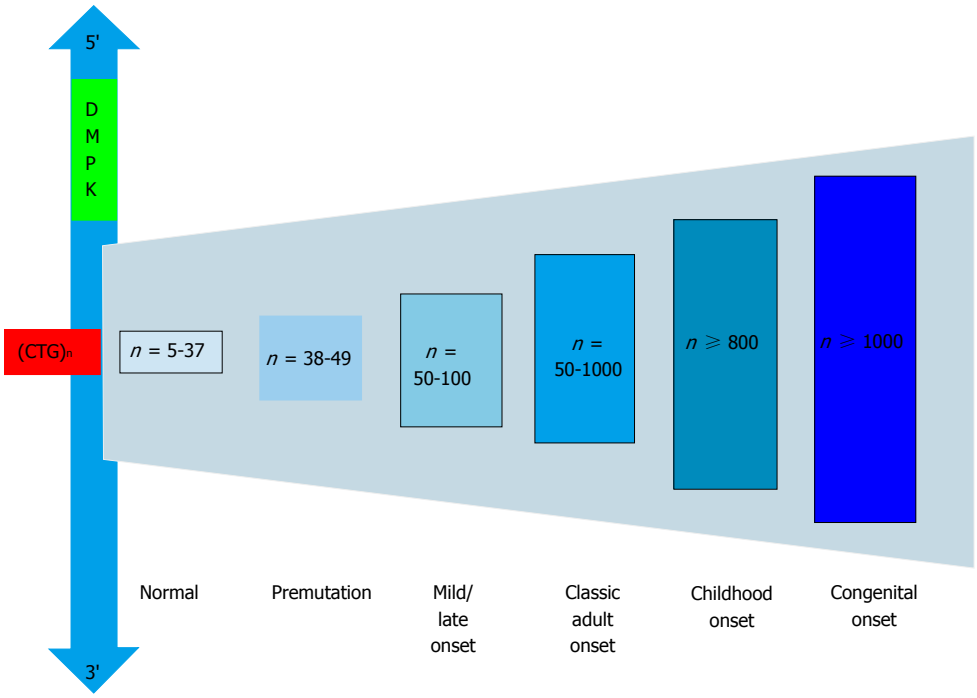

Figure 2 The genetic basis of myotonic dystrophy type 1. In DM1 there is an unstable CTG expansion at the DM1 locus, DMPK. Repeat size correlates with phenotype of DM1. DM1: Myotonic dystrophy type 1; DMPK: Dystrophia myotonica protein kinase.

MBNL 1 is most abundant in skeletal muscle, whilst MBNL 2 abnormalities have been identified in brain tissue[77,78]. In DM1, they are sequestered in the nucleus and unable to be utilised by the cell (RNA "loss of function"). CUG-BP, conversely is elevated in DM1 (RNA "gain of function") *via* increased activation and phosphorylation through several other protein mediators such as protein kinase C[79]. CUG-BP has been noted to bind to human cardiac troponin pre-mRNA[80], explaining cardiac abnormalities. Elevated CUB-BP also forms abnormally spliced insulin receptor (IR) pre-mRNA resulting in a switch to IR-A which is an abnormal isoform, thus explaining insulin resistance in adult DM1[81]. Furthermore, CUG-BP elevation has been noted to inhibit myoblast differentiation, form stress granules which reduce DNA repair, and result in loss of CIC-1 chloride channels through disruption of alternative splicing[75,82,83]. Other mechanisms identified include: overexpression of miRNA (non-coding RNA that modulates gene expression post-transcriptionally), increased myoblast cell decay, increased repeat-associated non-ATG translation (translation without an ATG

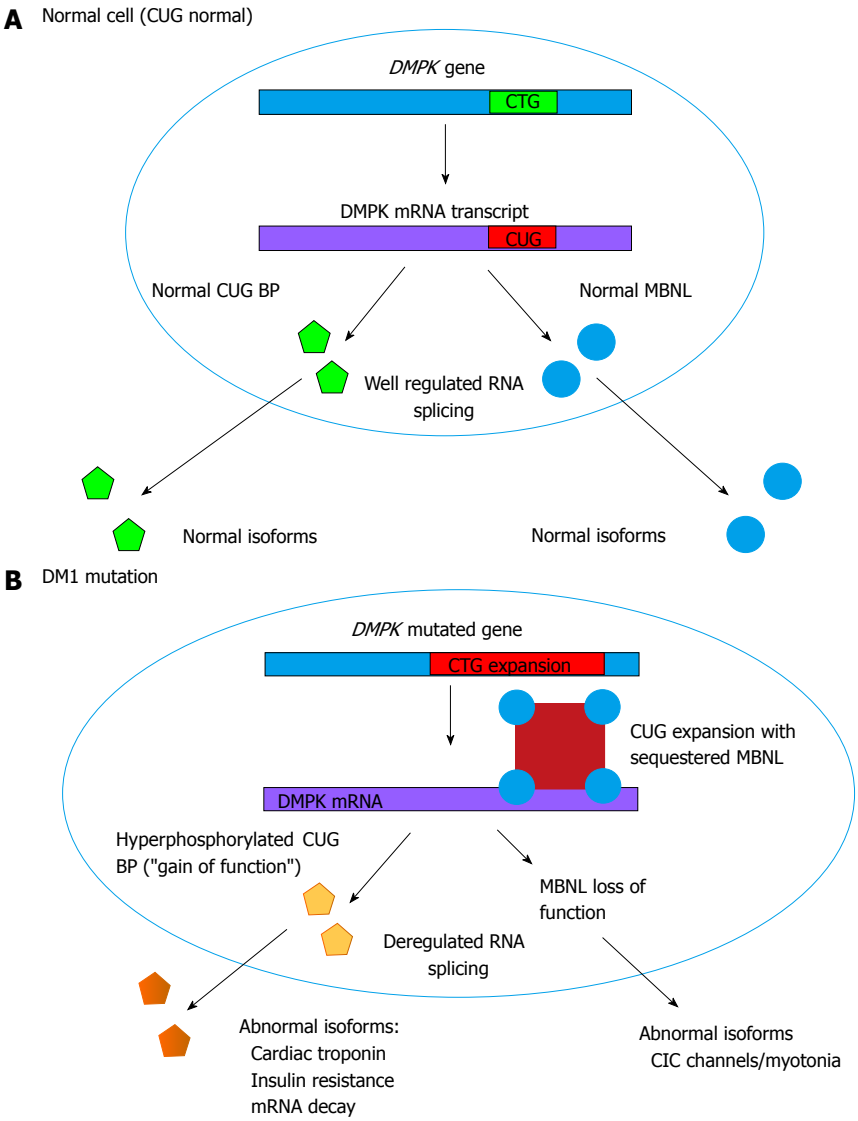

Figure 3 Pathogenic mechanisms in myotonic dystrophy type 1: (A) Normal RNA processing in cell with normal CTG repeats at the myotonic dystrophy type 1 locus; (B) Effects of expanded CTG repeat at the DM1 locus. A: Normal actions of MBNL and CUG BP in regulating alternative splicing within a cell; B: Pathogenic mechanisms involving MBNL and CUG BP, resulting in deregulated alternative splicing. While DM1 mutation is an untranslated CTG expansion, it is expressed at the RNA level and the CUG binds with two RNA binding proteins (CUGBP and MBNL) to disrupt RNA processing and splicing of other genes. For example, altered splicing of chloride channel and insulin receptor transcripts leads to myotonia and insulin resistance, respectively. DM1: Myotonic dystrophy type 1; MBNL: Musclebind-like protein; CUG BP: CUG binding protein.

start code resulting in abnormal protein aggregates), and there may even be a role for promoting oxidative stress[84-87].

NOVEL THERAPIES

There is exciting research in gene therapy that holds much promise for the treatment of myotonic dystrophy. Current management is supportive, but gene therapy may modify disease in the future. Most studies are RNA-based and focus on the RNA mediated pathways of disease (Figure 4). The most promising is antisense therapy. Strands of nucleic acid [called antisense oligonucleotides (AONs)] complimentary to target mutations are synthesised, in the hope that the target mutant sequence is silenced. Studies have effectively targeted exon 7a which codes for the defective chloride channel involved in DM1[88]. Others have effectively inhibited RNA sequestration by binding to CUG mRNA expansions[89] and sites for abnormal MBNL binding[90]. AONs have also been used to degrade the RNA expansions and the mutant DMPK allele through enzymatic actions[91-94]. Effective delivery of AONs remains the main problem with such therapies. Systemic delivery is ideal but AON levels have to be sufficiently abundant to penetrate muscle tissue and have an effect. This is greatly limited by the intact muscle surface membrane, and currently only mouse models have successfully enhanced AON uptake in muscle fibres with systemic administration[95]. Further, the effects of these novel drugs can be very specific and targets only myotonia in muscles, and thus not addressing the multi-

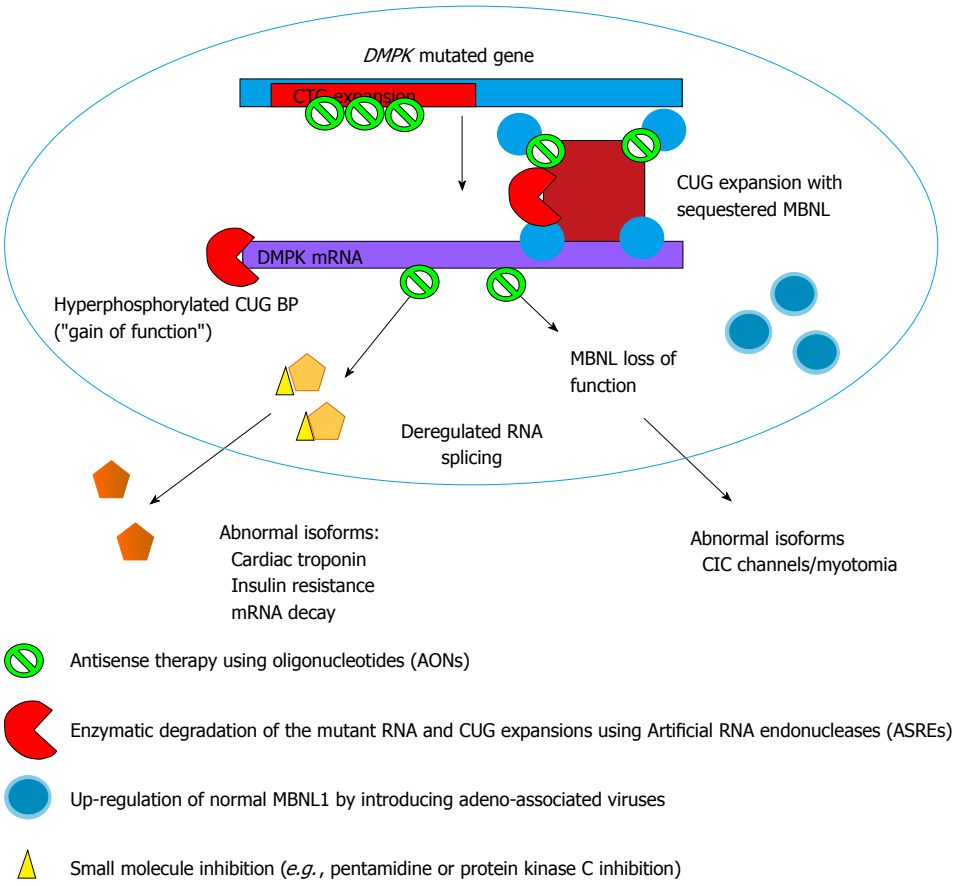

Figure 4 Novel therapies using RNA-based mechanisms to mediate RNA toxicity in a myotonic dystrophy type 1 cell. Promising trials have shown various means and targets of RNA mediated therapy with the aim of reversing or modifying "spliceopathy" and normalising cellular splice protein levels and actions. MBNL: Musclebind-like protein.

systemic problems.

MBNL-1 loss of function is well established as a feature of DM1 pathogenesis and studies have also explored means to up-regulate this splice mediator since it is abnormally sequestered in DM1. AONs have also been used for this but MBNL1 up-regulation has also been achieved in transgenic mice through the introduction of adeno-associated virus. This stimulates the overexpression of MBNL1, overcoming the sequestration and normalising MNBL function[96]. CUG-BP1 activity is increased in DM1, and down-regulation strategies by direct inhibition *via* small molecules like pentamidine or by inhibiting protein kinase C (involved in activating CUG-BP1) which potentially normalises CUG-BP1 levels[79,97]. There have also been studies looking specifically at reducing muscle weakness by introducing anabolic stimuli. Agents studied include testosterone, creatine[98-100], dehydroepiandrosterone[101] and recombinant insulin-like growth factor (IGF-1)[102]. Studies have yet to show improvements in muscle function in patients. Myostatin is known to down-regulate muscle growth and function, and inhibiting its production may be beneficial to DM1 patients; although no trial has been done specifically in DM1[95]. Future therapies will need to address the issues of efficient delivery and global effectiveness, especially in the CNS as this aspect is often most concerning for patients.

CONCLUSION

DM1 is a multisystem disease that predominantly affects muscle strength, cognition, respiratory, central nervous and gastrointestinal systems in neonates and children. Sleep disorders are often under recognised yet a significant morbidity. No effective disease modifying treatment is currently available and neonates and children with DM1 may experience severe physical and intellectual disability, which may be life limiting in congenital DM1. Novel therapies, which target the gene and the pathogenic mechanism of abnormal splicing, are emerging, but multidisciplinary management is currently supportive, incorporating regular surveillance and treatment of manifestations. It is important to develop a standard of care of congenital and childhood-onset patients to optimise outcomes.

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REVIEW

Caffeine therapy in preterm infants

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Abstract

Caffeine is the most commonly used medication for treatment of apnea of prematurity. Its effect has been well established in reducing the frequency of apnea, intermittent hypoxemia, and extubation failure in mechanically ventilated preterm infants. Evidence for additional short-term benefits on reducing the incidence of bronchopulmonary dysplasia and patent ductus arteriosus has also been suggested. Controversies exist among various neonatal intensive care units in terms of drug efficacy compared to other methylxanthines, dosage regimen, time of initiation, duration of therapy, drug safety and value of therapeutic drug monitoring. In the current review, we will summarize the available evidence for the best practice in using caffeine therapy in preterm infants.

Key words: Apnea; Caffeine; Preterm; Methylxanthines

Core tip: Caffeine is among the most commonly prescribed medications in neonatal intensive care units, it has now largely replaced other methylxanthines. Caffeine reduces the frequency of apnea, intermittent hypoxemia, facilitates extubation from mechanical ventilation, and reduces the incidence of bronchopulmonary and patent ductus arteriosus in preterm infants. There are controversies regarding the safety and efficacy of high-dose, early *vs* late administration, duration of therapy, value in older gestational age infants and the value of therapeutic drug monitoring.

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INTRODUCTION

Methylxanthines are among the most commonly used medications in preterm infants[1,2]. They have been used for the treatment of apnea of prematurity (AOP) over the past 40 years[3-8]. Caffeine has now largely replaced theophylline and aminophylline for treatment of AOP because of its wider therapeutic index and longer half-life that allows once daily administration[9]. In the pioneering study "Caffeine for Apnea of Prematurity (CAP) trial"[10], infants who received caffeine had a lower incidence

of bronchopulmonary (BPD) and severe retinopathy of prematurity (ROP). On follow-up at 18 mo, they had a lower incidence of cerebral palsy and cognitive delay. Approximately one-half of this neuroprotective effect was attributed to improved respiratory morbidity, including an approximate 1 wk reduction in the duration of mechanical ventilation[11]. By 5 years of age, the reduction in rates of cerebral palsy with caffeine treatment was no longer statistically significant, but the gross motor function improved and the incidence of developmental coordination disorder was reduced[12,13]. A recent study, demonstrated that early caffeine initiation is associated with reduced neonatal morbidity, including a decreased incidence of BPD and of patent ductus arteriosus (PDA) requiring treatment in very low-birth-weight (VLBW) infants. Many NICUs have changed their practice toward earlier initiation of caffeine therapy[14,15]. Cost-effectiveness analysis showed caffeine to be both cost-saving and beneficial[16]. Moreover, methylxanthines increase the success of extubation of preterm infants within 1 wk of age[17].

MECHANISM OF ACTION

The pharmacological effects of caffeine in AOP include: (1) stimulation of the respiratory center in the medulla; (2) increased sensitivity to carbon dioxide; (3) increased skeletal muscle tone; (4) enhanced diaphragmatic contractility; (5) increased minute ventilation; (6) increased metabolic rate; and (7) increased oxygen consumption[18-20]. Caffeine also stimulates the central nervous and cardiovascular systems, enhances catecholamine secretion, has a diuretic effect, and alters glucose homeostasis[21].

Caffeine acts as a selective adenosine antagonist at the A2a receptors and a non-selective adenosine antagonist at A1 receptor[22,23]. Through this action it modulates many neurotransmitters, such as noradrenaline, dopamine, serotonin, acetylcholine, glutamine, and gamma-aminobutyric acid[24]. It also increases cyclic adenosine 3',5' monophosphate and cyclic guanosine monophosphate leading to bronchodilatation[9,22,25]. Moreover, caffeine enhances peripheral chemoreceptors activity, thus it can terminate apnea and initiate normal breathing[26]. Caffeine may also have an anti-inflammatory action in the immature lung[27]. The benefits of caffeine therapy on respiratory functions increase the success of early nasal-continuous positive airway pressure (CPAP) therapy, facilitate earlier weaning from mechanical ventilation, and reduce ventilator-induced lung injury. This is particularly important in the early neonatal period, when AOP is prevalent and early nasal-CPAP therapy may not be successful in all infants[28-31].

PHARMACOKINETICS

The route of administration of caffeine does not affect its pharmacokinetics as there is almost complete bioavailability after its administration orally or intravenously. Caffeine is absorbed rapidly from the gastrointestinal tract with minimal-to-no first pass metabolism, and its peak plasma concentrations frequently occur in less than one h[20,32,33].

Caffeine is hydrophobic and distributes rapidly without tissue accumulation. It is rapidly distributed into the brain, and in preterm infants the levels of caffeine in the cerebro-spinal fluid approximate the plasma levels. In infants the mean volume of distribution is 0.8-0.9 L/kg compared to 0.6 L/kg in adults[33].

Biotransformation of caffeine occurs in the liver mainly by microsomal cytochrome P450 mono-oxygenases (CYP1A2) and partially by xanthine oxidase. The predominant process of caffeine metabolism in the preterm infant is N7-demethylation, which matures at about the age of 4 mo[31]. The demethylation process is postnatal age dependent, regardless of gestational age or birth weight[31,34-36]. There is a higher rate of caffeine metabolism in female than male neonates[31].

The metabolism of caffeine in the preterm infants is limited by immaturity of the hepatic enzymes. The plasma half-life of caffeine remains prolonged for as long as 38 wk gestation and reaches adult levels at the age of 3 to 4.5 mo[34,37]. Furthermore, the caffeine half-life may be prolonged further in exclusively breastfed infants and infants with cholestatic jaundice[38]. Interconversion between caffeine and theophylline has been reported with a greater rate of theophylline converting to caffeine than caffeine converting to theophylline. Approximately 3%-10% of caffeine converts to theophylline, whereas up to 50% of theophylline converts to caffeine[33,39,40].

In the first weeks of life, caffeine is eliminated mainly by renal excretion[38]. Caffeine elimination is slower in the premature and term neonate, compared with older children and adults, because of immaturity of renal functions. Several factors influence caffeine clearance in neonates including gestational age, post-conceptional age and parenteral nutrition; thus preterm infants receiving parenteral nutrition, may need closer monitoring of plasma caffeine concentrations[38,41]. Renal clearance of caffeine differs between preterm and full-term neonates due to lower glomerular filtration rates (GFR) in preterm infants[36]. The GFR increases rapidly during the first 2 wk of life and then rises steadily until 8-12 mo of age, when adult values are reached[42]. Theophylline has a serum half-life ranging from 24.7 to 36.5 h, and an estimated clearance from 0.02 to 0.05 L/kg per hour in premature neonates, compared with healthy adults, who have an estimated elimination half-life of 6.3 h[43]. On the other hand, caffeine has a longer serum half-life of 101 h in neonates[44], whereas its half-life ranges from 3 to 6 h in adults[43]. Differences in the pharmacokinetics of caffeine and theophylline are shown in Table 1.

CAFFEINE *VS* THEOPHYLLINE

The comparative effectiveness of caffeine *vs* theophylline

Table 1 Pharmacokinetics of caffeine compared to theophylline

	Caffeine	Theophylline
Mechanism of action:		
CNS stimulation	More active	Less active
Cardiac stimulation	Less active	More active
Diuresis	Less active	More active
Loading dose	20 to 40 mg/kg per dose Ⅳ/PO	4 to 8 mg/kg per dose Ⅳ
Maintenance dose	5 to 8 mg/kg per dose once daily Ⅳ/PO	1.5 to 3 mg/kg per dose every 8 to 12 h Ⅳ
Plasma half-life (h)	40 to 230 (mean, 103)	12 to 64 (mean, 30)
Therapeutic level (mg/L)	5 to 25	7 to 12
Toxic level (mg/L)	> 40 to 50	> 20
Adverse effects:		
Cardiovascular	Tachycardia, dysrhythmia	Tachycardia, dysrhythmia
Gastrointestinal	Feeding intolerance, GER	Feeding intolerance, GER
CNS	Jitteriness, irritability, seizures	Jitteriness, irritability, seizures, decreased CBF
Signs of toxicity	Tachycardia, cardiac failure, pulmonary edema, hypertonia, sweating, metabolic disturbances	Tachycardia, agitation, hypokalemia, diuresis, gastric bleeding, seizure
Metabolism	Excreted unchanged or N-demethylation *via* CYP P450 (CYP1A2) liver-methyltransferase pathway	Excreted unchanged or undergoes 8-hydroxylation *via* CYP1A2 and CYP2E1
Inter-conversion	3% to 8% converted to theophylline *via* CYP1A2	25% converted to caffeine *via* methylation
Routine blood level	Not required	Required
Elimination	86% unchanged in urine	50% unchanged in urine
CSF level	Similar to plasma concentrations	Crosses into the CSF
Clearance (L/kg per hour)[9,43]	0.002 to 0.017	0.02 to 0.05

CNS: Central nervous system; CBF: Cerebral blood flow; CSF: Cerebrospinal fluid; GER: Gastroesophageal reflux; GIT: Gastrointestinal tract.

regarding improving respiratory function has been evaluated by several small studies conducted over the past 40 years[45-48]. A meta-analysis of previous trials revealed that caffeine is as effective as theophylline on both apnea/bradycardia with some therapeutic advantages of caffeine over theophylline such as, better enteral absorption, higher therapeutic ratio, and longer half-life as well as less adverse effects such as tachycardia and feeding intolerance[49]. Moreover, caffeine has less plasma concentration fluctuations, and greater central nervous system penetration without producing fluctuations in cerebral blood flow[20]. Furthermore, theophylline therapy has been associated with seizures and hypokalemia in the neonatal population[50]. All the aforementioned benefits of caffeine make it the drug of choice in the treatment of AOP.

However, the results of the above mentioned meta-analysis[49] should be interpreted with caution due to limitations, including small sample size of the included studies; variations in the gestational age, birth weight and clinical status of the infants enrolled in the studies; and absence of data regarding drugs safety and their effects on neurodevelopmental term outcomes. Larger randomized controlled trials (RCTs) enrolling lower birth weight and gestational age infants are highly recommended to demonstrate the effectiveness and safety of varying doses of caffeine compared to theophylline with respect to important clinical outcomes such as safety, growth and long-term effects on neurodevelopmental outcome.

DOSAGE

The current loading and maintenance dosage of caffeine, which have been approved by the Food and Drug Administration (FDA) for treatment of AOP is 20 mg/kg (equivalent to 10 mg/kg of caffeine base) and 10 mg/kg per dose (equivalent to 5 mg/kg caffeine base) once daily, respectively[20,51]. The goal is to achieve a therapeutic blood level of 5 to 25 mg/L of caffeine in preterm infants less than 32 wk post-menstrual age (PMA). However, higher loading and maintenance doses of caffeine have been evaluated in various settings of treatment for AOP and to facilitate of extubation from mechanical ventilation (Table 2). In the CAP trial, Schmidt *et al*[10] used a loading dose of 20 mg/kg and a maintenance dose of 5 to 10 mg/kg per dose once daily of caffeine citrate for treatment of apnea in preterm infants. Prior to the CAP trial, a loading dose of 50 mg/kg caffeine citrate (25 mg/kg caffeine base) was shown to be more effective in reducing apneic episodes within 8 h than a loading dose of 25 mg/kg in preterm infants[48]. Furthermore, a daily maintenance dose of 30 mg/kg caffeine citrate was reported to be administered safely in preterm infants[52].

Steer *et al*[53] found that a high dose regimen of 20 mg/kg caffeine citrate, given 24 h before a planned extubation in preterm infants, reduced the rate of extubation failure compared to a low dose regimen of 5 mg/kg caffeine citrate with no effect on infant mortality, major neonatal morbidity, death, or severe disability. Shah and Wai[54] compared two dosing regimens of caffeine (loading dose of 20 mg/kg over 30 min and maintenance dose of 5 mg/kg per day *vs* loading dose of 10 mg/kg over 30 min and maintenance dose of 2.5 mg/kg per day) in preterm infants less than 34 wk gestation and found that the higher dose caffeine was associated with lower frequency of shallow breathing,

Table 2 Recommended caffeine doses

Trial	Design	Population	Intervention	Outcomes	Main results
Scanlon *et al*[48] United Kingdom	Prospective, randomized, controlled trial	44 preterm infants less than 31 wk gestation	High (loading 25 mg/kg and maintenance 6 mg/kg per day) *vs* low (loading 12.5 mg/kg and maintenance 3 mg/kg per day) caffeine citrate given 24 h prior to extubation	Frequency of apnea	High dose caffeine significantly decreased the frequency of apnea
Steer *et al*[52] Australia	Prospective, randomized, blinded, controlled trial	127 preterm infants less than 32 wk gestation	Three dosing regimens of caffeine citrate (3, 15 and 30 mg/kg) for peri-extubation management of ventilated preterm infants	Successful extubation defined as staying off ventilation for 7 d post-extubation	No statistically significant difference in the incidence of successful extubation however, infants in the two higher dose groups had statistically significantly less documented apnea
Steer *et al*[53] Australia	Prospective, randomized, blinded, controlled trial	234 preterm infants less than 30 wk gestation on mechanical ventilation	High (loading 80 mg/kg and maintenance 20 mg/kg per day) *vs* low (loading 20 mg/kg and maintenance 5 mg/kg per day) caffeine citrate given 24 h prior to extubation	Primary: Successful extubation of mechanically ventilated infants Secondary: Frequency of apnea	High dose caffeine significantly increased the chance for successful extubation, decreased the frequency of apnea and shortened the duration of respiratory support
Shah *et al*[54] Singapore	Prospective, case control trial	Preterm infants less than 34 wk gestation	High (loading 20 mg/kg and maintenance 5 mg/kg per day) *vs* low (loading 10 mg/kg and maintenance 2.5 mg/kg per day) caffeine citrate	Primary: Frequency of apnea, desaturation, and shallow breathing Secondary: Side effect of caffeine, BPD, and ROP	High-dose caffeine significantly reduced episodes of apnea and shallow breathing without side effects
Gray *et al*[125] Australia	Prospective, randomized, blinded, controlled trial	287 preterm infants less than 30 wk gestation exhibit AOP or require mechanical ventilation	Loading dose of 40 mg/kg followed by two maintenance doses of either 20 or 5 mg/kg per day	Primary: Cognitive development at 1 yr of age on the Griffiths Mental Development Scales Secondary: Neonatal morbidity, death and disability, temperament at 1 yr and behavior at 2 yr of age	High maintenance dose was associated with borderline benefit in cognitive outcome without increasing morbidity, temperament or behavior disorders
Mohammed *et al*[55] Egypt	Prospective, randomized, blinded, controlled trial	120 preterm infants less than 32 wk gestation exhibit AOP or require mechanical ventilation	High (loading 40 mg/kg and maintenance 20 mg/kg per day) *vs* low (loading 20 mg/kg and maintenance 10 mg/kg per day) caffeine citrate	Primary: Successful extubation of mechanically ventilated infants Secondary: Frequency and documented days of apnea	High dose caffeine significantly increased the chance for successful extubation, decreased frequency of apnea

BPD: Bronchopulmonary; ROP: Retinopathy of prematurity; AOP: Apnea of prematurity.

apnea, bradycardia and cyanosis without significant increase in the rate of side effects. In a recent RCT, we have found that the use of high loading (20 mg/kg caffeine base) and maintenance (10 mg/kg caffeine base) doses of caffeine was associated with a decreased chance for extubation failure in mechanically ventilated preterm infants and decreased the frequency of apnea without significant side effects[55].

Clinical practice varies considerably between NICUs. Most of NICUs in the US do not exceed a loading dose of 20 mg/kg and a maintenance dose of 10 mg/kg per day of caffeine citrate. Some NICUs outside the US use, maintenance doses as high as 20 mg/kg per day[15]. Until further evidence exists from large, well-designed RCTs and meta-analyses we recommend using the FDA-approved doses of 20 mg/kg and 10 mg/kg per day of caffeine citrate as loading and maintenance doses, respectively.

TIMING OF CAFFEINE THERAPY

Methylxanthines have been used to treat apnea in preterm infants for more than 40 years[3,56]. Subsequent studies reported potential advantages for early therapy, which prompted physicians to initiate methylxanthines as a prophylactic therapy before the occurrence of apnea[7]. Moreover, the initial beneficial neurodevelopmental effect demonstrated in the CAP trial[10,11] re-promoted the use of prophylactic caffeine therapy among different NICUs. In a meta-analysis of two RCTs that included 104 preterm infants, prophylactic caffeine therapy did not decrease the frequency of apnea, bradycardia, or episodes of hypoxemia and did not shorten the duration of mechanical ventilation[57]. However, none of the trials included in this meta-analysis reported long-term outcomes for prophylactic methylxanthine therapy. In a retrospective analysis of a large database including over 29000 VLBW infants from Pediatrix Medical Group, Dobson *et al*[14] found that early initiation of caffeine therapy (within 3 d of life) was associated with a lower incidence of BPD, less treatment of PDA, and a shorter duration of mechanical ventilation.

A recent study[58] demonstrated that early initiation of caffeine therapy (within 2 h of age) in non-intubated preterm infants was not associated with a reduction in the need for intubation or vasopressors by 12 h of age. However, it was associated with improved hemodynamic status as measured by blood pressure and superior vena cava flow. Patel *et al*[59] in a retrospective cohort study including 140 preterm neonates have demonstrated that early caffeine therapy (initiated within 3 d of life) was associated with decreased incidence of the composite outcome of death or BPD adjusted odds ratio (AOR: 0.26, 95%CI: 0.09-0.70), PDA requiring treatment (AOR: 0.28, 95%CI: 0.10-0.73), and duration of mechanical ventilation.

In a large retrospective study that included data from 29 NICUs participating in the Canadian Neonatal Network and conducted over more than 5000 preterm infants less than 31 wk gestation, prophylactic (initiated within 2 d after birth) caffeine therapy was associated with decreased odds of a composite outcome of death or BPD (AOR: 0.81, 95%CI: 0.67-0.98) and PDA (AOR: 0.74, 95%CI: 0.62-0.89) with no difference in mortality (AOR: 0.98, 95%CI: 0.70-1.37), necrotizing enterocolitis (NEC) (AOR: 0.88, 95%CI: 0.65-1.20), severe ROP (AOR: 0.78, 95%CI: 0.56-1.10), or severe neurological injury (AOR: 0.80, 95%CI: 0.63-1.01)[60].

Most of the previous trials were either retrospective data analysis, which could be subject to selection bias, or prospective but not powered or designed to detect short and long-term benefits of prophylactic caffeine therapy. It was also unclear from previous data, whether these beneficial short and long-term effects of caffeine are attributed to a real effect of the drug or due to shortening the duration of mechanical ventilation. Given the uncertainty of the evidence, more RCTs are needed to evaluate the short and long-term benefits of prophylactic caffeine therapy in mechanically ventilated and non-ventilated preterm infants.

DURATION OF CAFFEINE THERAPY

There are no clinical trials to support decisions about when to discontinue caffeine therapy in preterm infants. However, because AOP is not common past 34 wk gestation, caffeine therapy should be continued until preterm infants are 34 to 36 wk corrected gestational age and free of any apnea episodes for at least 8 d[61]. Despite the existence of apnea and sudden infant death syndrome in preterm and late preterm infants after discharge from the NICU[62], continuation of caffeine therapy at home is not recommended.

In a recent prospective RCT, late discontinuation of caffeine therapy at 40 wk PMA significantly reduced the episodes of IH in preterm infants compared to standard discontinuation at 34-35 wk gestation[63]. Although previous animal and human studies have shown that IH is pro-inflammatory and may result in cardio-respiratory instability, ROP, and neurodevelopmental deficits[64-66]; the clinical relevance of late discontinuation of caffeine therapy beyond 35 wk gestation is yet to be established in further RCTs.

THERAPEUTIC EFFECTS

Apnea of prematurity

AOP is a developmental disorder caused by immaturity of the respiratory control mechanisms[67,68], and consequently exhibited a widely variable incidence according to gestational age and birth weight. It was estimated to occur in virtually all infants born at less than 28 wk gestation or less than 1000 g[69,70], 50% of infants born between 30-32 wk[71], as well as in 50% of infants born at 33-35 wk gestation[72]. In most infants, apneic episodes cease by term gestation[73], though apnea might persist beyond term in the most immature infants born less than 28 wk gestation[74].

In 2012, an updated Cochrane review[75] with an aggregate meta-analysis of five trials (two trials of caffeine) that included 192 preterm infants with apnea, revealed that infants treated with methylxanthine compared with those who received placebo had less apneic events relative risk (RR: 0.44, 95%CI: 0.32-0.60) and less need for intermittent positive pressure ventilation (RR: 0.34, 95%CI: 0.12-0.97). Analysis of the two trials evaluating caffeine use[76,77], also found significantly less treatment failure (RR: 0.46, 95%CI: 0.27-0.78). Although, the CAP trial[10] was included in the updated review, the data from this trial were not pooled with the other studies as it was not primarily designed to evaluate the efficacy of caffeine for alleviation of apnea-related symptoms. In the CAP trial[10], caffeine therapy was associated with younger PMA at last supplemental oxygen use compared to placebo. The earlier weaning from mechanical ventilation with caffeine ultimately

supports a decrease in the frequency of apnea[27].

Of particular interest, in a subsequent report of the CAP trial[10], the reduction of duration of mechanical ventilation was only evident in those who received caffeine in the first 3 d of life[78]. In response to this result, several retrospective analyses comparing early (within 3 d of life) *vs* late start of caffeine therapy were conducted and revealed that the early start of therapy was associated with less incidence of BPD, less treatment of PDA, and shorter duration of mechanical ventilation[14,59,60].

According to the evidence above, caffeine is considered the first-choice drug for treatment of AOP as a result of the better safety profile compared to theophylline, alongside its associated respiratory and neuroprotective benefits.

Prevention of extubation failure

The CAP trial had not directly reported extubation failure rates, but the caffeine group was associated with reduction in PMAs at last use of positive pressure ventilation, and endotracheal intubation[10]. A meta-analysis of six studies reported that prophylactic methylxanthine treatment in intubated preterm infants results in a significant reduction in failure of extubation within 1 wk (RR: 0.48, 95%CI: 0.32-0.71)[17]. Steer *et al*[52] conducted two randomized, double-blind clinical trials comparing different dosing regimens of caffeine commenced in the pre-extubation period. In the first trial, 127 infants born at less than 32 wk were enrolled and randomly assigned to 3 groups according to maintenance dosages of caffeine citrate (3, 15 and 30 mg/kg). Although there was no statistically significant difference in the primary outcome of the failure of extubation between groups, reported apnea episodes were significantly reduced in infants in the 2 higher dose groups. The second trial[53], compared a two dose regimens (20 mg/kg *vs* 5 mg/kg) in 120 preterm with gestational age less than 30 wk, the high-dose regimen was associated with a significant reduction in extubation failure (15% *vs* 29.8%; RR: 0.51, 95%CI: 0.31-0.85) number needed to treat (NNT: 7). The two groups did not differ in infant mortality, major neonatal morbidity, or severe disability at 12 mo corrected age. Furthermore, subgroup analysis based on gestational age revealed that infants born at less than 28 wk gained more respiratory benefit of a higher dose of caffeine as evidenced by a significant reduction of mechanical ventilation duration and more marked reduction of extubation failure rate (NNT: 3). In a recent pilot, randomized, double blinded study comparing two different dosing regimens of caffeine citrate (loading dose, 20 mg/kg; maintenance dose, 10 mg/kg *vs* loading dose, 40 mg/kg; maintenance dose, 20 mg/kg); the use of high, in comparison to low, dose caffeine was associated with a significant reduction of extubation failure among mechanically ventilated preterm infants and fewer apnea episodes[55].

The exact mechanisms of increased chances of successful extubation in association of caffeine are still unclear, however, caffeine may improve respiratory mechanics through mounting central respiratory drive[79,80], improving respiratory muscle strength[81], inducing diuresis and hence improving lung compliance[82].

Postoperative apnea

Preterm infants, who undergo general anesthesia for surgical procedures may exhibit postoperative apnea episodes. The risk of postoperative apneas is increased in babies who previously experienced apnea[83,84], younger PMA[84,85], BPD[84] and pre-operative anemia[86]. Henderson-Smart *et al*[87] conducted a meta-analysis of three trials that compared administration of caffeine during or immediately after induction of anesthesia, with placebo, as prophylaxis for postoperative apnea. Results revealed that caffeine use was associated with significant reduction of postoperative apnea and bradycardia (RR: 0.09, 95%CI: 0.02-0.34). Therefore, use of caffeine to prevent postoperative apnea in infants born prematurely is recommended; however, more studies are warranted to resolve if all preterm infants should receive caffeine adjunctive to general anesthesia or only those with one of the previously mentioned risk factors.

Bronchiolitis-related apnea

Infants with bronchiolitis may exhibit episodes of apnea, which may require assisted ventilation. Infants who were born prematurely and those less than two months old are more vulnerable to bronchiolitis-related apnea[88]. Two case reports involving a total of 3 infants, who were born preterm and presented with bronchiolitis-related apneas, showed improvement of apnea after aminophylline therapy[89,90]. Furthermore, two retrospective reviews showed that caffeine use in those infants may be associated with significant reduction of need for mechanical ventilation[91,92]. So an appropriately powered RCT evaluating efficacy and safety of caffeine as a treatment of bronchiolitis-related apnea is needed.

Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) is a common complication in preterm infants, which may be associated with significant mortality[93], alongside deleterious long-term pulmonary[94,95] and neurodevelopmental morbidities[96,97]. One of the major findings for the secondary short-term outcomes of the CAP trial is significant reduction of BPD incidence in infants who received caffeine (36%) *vs* (47%) in the placebo group (OR: 0.63, 95%CI: 0.52-0.76; $P < 0.001$). This decrement of BPD rates was attributed in part to a shorter duration (about 1 wk) of endotracheal intubation and positive pressure ventilation in the caffeine-treated patients compared with the controls[10]. Notably, the short-term respiratory benefits of caffeine were most significant when treatment was started in the first 3 d of life[78].

Recently, in a large multicenter cohort study using data of 62056 VLBW infants, the use of early caffeine therapy within the first three days of life was associated with a lower incidence of BPD compared with later use (23% *vs* 31%, OR: 1.23, 95%CI: 1.05-1.43)[14]. Another two retrospective reports revealed similar results[60,98]. A clinical trial is currently conducted by Bancalari to evaluate short-term respiratory benefits of early caffeine use commenced within the first five days of life in mechanically ventilated preterm infants born less than 31 wk of gestation (ClinicalTrials, gov, NCT01751724).

The pulmonary protective effects of caffeine in neonates may be, at least partly due to reduction of pulmonary inflammation[99], as evidenced by inhibition of proinflammatory cytokines in both *in vitro* and *in vivo* clinical studies[100-103]. In addition, accumulating evidence has established beneficial effects of caffeine on pulmonary mechanics. In animal models with respiratory distress syndrome, early caffeine therapy in combination with prophylactic surfactant was associated with reduced airway resistance, enhanced lung compliance, and improved ventilator efficiency index within the first 24 h after birth[29]. In agreement with this, human studies reported upgrading of pulmonary function parameters following caffeine administration as exhibited by improved minute ventilation[18], decreased total lung resistance[28], and increased respiratory muscle contractility[19,81].

Intermittent hypoxemia

Intermittent hypoxemia (IH) is defined as brief, repetitive episodes of decreased hemoglobin oxygen saturation from a normoxic baseline followed by reoxygenation and return to normoxia. IH occurs frequently in preterm infants, even until term-equivalent age and after cessation of any clinically apparent apnea-associated symptoms[63,104]. Severe and frequent episodes of decreased hemoglobin oxygen saturation in early infancy have been shown to increase the risk of later neurodevelopmental impairments[105,106]. Furthermore, Di Fiore *et al*[66] reported a significant association between IH and severity of ROP.

A recent prospective, multicenter RCT enrolled 105 infants, who were born less than 32 wk gestation and formerly treated with caffeine, were randomly assigned to either extended caffeine treatment compared to usual caffeine discontinuation. The results revealed significant reductions in IH at 35 and 36 wk PMA with prolonged caffeine treatment[63]. However, further studies are needed to evaluate the optimum dosing regimen of caffeine required to alleviate IH and long-term effects of extended use.

PDA

The post-hoc analysis of the CAP trial revealed that infants in the caffeine group were significantly less likely to require pharmacological treatment for PDA closure compared with infants in the control group (29% *vs* 38% adjusted OR: 0.67, 95%CI: 0.54-0.82). In addition, caffeine therapy was associated with reduced risk of surgical ligation of PDA (adjusted OR: 0.29, 95%CI: 0.2-0.43)[10]. Furthermore, evidence from retrospective studies found that early caffeine therapy within the first 3 d of age was associated with significant reduction of incidence of PDA requiring treatment compared with later initiation of therapy[14,59,61].

The beneficial effects of caffeine on PDA may be attributed to favorable hemodynamic changes, including increase in cardiac index, stroke volume, and heart rate, alongside its diuretic and prostaglandin antagonistic properties[107-109]. Also, caffeine use was reported to be associated with increased blood pressure with no significant changes of systemic vascular resistance[107].

Neuroprotective effects

Animal studies found that adenosine A1 receptors activation contributed to hypoxia-induced periventricular white matter injury[110-112]. In agreement with this, caffeine administration in hypoxia-exposed neonatal pups was associated with enhanced myelination and reduced ventriculomegaly[110,111,113]. Moreover, caffeine potentiates neural plasticity at the level of N-methyl-D-aspartate receptors with documented altered morphology of neural synapses and increased size of dendritic spines[114,115]. However, other animal studies raised concerns about long-term consequences of exposing the growing brain to caffeine. Silva *et al*[116] reported that maternal caffeine consumption in rodents during pregnancy and lactation may have adverse effects on the neural development and adult behavior of their offspring. Also, postnatal caffeine treatment of neonatal mice was associated with altered astrocytogenesis[117].

Several studies evaluated short-term neurological effects of caffeine use in preterm infants. Two observational studies reported enhanced cerebral cortical activity in the brains of preterm infants treated with caffeine[118,119]. Also, caffeine-treated preterm infants exhibited improved measures of auditory processing[120]. Studies assessing the effect of caffeine on sleep organization in preterm infants exhibited contradictory results[26,121,122]. However, in a recently published study, evaluation of sleep architecture of 201 children aged 5-12 years who were previously enrolled in the CAP trial revealed no long-term effects on sleep duration or sleep apnea during childhood[123].

The CAP trial[10] found a higher patient survival rate without neurodevelopmental disability (cognitive delay, cerebral palsy, severe hearing loss or bilateral blindness) at a corrected age of 18 to 21 mo in infants within the caffeine group compared with those in the placebo group (59.8% *vs* 53.8%; adjusted OR: 0.77, 95%CI: 0.64-0.93, P = 0.008). Of note, caffeine use nearly halved the rate of cerebral palsy[11]. Subsequent follow-up of 1640 of infants enrolled in the CAP trial, at the age of 5 years, demonstrated no significant difference between the two groups in the combined outcome of death or severe neurodevelopmental impairment (78.9% *vs* 75.2% adjusted OR: 0.82, 95%CI: 0.65-1.03)[78].

Although, by 5 years of age, there was no significant difference in rates of cerebral palsy between both groups, there was a significant reduction of the incidence of developmental coordination disorder in the caffeine treated group (11.3% *vs* 15.2% adjusted OR: 0.70, 95%CI: 0.51-0.95)[13]. The authors attributed the improvements in motor function to improved cerebral white matter micro-structural development as demonstrated in magnetic resonance imaging (MRI) done at term equivalent age[124].

Gray *et al*[125] randomized 287 infants to receive one of two maintenance-dose regimens of caffeine citrate (20 *vs* 5 mg/kg per day). The results of their trial revealed no significant difference in adverse outcomes related to temperament and behavior at 1 and 2 years of age. In addition, infants in the higher-dose group exhibited a trend towards higher cognitive scores at 1 year of age.

Cerebral blood flow

Methylxanthines are non-specific inhibitors of A1 and A2a adenosine receptors, therefore, attenuates adenosine induced vasodilation that can potentially impair cerebral blood flow. Such effect has been reported in adults[126]. Hoecker *et al*[127,128] found that caffeine citrate administration at a loading dose of 50 mg/kg in preterm infants; either as a single or divided doses; was associated with significant reduction of cerebral blood flow. Another trial revealed a significant reduction in the cerebral oxygenation, and cerebral blood flow velocities 1 h after administration of 20 mg/kg loading dose of caffeine citrate with partial recovery at 4 h[129]. However, there were no documented changes of cerebral hemodynamics in preterm infants after the administration of the maintenance dose of caffeine citrate (5 mg/kg once a day)[130].

ROP

In the CAP trial, ROP detection rates did not differ significantly between both groups[10], however fewer infants in the caffeine group exhibited severe ROP compared to the control group (5.1% *vs* 7.9%; adjusted OR: 0.61, 95%CI: 0.42-0.89)[11]. The authors attributed that to the shorter duration of positive airway pressure and supplemental oxygen in caffeine-treated patients. In addition, improvement of IH episodes associated with caffeine use may decrease the severity of ROP[63].

Growth

The CAP trial revealed that infants in the caffeine group gained less weight than those in the control group during the first 3 wk after randomization[10]. However, follow-up of infants at 18 to 21 m showed no long-term difference in weight gain among infants in both groups[11]. Moreover, Bauer *et al*[131] reported increased energy expenditure (2.1 to 3 kcal/kg per hour) and oxygen consumption (7 to 8.8 mL/kg per minute) in caffeine-treated preterm infants compared with baseline measurements. Also, caffeine use was associated with less weight gain during the four-week study period and infants receiving caffeine required a lower incubator temperature to maintain a normal body temperature[131]. In a recently published clinical trial comparing two dosing regimens of caffeine citrate in preterm infants (loading dose, 20 mg/kg; maintenance dose, 10 mg/kg *vs* loading dose, 40 mg/kg; maintenance dose, 20 mg/kg); we reported no significant difference in weight gain between both groups. In agreement with this, Steer *et al*[53] have conducted a study comparing maintenance caffeine doses of 5 and 20 mg/kg per day and found no difference in the overall weight gain between both groups, however infants who received higher dose required longer time to regain birth weight.

Renal

Caffeine exerts a diuretic effect through increasing creatinine clearance, as an indicator of GFR, within 12 h of administration[108]. Also, methylxanthines use was reported to be associated with increased urinary calcium excretion[132]. However, caffeine did not alter serum calcium, phosphorus, sodium, or potassium concentrations[9].

Gastrointestinal

AOP and gastroesophageal reflux (GER) are relatively common in preterm infants, however, there is no evidenced temporal relationship between both conditions[133,134]. Mehtylxanthines may aggravate reflux through delayed gastric emptying and decreasing tone of lower oesophageal sphincter[135,136], they also increase gastrin secretion[137]. Clinical trials did not find aggravation of GER symptoms in caffeine-treated preterm infants[138].

Caffeine citrate administration in preterm infants at a loading dose of 25 to 50 mg/kg were reported to be associated with a reduction of mesenteric blood flow velocities[119,127,128,139], whereas a single 20 mg/kg intravenous loading dose of caffeine citrate did not cause significant changes in superior mesenteric artery flow velocities. In the CAP trial, there were no significant differences in the rates of NEC between both groups[10]. In a recent RCT study, we reported no increment in the rates of NEC in preterm infants after receiving a loading dose of caffeine citrate of 20 mg/kg per day followed by maintenance doses of 10 mg/kg per day compared to standard-dose regimen[55].

Anti-inflammatory effect

The immunomodulatory effects of caffeine may be related to blocking of adenosine receptors located on the surface of immune cells and subsequent up-regulation of Toll-like receptors[140]. Chavez Valdez *et al*[103] had conducted an observational study to determine cytokine level changes in 26 caffeine-treated preterm infants. Results revealed that caffeine levels within the therapeutic range (10-20 mg/L) were associated with a decrease in interleukin-6, tumor necrosis factor-α (pro-inflammatory cytokines) levels, and an increase in interleukin-10 (anti-inflammatory cytokine) levels. However, caffeine levels outside the therapeutic range

were associated with a proinflammatory profile.

ADVERSE EFFECTS

Caffeine has various dose-related side effects on different systems. Accidental administration of high dose caffeine in preterm infants was associated with tachycardia, tachypnea, agitation, irritability, tremor, hypertonia, and tonic-clonic movements representative of seizure activity[141]. The CAP trial and its subsequent reports of outcomes did not reveal any significant short or long-term adverse effects of caffeine therapy in the NICU[10,11]. In the RCTs using high-dose caffeine therapy, the initial slow rate of growth[53] and clinically insignificant tachycardia[55] were the only reported side effects. Metabolic acidosis and hyperglycemia have been reported in acute caffeine toxicity and accidental overdose[141,142].

THERAPEUTIC DRUG MONITORING

Most published researches do not support routine therapeutic drug monitoring (TDM) when caffeine is given at standard doses, as the majority of neonates were found to have plasma concentrations within the recommended therapeutic range (5.5-23.7 mg/L)[51,143,144]. However, TDM may be necessary when higher doses are used or toxicities are suspected[143].

ECONOMIC IMPACT OF CAFFEINE THERAPY

A recent study evaluated the cost per survivor without neurodevelopmental impairment in patients enrolled in the CAP trial (n = 1869); caffeine was found to be a cost-saving therapy compared with the placebo. This effect is mainly caused by the reduced number of days on mechanical ventilation[16]. However, this study has some limitations which may affect the precision of these results such as the existence of retrospective analysis of cost-effectiveness data. In addition, certain resource utilization data were not evaluated adequately in the CAP trial such as costs of inter-hospital transport, post-discharge use of drugs, and other outpatient healthcare services. Moreover, consensus panels recommended that outcomes measured should be expressed in terms of quality-adjusted life-years rather than biological outcomes used in the CAP trial, such as the survival without neurodevelopmental impairment. Finally, they applied Canadian costs from a single center although the trial was an international multicenter trial involving 9 countries.

CONCLUSION

Caffeine is the preferred first-line of treatment of AOP as it has a wider therapeutic range and is associated with less adverse events compared to theophylline. Further RCTs are needed to assess the safety and efficacy of high-dose caffeine especially on long-term neurodevelopmental outcomes, early prophylactic *vs* late caffeine therapy, which gestational age candidate for prophylactic therapy, duration of caffeine therapy, and efficacy of caffeine therapy in infants older than 34 wk gestation.

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REVIEW

Current management of pediatric soft tissue sarcomas

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Abstract

Pediatric soft tissue sarcomas are a group of malignant neoplasms arising within embryonic mesenchymal tissues during the process of differentiation into muscle, fascia and fat. The tumors have a biphasic peak for age of incidence. Rhabdomyosarcoma (RMS) is diagnosed more frequently in younger children, whereas adult-type non-RMS soft tissue sarcoma is predominately observed in adolescents. The latter group comprises a variety of rare tumors for which diagnosis can be difficult and typically requires special studies, including immunohistochemistry and molecular genetic analysis. Current management for the majority of pediatric sarcomas is based on the data from large multi-institutional trials, which has led to great improvements in outcomes over recent decades. Although surgery remains the mainstay of treatment, the curative aim cannot be achieved without adjuvant treatment. Pre-treatment staging and risk classification are of prime importance in selecting an effective treatment protocol. Tumor resectability, the response to induction chemotherapy, and radiation generally determine the risk-group, and these factors are functions of tumor site, size and biology. Surgery provides the best choice of local control of small resectable tumors in a favorable site. Radiation therapy is added when surgery leaves residual disease or there is evidence of regional spread. Chemotherapy aims to reduce the risk of relapse and improve overall survival. In addition, upfront chemotherapy reduces the aggressiveness of the required surgery and helps preserve organ function in a number of cases. Long-term survival in low-risk sarcomas is feasible, and the intensity of treatment can be reduced. In high-risk sarcoma, current research is allowing more effective disease control.

Key words: Pediatric tumor; Rhabdomyosarcoma; Soft tissue sarcoma; Non-rhabdomyosarcoma pediatric soft tissue tumor

Core tip: The manuscript describes current management of pediatric soft tissue sarcomas, a large group of rare tumors in pediatric age group. The group has two main categories; rhabdomyosarcoma (RMS) and non-RMS pediatric soft tissue tumors. Treatment of these tumors is in multidisciplinary fashion comprising of surgery, chemotherapy and radiation therapy. Decision making in management protocol for each patient is based on

the risk determined by various clinical and pathological parameters. For cases with low-risk, surgical removal is usually adequate when adjuvant chemoradiation are proven helpful in cases with significant risk of recurrence. The overall survival in these tumors has become brighter in the recent decades.

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INTRODUCTION

Pediatric soft tissue sarcomas are part of a heterogeneous group of tumors originating from embryonic mesodermal tissues during the process of differentiation into various mesenchymal tissue components of the human body. These tumors constitute 6% to 8% of all cancers in children less than 15 years of age[1-5]. Age-standardized incidence rates in Western countries are slightly increased compared with Asian countries[5]. Of all soft tissue sarcomas in this age group, approximately 50% to 60% are rhabdomyosarcoma (RMS), whereas the remainder are non-RMS soft tissue sarcomas (NRSTS), a designation that includes a variety of rarer soft tissue tumors including fibrosarcomas, synovial sarcomas, the extraosseous Ewing's family of tumors, malignant peripheral nerve sheath tumors (MPNSTs) and inflammatory myofibroblastic tumors (IMT)[6,7]. According to the International Classification of Childhood Cancers, version 3, Kaposi sarcoma is also categorized as a NRSTS tumors[8]. Approximately two-thirds of RMSs are diagnosed before 6 years of age, and the incidence decreases with age[7,9]. In contrast, NRSTSs occur in older children, increasing in incidence throughout adolescent years[6]. In African countries wherein the human immunodeficiency virus is endemic, an exceptionally increased incidence of Kaposi sarcoma has been reported[2].

Although most soft tissue sarcomas occur sporadically, these lesions are associated with cancer predisposition syndrome in some patients, (*e.g.,* Li-Fraumeni syndrome, which is linked to p53 germline mutations). Neurofibrosarcomas typically develop in individuals affected with neurofibromatosis type 1, an autosomal dominant disorder caused by mutations in the neurofibromatosis 1 gene (*NF1*). Individuals harboring germline mutations of NF1 are also prone to the development of embryonal RMS[10]. At the somatic level, specific chromosomal translocations and an expression of chimeric transcription factors are molecular signatures in a number of pediatric sarcomas. In RMS, PAX-FOXO1 fusion is a characteristic of the unfavorable histology or alveolar RMS. Such specific molecular patterns help differentiate sarcoma subtypes in which accurate pathological diagnosis may be difficult at a histopathological level.

The outcomes of pediatric soft tissue sarcomas have improved significantly during the past 3 decades[11]. The prognosis of pediatric soft tissue sarcoma, particularly RMS in younger children, is far better than that for sarcomas in adults. With modern evidence-based medicine, a multidisciplinary therapeutic approach not only increases survival rates but also provides a better chance to preserve the affected organ, particularly in the extremities and genitourinary organs. This article reviews current management practices for pediatric soft tissue sarcomas, with an emphasis on RMS and some soft tissue tumors that are more commonly found in the pediatric age group.

CLINICAL PRESENTATION AND DIAGNOSIS OF PEDIATRIC SOFT TISSUE SARCOMA

As soft tissue sarcomas are derived from primitive mesenchymal cells during their development into various mature mesenchymal tissue types (including muscle, fascia and fat), these tumors can be located in any part of the human body. The most common sites of primary RMSs are the head and neck, the genitourinary system and the limbs. The classic presentation is a growing lump that may or may not affect the function of nearby organs. RMS in some organ systems may cause specific symptoms. For example, frequent urination can be an initial presentation of an RMS that arises within the urinary bladder. Obstructive jaundice is one manifestation of bile duct RMS. Multiple plexiform neurofibrosarcomas can be benign tumors that follow neurofibrosarcoma in an individual with neurofibromatosis. Localization of the tumor site and its relation to the surrounding organs is typically accomplished by an imaging study, preferably magnetic resonance imaging (MRI) and/or computerized tomography (CT)[12]. From a surgical standpoint, the location, proximity to vascular structures, and potential morbidity caused by surgical resection determine the "resectability" of a sarcoma. To date, no serum markers are available for the diagnosis of soft tissue sarcomas. Image-guided core needle biopsy typically, but not always, provides a definitive diagnosis[13]. During a biopsy, extra tissue can be collected for further studies, *i.e.,* electron microscopy and molecular diagnosis. Repeat biopsy using an open technique is performed when a histopathological diagnosis cannot be made upon examining a small strip of tissue obtained from a needle coring-out. Suspected lymph node metastasis should be confirmed by histopathology, particularly in sarcoma of the limbs and the paratesticular area.

Pre-treatment clinical staging aims to categorize the disease according to the tumor site, size, local invasion, regional lymph node involvement and distant metastasis. The metastatic work-up includes bone marrow aspiration/biopsy, bone scintigraphy, and axial imaging studies of the brain, lung and liver (CT or MRI).

Table 1 Intergroup rhabdomyosarcoma study pretreatment staging and clinical grouping classification

Stage	Sites	T[1]	Size[2]	N[3]	M[4]
1	Orbit, head and neck (excluding parameningeal), genitourinary tract (non-bladder, non-prostate), biliary tract	T1 or T2	a or b	N0 or N1 or Nx	M0
2	Bladder.Prostate, extremity, parameningeal, others (trunk, retroperitoneum, *etc.*)	T1 or T2	a	N0 or Nx	M0
3	Bladder.Prostate, extremity, parameningeal, others (trunk, retroperitoneum, *etc.*)	T1 or T2	a	N1	M0
			b	N0 or N1 or Nx	M0
4	Any sites	T1 or T2	a or b	N0 or N1	M1
Clinical group	Description				
Ⅰ	Localized disease, completely resected				
Ⅱ	Grossly resected tumor with evidence of regional spread				
	Ⅱ A: Grossly resected tumor with microscopic residual disease				
	Ⅱ B: Involved regional nodes completely resected with no microscopic residual disease				
	Ⅱ C: Involved regional nodes grossly resected with evidence of microscopic residual disease				
Ⅲ	Incomplete resection with gross residual disease after biopsy or after gross or major resection of the primary tumor				
Ⅳ	Distant metastatic disease present at diagnosis				

[1]T: Tumor; T1: Confined to the anatomic origin; T2: Extension and/or fixation to surrounding tissue; [2]Size, a: ≤ 5 cm; b: > 5 cm; [3]N: Regional nodes; N0: Regional nodes not clinically involved; Nx: Clinical status of regional nodes unknown; N1: Regional nodes clinically involved; [4]M: Metastasis; M0: No distant metastasis; M1: Distant metastasis present (includes positive cytology in pleural, peritoneal or cerebrospinal fluid).

Table 2 Risk group stratification for rhabdomyosarcoma according to the International Rhabdomyosarcoma Study

Risk group	Histology	Pretreatment stage	Clinical group
Low (subset 1)	Embryonal	1	Ⅰ, Ⅱ
		1	Ⅲ (orbit)
		2	Ⅰ, Ⅱ
Low (subset 2)		1	Ⅲ (non-orbit)
		3	Ⅰ, Ⅱ
Intermediate	Embryonal	2, 3	Ⅲ
	Alveolar	1, 2, 3	Ⅰ, Ⅱ, Ⅲ
High	Any	4	Ⅳ

A spinal tap for cerebrospinal fluid is indicated in cases of suspected parameningeal tumor. A recent systematic review suggested the potential benefit of a functional imaging study, such as positron emission tomography (PET-CT), for increasing the accuracy of pretreatment staging, particularly in the evaluation of nodal status and distant metastasis[14,15]. Sentinel lymph node biopsy using radio-tracer exhibits feasibility and good concordance with PET-CT results in pediatric soft tissue sarcomas[16,17].

MULTIDISCIPLINARY MANAGEMENT OF PEDIATRIC SOFT TISSUE SARCOMA

RMS

RMS is a malignant mesenchymal tumor originating from immature striated muscle. Approximately 40% of RMSs occur in the head and neck region, 20% occur at genitourinary sites, 20% in the extremities, and 20% in other locations[9,12] (Figure 1). On hematoxylin and eosin histology, the tumor is characterized by the presence of spindle-shaped or small round-cell rhabdomyofibroblasts with eosinophilic cytoplasm. Cross-striations can be observed in some cases with relatively high tumor differentiation. Immunohistochemical studies that support the diagnosis of RMS include actin, desmin, myoglobin, myogenin and Myo-D. Pediatric RMS cases are generally categorized into 2 types: embryonal RMS (80%) and alveolar RMS (15%-20%)[12]. The botryoid subtype is a variant of embryonal RMS commonly located in the genitourinary tract, vagina, and biliary and nasopharyngeal sites. The spindle cell subtype is another subtype of embryonal RMS found in paratesticular locations. Alveolar RMS is observed in older children and generally has a more unfavorable histology.

After the diagnosis is made, pre-treatment staging is performed according to a standard classification, such as the InterGroup Rhabdomyosarcoma Pretreatment Staging Classification (Table 1). The value of pretreatment staging involves determining disease prognosis. In addition to the stage, completeness of tumor removal defines the "clinical group" of RMS. Management plans for RMS can be divided into local control and systemic therapy and generally rely on risk categorization as determined by the Intergroup Rhabdomyosarcoma Studies (IRS) stage with the clinical group (Table 2). Surgery therefore has an integral role in the initial stages of decision-making on multimodality treatment in pediatric RMS.

Local control

Surgery has been the most effective method to eliminate pathology. Surgery should be conducted in a manner that maintains function and cosmesis. In primary surgery, the extent of the initial surgery is generally subject to the judgment of the surgical team. In principle, resectability means that a tumor and its tumor-free surrounding tissue can be removed without operative risk or unacceptable post-operative morbidity. In the cases in which an excisional biopsy is performed without awareness of an adequate surgical margin, re-excision of the tumor bed should be considered[18,19].

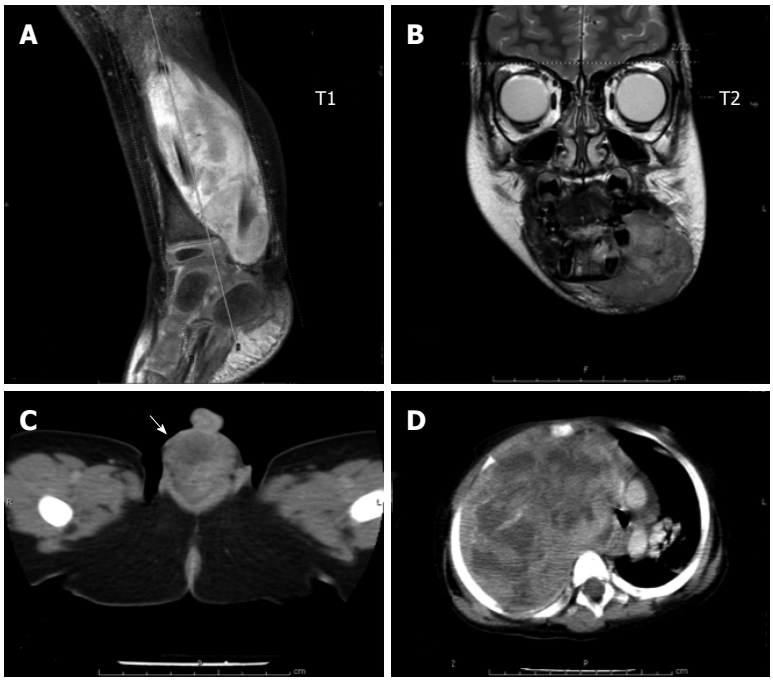

Figure 1 Radiographic images of common rhabdomyosarcoma. A: Extremity; B: Head and neck; C: Genitourinary (paratesticular); D: Axial (intraabdominal).

In general, factors determining resectability include anatomical characters, such as site, size and vital structure involvement. However, in cases in which primary definitive surgery is not likely to provide complete resection without significant morbidity, delayed primary resection after upfront chemotherapy should be considered with an aim for organ salvage without compromising the long-term survival outcome. When delayed primary resection after neoadjuvant treatment is planned, compliance should also be considered. Intractable symptoms from the tumor and psychosocial factors may impact therapeutic compliance. Symptom control surgery during induction therapy (*i.e.,* temporary urinary diversion in urinary bladder RMS) might be indicated[20]. Radical surgery is indicated in patients who are unable to tolerate intensive chemoradiation.

A recent multi-institutional data review demonstrated that approximately 90% of clinical group Ⅲ embryonal RMS patients experienced a volume reduction of 33% or greater after induction chemotherapy[21]. Although the effect of the chemotherapeutic response on event-free survival (EFS) remains unclear, the study found that cases with at least a partial response experienced significantly enhanced overall survival (OS), particularly in head and neck RMS[21]. These results were consistent with a recent report using functional imaging tool 2-fluoro-2-deoxy-d-glucose-positron emission topography from the Memorial Sloan Kettering Cancer Center suggesting that the response after induction chemotherapy significantly predicted both EFS and OS[22]. An earlier report from the Intergroup Rhabdomyosarcoma Study Ⅳ (IRS-Ⅳ) revealed an 81% response to chemotherapy in group Ⅲ RMS cases with no significant difference in the response rate between embryonal and alveolar RMS, and the size of the initial tumor had no influence on the response[23]. According to both studies, parameningeal RMS appeared to have a poorer response rate even when chemotherapy was administered with radiation[24]. Although the number of cases was lower, genitourinary tract sites (except bladder and prostate) exhibited better response rates[21]. The delayed primary resection strategy has reduced the extent of surgery in pelvic RMS. Pelvic exenteration, a historical standard in bladder and vaginal RMS, is rarely practiced today.

Second-look exploration aims to confirm the clinical/radiological response and to achieve oncologic resection when possible. Imaging evaluation may underestimate the degree of the response. According to IRS-Ⅲ data, 46% of patients who achieved partial remission were found to be in complete remission at surgical exploration, and an additional 28% could be converted to complete remission. In addition, 30% of patients who had clinically stable disease after induction chemotherapy exhibited pathological complete remission, and an additional 43% could be converted to complete remission[23]. To achieve oncologic resection, radical organ removal must be performed in some situations. In urinary bladder RMS that arises at the base of the bladder or prostate, a partial cystectomy is not sufficient given the high risk of local failure. Total cystectomy and urologic conduit is a surgical option that potentially leads to long-term, disease-free survival with an acceptable quality of life. Bladder-preserving surgery is reserved for cases with a good response to induction chemoradiation therapy. In addition, the tumor location must allow a 2- to 3-cm tumor-free margin, and at least two-thirds of the bladder must be retained[20,25]. In vaginal RMS, residual tumor after chemotherapy is an indication

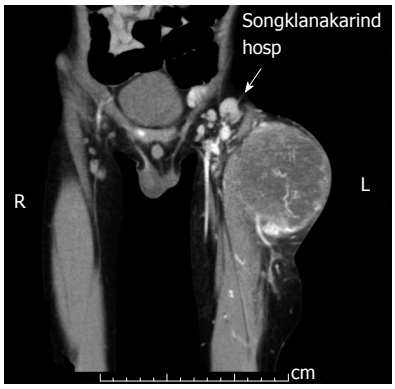

Figure 2 Inguinal lymph node enlargement in a case of extremity rhabdomyosarcoma.

for total hysterectomy with gonadal preservation[26]. Pancreaticoduodenectomy is the operation of choice in cases in which the RMS involves the distal common bile duct[27].

Lymph node management is of prime importance in pre-treatment staging and clinical grouping of RMS, both of which determine the risk category. Radical lymph node dissection does not impact outcome. Enlarged nodes detected clinically or by radiologic evidence should be excised for histopathological examination (Figure 2). Regardless of radiologic evidence, lymph node sampling is indicated in extremity RMS and for children older than 10 years with paratesticular tumor[9,11,28]. When an adjacent node is positive, more distant nodes should be searched for and biopsied. To reduce the morbidity caused by extensive lymph node sampling, the concept of sentinel lymph node sampling, which is the current standard in melanoma and breast cancer, has also been adapted for pediatric soft tissue sarcoma. Trials in pediatric sarcomas had relatively small numbers in each series[16,17,29]. Most studies used the lymphoscintigraphy technique and reported that the technique was feasible in pediatric sarcomas; however, specific data regarding identification rates and false negative rates in RMS remain inconclusive.

Radiation therapy is unnecessary for embryonal RMS in clinical group Ⅰ (completely resected) when it provides better failure-free survival in alveolar RMS. Radiation enhances local control in cases with residual disease after definitive surgery, positive locoregional lymph nodes and unresectable RMS after tumor biopsy. Radiation doses to microscopic residual tumors (total 36 Gy) are typically less than those for gross residual or primary unresectable tumors (50.4 Gy)[11]. Orbital tumors are an exception as their clinical group Ⅲ requires 45 Gy. Data from the German trial CWS91 indicated that hyperfractionated accelerated radiotherapy may reduce the total radiation dose in RMS (32 Gy in low-risk and 48 Gy in high-risk patients) without compromising treatment outcomes[30]. Alternative radiation therapy techniques, such as intensity modulated radiation therapy, brachytherapy, and proton beam therapy, are used in some centers with the aim of reducing locoregional side effects[31].

Systemic therapy

Chemotherapy is an essential component of the multimodality treatment of RMS. The standard regimen in non-metastatic RMS is a combination of vincristine, actinomycin-D and cyclophosphamide (VAC)[32]. Omitting cyclophosphamide from the regimen has been attempted in low-risk RMS cases to reduce the cumulative dose of cyclophosphamide (IRS-D9602 protocol). Although VA produced an excellent outcome in a subset of low-risk RMS cases, including group Ⅰ-Ⅱ, stage 1-2 and group Ⅲ orbital tumor (subset 1, Table 2), the data suggested that cyclophosphamide should be retained with vincristine and actinomycin-D in the other subset of low-risk RMS cases (subset 2: group Ⅰ-Ⅱ, stage 3 and group Ⅲ, stage Ⅰ except orbital tumor) because the failure-free survival was poorer than that of comparable patients in the IRS-Ⅳ study who received a triple drug regimen[33]. IRS-Ⅳ data also demonstrated that substitution of cyclophosphamide with ifosfamide (VAI) or substitution of actinomycin-D/cyclophosphamide with ifosfamide and etoposide did not improve the failure-free survival in non-metastatic RMS[34]. A subsequent study from the Children's Oncology Group (COG), directed toward a shorter duration of VA and dose reduction of cyclophosphamide (ARST0331) in low-risk RMS patients, was recently published. Although the study reported an increased incidence of local failure with use of the shorter therapy, the study recommended its use in low-risk RMS cases given the reduced toxicity[35]. For intermediate- and high-risk patients, successive COG trials have attempted to improve the survival outcome by incorporating novel agents, such as doxorubicin, ifosfamide and etoposide (VDC/IE), and irenotecan (VAC/VI), with the aim of reducing the cumulative cyclophosphamide dose[36]. Various molecular targeting drugs are being explored in high-risk RMS cases, including vascular endothelial growth factors (bevacizumab), mTOR (temsirolimus) and IGF-1R (temozolomide). A phase Ⅱ trial of temozolomide has demonstrated its safety and feasibility; however, the preliminary response rate was not impressive[37]. For metastatic RMS, another study found that the incorporation of VDC-IE or Ⅵ with VAC therapy resulted in improved outcomes in embryonal RMS[38].

Outcome of current multimodality management in RMS

Since the establishment of the International Rhabdomyosarcoma Study Group in 1972 (currently the Cooperative Soft Tissue Sarcoma Study Group), survival of pediatric RMS patients has been steadily improving. Before the era of multimodality treatment, surgery alone resulted in survival rates less than 20% (11). With the new available treatments, the five-year OS increased from 55% in IRS-Ⅰ to 63% in IRS-Ⅱ and to 71% in IRS-Ⅲ and IRS-Ⅳ. Data from IRS-Ⅱ to IRS-Ⅳ

Table 3 Risk stratification in nonrhabdomyosarcoma soft tissue sarcoma and treatment proposal according to the Children's Oncology Group (NCT00346164)

Risk group	Factors				Proposed treatment
	Grade	Size	Stage	Initial resectability	
Low	Low	Any	Nonmetastatic	Gross resection	Observation
	High	< 5 cm	Nonmetastatic	Without microscopic margins	Observation
	High	< 5 cm	Nonmetastatic	With microscopic margin	Adjuvant radiation therapy
Intermediate	High	> 5 cm	Nonmetastatic	Gross resection	Adjuvant chemotherapy and radiation therapy
	High	> 5 cm	Nonmetastatic	Unresected	Neoadjuvant chemoradiotherapy, surgery, adjuvant chemotherapy with or without radiation therapy
High	Low	Any	Metastatic	Gross resection	Observation
	High	Any	Metastatic	Gross resection	Adjuvant chemotherapy and radiation therapy
	High	Any	Metastatic	Unresected	Neoadjuvant chemoradiotherapy, surgery, adjuvant chemotherapy with or without radiation therapy

revealed an 88% 3-year failure-free survival in low risk embryonal RMS. Intermediate-risk embryonal RMS had a 4-year failure-free survival rate of approximately 68% to 78%; however, survival in high-risk patients remains poor at less than 25%[39].

NON-RMS SOFT TISSUE SARCOMAS

NRSTSs are a heterogeneous group of rare mesenchymal tumors that exhibit a wide variety of histopathologies and biologies. The majority of NRSTSs occur more frequently in adult patients, and the prognosis is generally poorer than for pediatric sarcomas. Given their heterogeneity, ambiguity in pathological diagnosis is common, and care should be taken when obtaining tissue samples[40]. A multidisciplinary conference before the initiation of treatment for any individual case allows the team to arrive at a consensus and understand the role of each discipline in the treatment process. Surgery has a primary role in the treatment of resectable NRSTSs, whereas adjuvant treatment relies on a Children's Oncology Group risk stratification guideline[41] (Table 3). Basically, radiation therapy is administered to patients whose resection margins are close to the tumor (except for very low-risk tumors). Chemotherapy provides a poorer response than pediatric RMS and is advocated in select types of NRSTS. Ifosfamide and doxorubicin are backbones recommended as post-operative adjuvant therapy for localized resectable STSs[42,43]. A recent systematic review found that autologous hematopoietic stem cell transplantation following high-dose chemotherapy in locally advanced or metastatic NRSTS did not result in better OS than standard-dose chemotherapy[44].

Extraosseous Ewing's sarcoma family of tumors

Extraosseous primitive neuroectodermal tumors, namely, Ewing's sarcoma and Adkin tumor of the chest wall, are grouped together as the Ewing's family of tumors because they share a chromosomal translocation, t(11;22)(q24;q12), leading to a chimeric fusion, EWSR1-FLI1[45]. Extraosseous Ewing's sarcoma presents predominately in the second decade of life. The tumor is comprises 15% to 20% of all Ewing's sarcomas[46,47]. The tumor can occur anywhere in the body but commonly presents on the extremities, chest and pelvis. Histologically, the tumor belongs to the small round blue cell group and demonstrates positive immunoreactivity to the surface glycoprotein CD99. Poor prognostic indicators include axial site tumors, particularly in the pelvic region; large tumor size; late stage; poor response to induction chemotherapy; advanced age; and high serum lactate dehydrogenase levels[46-49]. The definitive treatment for extraosseous EFSTs is surgical removal. Complete resection is the best option for cure, and the likelihood of achieving negative surgical margins is increased when induction chemotherapy is administered[50]. Although these tumors are relatively sensitive to radiation, radiation is reserved for cases with positive surgical margins or incompletely resected tumor because late effects of radiation, such as a second malignancy, are of concern. Post-operative chemotherapy aims to improve OS and reduce the likelihood of local recurrence. The therapeutic regimen in extraosseous EFST follows that used in either NRSTS or Ewing's sarcoma of the bone and typically comprises ifosfamide/etoposide with or without carboplatin (ICE) alternated with a combination of vincristine, doxorubicin and cyclophosphamide (VDC)[47]. The results from the EICESS-92 study and the successive trial Euro-Ewing-99-R1 from the European InterGroup Cooperative Ewing's Sarcoma Study concluded that ifosfamide can be substituted with cyclophosphamide in the consolidation phase in standard risk EFST (localized tumor with either good histological response after induction chemotherapy, small tumor resected at diagnosis, or receiving radiotherapy alone as a local treatment)[48,51]. A report from the French Society of Pediatric Oncology (SFOP-EW93) suggested that induction with cyclophosphamide and doxorubicin followed by histopathological response-based chemotherapy (VAC or VAC/VIE or IE + high dose busulfan/melphalan) provided superior outcomes to those of an ifosfamide-based regimen (VAI) for all cases[52]. Other studies reported a five-year OS of between 60% and 70% in non-metastatic extraosseous EFSTs[46,52,53], whereas another study reported that

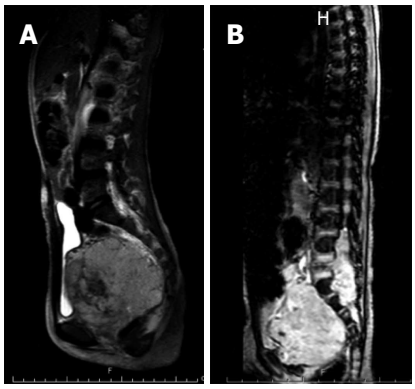

Figure 3 Magnetic resonance imaging T2: Providing a comparison between growth patterns. A: Pelvic RMS; B: MPNST. Although RMS is a locally advanced tumor, a thin surgical plane typically exists between the tumor and the adjacent bone when the MPNST involves the dural space and nerve root. RMS: Rhabdomyosarcoma; MPNST: Malignant peripheral nerve sheath tumor.

metastatic EFST exhibited a 5-year OS of approximately 25%[53].

MPNST

MPNSTs, malignant schwannomas, neurofibrosarcomas and neurogenic sarcomas account for approximately 6% of all NRSTSs[54], and approximately half of these cases are associated with neurofibromatosis type 1 syndrome[55]. An individual with the NF1 mutation has a cumulative 8% to 13% lifetime risk of developing MPNST[56]. MPNST develops within benign neurofibromas in NF1 patients[57]. In the pediatric age group, the incidence increases with age, with more than 80% of cases diagnosed at the age 10 years or older[58]. Among pediatric NRSTSs, the tumor has the worst prognosis, with a 5-year OS of 43% to 59%[59]. Complete surgical removal is the only chance for cure. Unfortunately, a number of MPNSTs involve the nerve root, preventing complete removal (Figure 3). Radiation therapy is recommended in cases with residual tumor after surgery; however, no evidence indicates that this improves survival[60]. Studies have reported that adjuvant chemotherapy exhibits only minimal benefit[58,61,62].

Synovial sarcoma

Synovial sarcoma (SS) is an aggressive spindle cell tumor that accounts for approximately 10% of all STSs[63]. Although the tumor is principally located in the lower extremities, primary SS at other sites (including the head and neck, hands, retroperitoneum, digestive system and mediastinum) have been reported[64-66]. Histologically, SS contains spindle cells with a varying degree of epithelial differentiation[67]. On immunohistochemical study, SS is marked with both mesenchymal and epithelial markers. The cytogenetic signature of SS is a reciprocal translocation t(X;18) (p11.2;q11.2) that leads to a chimeric fusion between SS18 from chromosome 18 and one of the SSXs (SSX1, SSX2 or SSX4) from chromosome X. The SS18-SSX2 fusion protein activates canonical Wnt/beta-catenin signaling, which suggests a future therapeutic target in a subset of SS[68,69]. The current management of SS is based on risk categorization, and risk determinants include the clinical group (as in RMS), size (5 cm) and sites[70]. Low-risk tumors include group I SS and are less than 5 cm in size. Axial site tumors (head and neck, trunk, lungs and pleura) are considered high risk[71]. According to the European Pediatric Soft Tissue Sarcoma Study Group Trial (EpSSG NRSTS2005), low-risk SSs are best treated with surgery alone, with 91.7% experiencing 3-year EFS and 100% OS[71]. In that study, the surgical strategy recommended in most low-risk cases was conservative surgery. Survival in intermediate-risk SSs (group Ⅰ, size > 5 cm and group Ⅱ) after surgery followed by chemotherapy (ifosfamide and doxorubicin) with or without radiation is comparable with that of the low-risk group. Chemotherapy is the mainstay treatment in high-risk (group Ⅲ or axial SS) patients. The chemotherapy response rate in group Ⅲ SS was 55%, and OS was 74%[71].

Congenital infantile fibrosarcoma

Unlike tumors in the adult-type NRSTS group that are typically found in teenagers and adolescents, congenital infantile fibrosarcoma (CIF) can be noted during the first month of life and is often misdiagnosed as a hemangioma or vascular malformation. A rapid growth rate and ulceration are clinical clues necessitating a biopsy[72]. Histologically, CIF is densely packed with spindle cells arranged in bundles and fascicles. Tumor cells typically exhibit positive immunoreactivity with the mesenchymal marker vimentin but are negative for desmin and S100 protein. A chromosomal translocation t(12;15)(p13;q25), which leads to a fusion ETV6-NTRK3, has been reported. The tumor is locally aggressive, and distant metastasis is rarely reported. Destruction of adjacent bony structures can be observed (Figure 4). Surgical removal of the lesion is the recommended primary treatment. Adjuvant treatment is generally unnecessary except when the mass is very large and involves vital structures. In such instances, neoadjuvant chemotherapy may help down-size the tumor[73,74]. Prognostic factors include the site and extent of the lesion at the diagnosis. Extremity IF has a more favorable outcome than do axial tumors. In addition, pediatric CIF has a better outcome than adult fibrosarcoma. The five-year OS is approximately 90%[75,76].

Desmoplastic small round cell tumors

Desmoplastic small round cell tumors (DSRCT) is a rare, highly aggressive mesenchymal tumor originating on the peritoneal surface typically in an adolescent[77]. The tumor can also be found at other sites, such as the head and neck, pleura, kidneys, ovaries and testes[78-81] and was first described in 1989 in a pathological case report by Gerald and Rosai[82]. Histologically, DSRCT exhibits

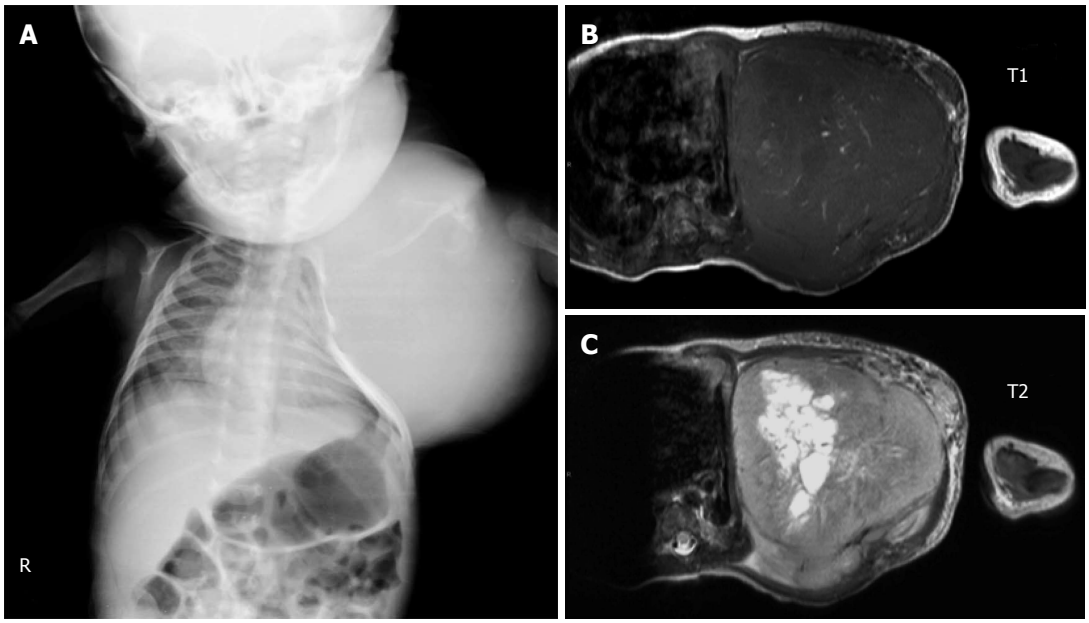

Figure 4 Plain radiographic and magnetic resonance images demonstrating deformity of the left chest wall caused by a congenital infantile sarcoma (A, B and C).

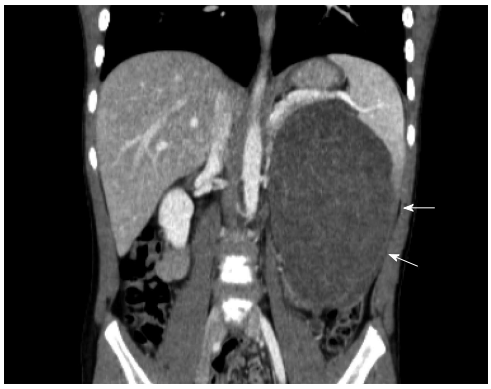

Figure 5 Computerized tomography image of a case of splenic inflammatory myofibroblastic tumor.

small round cells arranged in nests within abundant desmoplastic stroma[77]. Central necrosis and trabecular or indian fire arrangements are also observed[83]. The tumor expresses polyphenotypic differentiation with co-expression of epithelial, mesenchymal and neuronal markers[77]. In addition, nuclear staining of the WT1 protein has been reported[83]. The tumor is highly aggressive, and approximately 60% of patients die of the disease within 2 years[84]. Complete resection is not possible in the majority of cases. Surgical debulking of the primary tumor followed by radiation therapy is recommended[85,86]. The tumor appears to respond to multi-agent chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, ifosfamide and etoposide; however, recurrent disease is common[85,87]. The use of alternative therapies, including molecular targeting therapy and intraperitoneal infusion of chemotherapy, is reported infrequently[88-90]. In one study, the 3-year OS was reported at 44%, with a 5-year OS of 15%[85].

IMT

IMT (IMT, also known as inflammatory pseudotumor or plasma cell granuloma) is a rare benign tumor with recurrence potential that most often occurs in children and young adults. The lung is the most common site of IMT. Other reported sites include the urinary bladder, intestine and mesentery, spleen, liver and kidney[91-94]. The etiology of IMT may include certain infections, such as Epstein Barr virus. Whether the tumor is a true neoplasm or an inflammatory response remains controversial. However, recurrence after surgery is common and malignant transformation has been reported[95,96]. Studies have demonstrated that a number of IMT involve fusion between the *AKT* gene in chromosome 2 (2q23) and various fusion partners, including IMT, TPM3, TPM4, CLTC, CARS, RANBP2, ATIC, SEC 31L1 and PPFBP1[97-103]. CT typically reveals a coin lesion that is difficult to differentiate from other causes of similar lesions. The diagnosis is typically made by tissue biopsy that often exhibit spindle-shaped myofibroblast-like cells and chronic inflammation comprising plasma cells, lymphocytes and histiocytes[104]. Surgical resection is the only treatment option. Radiation and chemotherapy have no role in IMT (Figure 5).

STSs in the pediatric age group are a heterogeneous group of rare mesenchymal tumors. Survival outcome in pediatric STS has improved since cooperative studies were initiated by various international organizations, particularly the International Rhabdomyosarcoma Study Group. Treatment of these tumors relies on knowledge of their natural history and tumor biology as this information is used to categorize STSs according to their risk. Although surgery has been the main treatment in localized low-risk tumors, good outcomes are not achieved without adjuvant radiation and chemotherapy. Future studies in the treatment of STS are directed

toward the use of molecular diagnosis as an integral part of tumor classification. While novel modalities for the treatment of advanced stage tumors are under investigation, trials should be conducted on the reduction of treatment intensity in low-risk patients.

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Fever tree revisited: From malaria to autoinflammatory diseases

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Abstract

Over the centuries the idea of recurrent fevers has mainly been associated with malaria, but many other fevers, such as typhoid and diphtheria were cause for concern. It is only in recent times, with the more severe forms of fever from infectious origin becoming less frequent or a cause for worry that we started noticing recurrent fevers without any clear infectious cause, being described as having a pathogenesis of autoinflammatory nature. The use of molecular examinations in many cases can allow a diagnosis where the cause is monogenic. In other cases, however the pathogenesis is likely to be multifactorial and the diagnostic-therapeutic approach is strictly clinical. The old fever tree paradigm developed to describe fevers caused by malaria has been revisited here to describe today's periodic fevers from the periodic fever adenitis pharyngitis aphthae syndrome to the more rare autoinflammatory diseases. This model may allow us to place cases that are yet to be identified which are likely to be of multifactorial origin.

Key words: Recurrent fevers; Malaria; Autoinflammatory diseases; Periodic fever adenitis pharyngytis aphthe syndrome; History of medicine; Interleukin-1; Genetics; The fever tree

Core tip: Periodic fevers of autoinflammatory nature have been increasingly recognized in recent decades, in many cases reflecting monogenic disorders of inflammation. However, patients can be encountered in clinical practice who don't fit in any definite category of periodic fever, despite of extensive molecular analyses. A clinical approach based on the analogy with the well defined monogenic diseases can be reasonable in these cases, which likely represent an heterogeneous group of multifactorial disorders. We propose revising the

historical image of the fever tree to figure the possible existence of a disease continuum between multifactorial and monogenic periodic fever syndromes.

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THE CONCEPT OF FEVER: FROM FEBRILE ILLNESS TO HYPERSENSITIVITY

Fever has been considered for a long time as a primary illness in itself rather than a physiologic process occurring with disorders of various origin, marked by a raised body temperature mostly of infectious nature. In spite of this, since antiquity, some physicians believed that the high temperatures during a febrile illness could have some beneficial effects, being followed usually by a spell of sweating and subsequent resolution[1]. The idea of fever as "a mighty engine which Nature brings into the world for the conquest of her enemies" was promoted by Thomas Sydenham, even though he was unsuspecting that fever occurs as the result of immune activation caused by such "enemies" usually represented by bacteria or viruses[2].

In recent centuries, following the urbanization and the overcrowding of cities, fevers caused by epidemics such as diphtheria, flue, smallpox, measles and pertussis became a serious concern in most areas of the World, being accountable for a high death rate in early childhood. These epidemiological changes probably conditioned the notion of fever, which started to be considered a harmful reaction to infections by the body. Thus, antipyretics were initially introduced rather as an attempt to cure the fever instead of relieving sufferers from their discomfort. In actual fact, enhanced microbiological knowledge didn't immediately result in downgrading the importance of febrile temperature vis-à-vis to the infection itself, until the beginning of the twentieth century when a new concept emerges which considers fever as a manifestation of immune activation to exogenous agents[3]. At the same time, on the other hand, it was becoming apparent that hyperthermia or fever could be beneficial in supporting the healing process following various diseases such as gonorrhea and syphilis[4].

Although the mortality rate caused by infectious febrile illnesses dramatically decreased in western countries around the mid XX century, the fear of fever, or "fever phobia" quoting a term coined by Schmitt[5] in 1980, persisted within folklore beliefs to some extent until today. Moreover, it has been argued that the unrealistic concerns about fever sprung from the patient's and the caregiver's misconceptions concerning what constitutes a high temperature[1,6,7]. It may be worth recalling that as far back as 1871 Wunderlich, after collecting data on one million measurements of body temperature, established 37.0 ℃ (range 36.2-37.5) as the normal human body temperature, suggesting that temperatures above 38.0 ℃ had to be considered "suspicious" of febrile nature[8].

RECURRENT FEVERS: FROM MALARIA TO AUTOINFLAMMATORY PERIODIC FEVERS

Flares of fever recurring with a repetitive clinical picture characterize recurrent fevers, suggesting that they are brought about by a single and persistent cause[9,10]. In ancient civilizations, fever caused by malaria and typhoid was probably among the febrile illnesses of major concern. Indeed, medical historicists are still debating whether Alexander the Great died of malaria or typhoid fever[11]. Especially malaria has been for many centuries the most common and alarming recurrent fever among people living around the Mediterranean Sea. Ancient Romans celebrated the Etruscan divinity Februs with a purification ritual on the month of February. The celebration was later dedicated to the divinity febris (fever), protector from recurrent seasonal fevers due to malaria. This is where the Valentine Day celebration probably later originated from, maybe in reference to "love fever". Malaria was so rooted in the Italian wetlands that people venerated the Virgin Mary of fevers to seek for protection (Figure 1)[12].

In 1712, a few decades after quinine had become available to cure the disease, the Italian physician Torti[13] proposed a classification of febrile illnesses based on the response to quinine, which was represented in his famous figure of the fever tree (Figure 2). The fever tree was not only about malaria, but it covered all types of fever known at that time. Regardless of the real utility of a classification based on apparent response to quinine, this figure reflected the concept of fever as a leading feature of diseases.

During the first decades of the XX century, eradication of malaria from most Western countries, together with improved socioeconomic conditions and the availability of vaccines and drugs for many infectious diseases, contributed to a dramatic reduction in the mortality rates caused by febrile illnesses. At the same time, the development of laboratory diagnostics and the observation of ex juvantibus' response to antibiotics allowed the identification, in many cases, of the fever's infectious cause. It is not surprising that only in this scenario was the recurrence of fevers beginning to be noticed in some individuals without a putative infectious cause. Indeed, only after the Second World War did physicians start describing subjects with seemingly unprovoked episodes of fever, simultaneously recurring with a set of various other complaints, usually on the skin, in the joints, muscles, abdomen, chest and lymph

Figure 1 The Virgin Mary of Fevers, by Nicola Mellini, XIX century, Bologna, Italy.

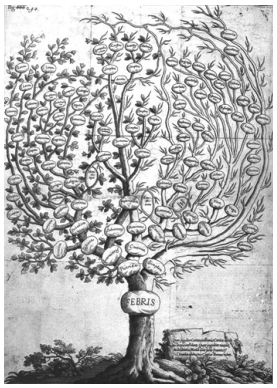

Figure 2 The fever tree, Francesco Torti (image from the Comenius Project, http://89.97.218.226/web1/pontina/biologia/p_37.htm)[10].

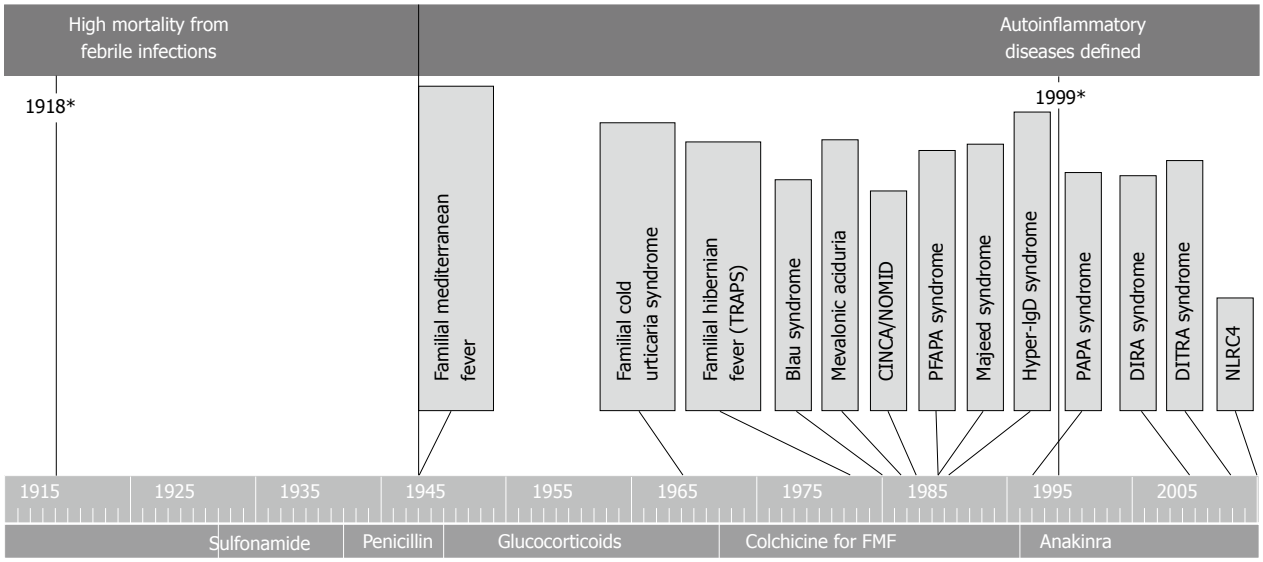

Figure 3 Timeline discovery periodic fevers autoinflammatory disease. PFAPA: Periodic fever adenitis pharyngitis aphthae; DITRA: Deficiency or interleukin-36-receptor antagonist deficiency; DIRA: Deficiency of interleukin-1–receptor antagonist; PAPA: Pyogenic arthritis, pyoderma gangrenosum, and acne.

nodes (Figure 3).

It was quite clear that such recurrent fevers were the result of a pathologic immune mechanism, but the term "autoinflammatory" was only proposed at the end of the century to describe the particular pathogenesis of these disorders[14]. The pivotal role of Interleukin 1 (IL-1) in the pathogenesis of autoinflammatory disorders (ADs) was highlighted both in experimental studies as well as in therapeutic trials with IL-1 blocking agents[15]. This change in knowledge was of particular importance, as a proper identification of this category of disorders could allow better diagnostic and therapeutic choices, avoiding useless examinations and treatments such as antibiotics[16]. Moreover, the conception of fever was changing once again, from beneficial in most infections, to harmful when becoming the expression of immune dysregulation. Actually, it is not fever in itself that is harmful, but IL-1 related inflammation.

The first AD described was familial Mediterranean fever (FMF) called by the name of "benign paroxysmal peritonitis". Clinically, FMF is characterized by recurrent and self-limited attacks of fever lasting 12-72 h with peritonitis, pleurisy, arthritis or erysipelas-like skin disease and a marked acute-phase response. Subsequent complications of untreated patients are due to renal amyloidosis. The temperature may reach 38-40 ℃ and can anticipate other symptoms, although some patients may only have a fever. Diagnosis of FMF is primarily clinical and based on the use of the diagnostic criteria[17-19].

After FMF, a number of other monogenic AD's are described, presenting recurrent fever together with several other combinations of clinical features (Figure 3).

Actually, there is a great heterogeneity among AD's concerning prevalence, severity and clinical features. On one end of the spectrum one finds the rare and often severe disorders due to mutations in a number of inflammasome-related genes, as is the case for Cryopyrinopathies, DIRA, DITRA and others, and on the opposite end there is the periodic fever adenitis pharyngitis aphthae syndrome (PFAPA). This is a relatively common disorder with likely multifactorial pathogenesis,

usually characterized by mild symptoms and a benign course[20]. It is worth noting that, although it is the most common among autoinflammatory periodic fevers, PFAPA has been described relatively late, in 1989. This delay may be related to concerns raised during the previous two centuries about rheumatic fever, in addition to the higher incidence of other serious febrile illnesses of infectious origin. Indeed, in the first decades of the XX century, Rheumatic Fever, usually occurring as a sequel of Group A Streptococcus (GAS) tonsillitis, was still a prominent health problem in developed countries, being associated with the high risk of carditis. In some subjects GAS tonsillitis could recur, increasing the risk of developing chronic hearth injury. In fact, almost one third of children underwent early tonsillectomy in the years before the Second World War and we cannot know how many of them could have had PFAPA syndrome rather than GAS tonsillitis. More often than not tonsillectomy was performed as prevention in subjects who had never developed tonsillitis. Actually, during the past century, Western countries witnessed a progressive decline in the incidence of rheumatic fever, mostly irrespective of the availability of antibiotics and to the practice of tonsillectomy[21]. Nevertheless, fear of Rheumatic Fever persisted for decades and might have been in part responsible for the delayed identification of PFAPA[22].

Half way between PFAPA and rare monogenic AD, there is a group of well characterized hereditary periodic fevers that can show up with a higher frequency in certain populations, as FMF in Mediterranean people, mevalonate kinase deficiency (MKD) in Dutch and tumor necrosis factor associated periodic fever (TRAPS) in people with Northern European ancestry[23]. Patients with MKD present fever episodes lasting 3 to 7 d that typically recur every 4 to 6 wk. The fever may be accompanied by lymphadenopathy, abdominal pain with diarrhea or vomiting, headache, polyarthralgia or arthritis of large joints, skin lesions such as papular, urticarial, nodular or purpuric rash. Patients with TRAPS show attacks of extremely variable duration and intensity (from 1-2 d to 3-4 wk), characterized by fever accompanied more or less constantly by sterile peritonitis with abdominal pain, diarrhea or constipation, nausea, and vomiting. Mono- or bilateral periorbital edema is a very characteristic and almost pathognomonic sign of the disease, often associated with conjunctivitis and periorbital pain. Also very frequent are arthralgias, muscle cramps, centrifugally spreading migratory myalgias, chronic fasciitis, serpiginous rash, consisting of migratory and painful patches[24,25].

Besides a few exceptions, a common feature of periodic fever syndromes is the reversibility of symptoms with a complete sense of wellbeing outside the flares, lacking the development of sustained autoimmunity and progressive inflammatory damage. Exceptions are severe ADs which tend to present a continuous course rather than a periodic one as well as specific syndromes such as FMF and TRAPS which, if not treated, present a varying high risk of developing amyloidosis[26].

NOVEL CONCEPTS AND THE FEVER TREE REVISITED

In the last decade, some evidences have been accumulated demonstrating a poor correlation between phenotype and genotype in AD. Environmental factors can modify the clinical presentation, as in the case of FMF. This was elegantly demonstrated by the evidence represented by the people with FMF who immigrated to Germany and in spite of similar genetic backgrounds, tended to present milder symptoms compared with their cousins who remained in Turkey[27]. In addition, although it is well known that FMF is transmitted with autosomal recessive inheritance, in certain families some mutations can be associated with a dominant inheritance, this has lead to the belief that there are other possible contributions in the pathology stemming from other genetic and environmental factors.

Indeed, patients with heterozygous mutation or with multiple low penetrance variants in the *MEFV* gene may display attenuated phenotypes resembling more PFAPA than FMF, making it difficult to definitely confirm the diagnosis of FMF[28].

A similar behavior is also described when talking about other periodic fever syndromes, such as TRAPS. Some genetic variants for example, relatively common in the general population, may have low penetrance occurring mostly in healthy people, that can also be associated, in some individuals, with a typical manifestation of the disease[29]. In fact, the correlation between genotype and phenotype in patients with AD is often incomplete and many patients could receive the wrong diagnoses such as inflammatory bowel disease, Behçet disease or adult onset Still disease, being excluded from genetic testing for AD[16,30].

In addition, a number of recent reports showed that it could be relatively common, even following extensive molecular analysis, to find subjects with periodic fever lacking a definite genetic diagnosis[31-34]. In some cases genetic variants of uncertain significance in AD-related genes may be found, yet their relevance for diagnosis is currently unpredictable[35,36]. Recently, evidence-based provisional clinical classification criteria for autoinflammatory periodic fevers have been proposed, which may help diagnosing patients with uncertain genetic results[37]. In addition, these criteria can be used to classify patients with undifferentiated diseases based on the similarity of their clinical pictures with the known hereditary periodic fever syndromes.

To represent this complexity, we proposed revisiting the ancient figure of the fever tree (Figure 4).

The figure of the tree can serve to represent AD as a disease continuum, from the common multifactorial PFAPA syndrome, which is figured by the trunk, to the rare monogenic diseases, represented by the tip of the branches. Going from the trunk to the major limbs

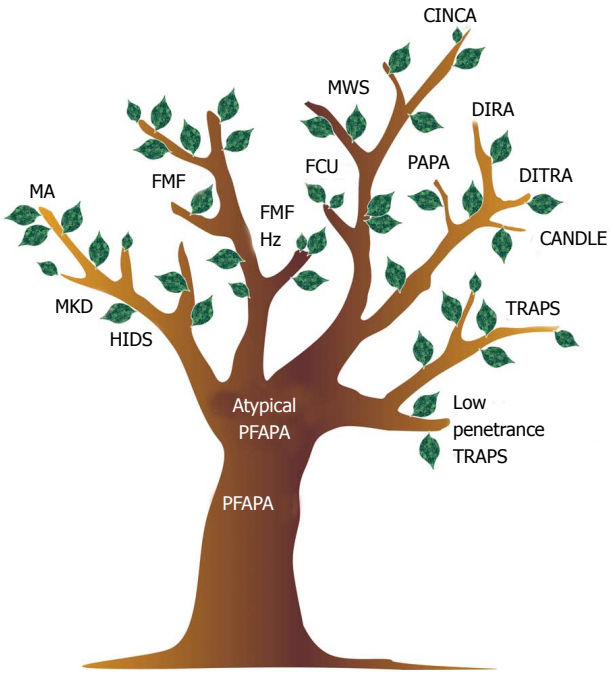

Figure 4 The fever tree revisited. PFAPA: Periodic fever adenitis pharyngitis aphthae; MKD: Mevalonate kinase deficiency; FMF: Familial mediterranean fever; HIDS: Hyper-IgD syndrome; CINCA: Chronic infantile neurologic cutaneous and articular syndrome; MWS: Muckle wells syndrome; DIRA: Deficiency of the interleukin-1 receptor antagonist; FCU: Familial cold urticaria; DITRA: Deficiency or interleukin-36-receptor antagonist deficiency; MA: Mevalonic aciduria.

and then up to the top of the smaller branches, we can find a number of intermediate phenotypes, which might be underpinned by a variety of genetic variants in the same genes, which have evolved towards more severe forms, or other genes altogether which are yet to be identified. For example, low penetrance mutations in the genes responsible for FMF, TRAPS and MKD have been associated with PFAPA-like phenotype[28,29]. Indeed, MKD encompasses a wide range of phenotypes, from the most severe end, represented by mevalonic aciduria which we can figure on the tip of the branch, to MKD and Hyper-IgD syndrome, which in milder cases can closely resemble PFAPA[38].

PFAPA itself may not be actually considered as a single disease, but rather as a heterogeneous syndrome. Atypical cases have been described, and can currently be encountered. Typically, patients with PFAPA present episodes of tonsillopharyngitis accompanied by enlarged neck lymph nodes and mouth aphthae: the periodic recurrence of fever episodes, the response to a single administration of low dose glucocorticoids, and the conclusive healing after tonsillectomy are all characteristic features of the disease. However, it is not uncommon to encounter patients with periodic fever and tonsillitis who present atypical signs, such as a poor response to glucocorticoids, a recurrence following tonsillectomy or the presence of significant cutaneous, articular or abdominal symptoms, in addition to pharyngeal involvement. In a small proportion of these atypical PFAPA cases, a definite diagnosis of hereditary periodic fever can be done (*e.g.*, MKD or TRAPS), while in most cases the analysis of a more or less complete set of genes associated with HPF can only reveal the presence of common genetic variants of vague significance or no variants at all. Few cases in this group may still be due to yet unidentified monogenic disorders or to somatic mosaicism for mutations in autoinflammatory genes, similarly to what has been described for subjects with cryopirin associated periodic syndromes or Blau sindrome[39,40]. In most cases, however, it is reasonable to assume that this group is composed by patients with true multifactorial disorders with intermediate characteristics between PFAPA and various types of autoinflammatory diseases. In this regard, it is worth noting that some patients with atypical PFAPA may respond to colchicine, in analogy with FMF. Operatively, we could represent the disease of such patients on the fever tree positioned between the PFAPA trunk and the bottom of the FMF branch.

This picture doesn't claim to be complete but can help to be confronted with an expanding spectrum of AD's, including patients with atypical presentations lacking a definite genetic diagnosis. Further studies are needed to understand the role of genetic and environmental factors in these cases. Moreover, it remains to be evaluated whether a practical approach based on the clinical analogies with well defined AD's can represent a reasonable choice in these cases.

In fact, so far, we can identify only a few groups of diseases based on the response to treatments and in particular if there is a preferential response to low dose glucocorticoids, colchicines or cytokine inhibitors (IL-1 or TNF-α).

It may be worth recording that, in regards to autoinflammatory diseases, fever in itself, is never the harm. Treatments should be aimed at relieving patients from pain and discomfort and, in some diseases in preventing long-term damage from chronic inflammation.

This review may tell just a part of the story and represent a simplification of the field. However, as physicians, we still need to be able to cure, understand, and act expediently in daily practice when dealing with the disease, without necessarily knowing the genetic makeup of each individual patient with his or her individual variability, manifestation and diseases development, keeping in mind that the personalization of medicine is not just genetically driven.

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Efficiency of upper gastrointestinal endoscopy in pediatric surgical practice

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Abstract

After the introduction of flexible fiber optic endoscopy to pediatric gastroenterology in the 1970s, upper gastrointestinal (UGI) endoscopy can be performed for the diagnosis and treatment of all age groups of children. We review indications, contraindications, preparation of patients for the procedure, and details of diagnostic and therapeutic UGI endoscopy used in pediatric surgery. We also discuss potential complications of endoscopy.

Key words: Endoscopy; Upper gastrointestinal system; Pediatric surgery; Diagnosis; Treatment

Core tip: Flexible upper gastrointestinal (UGI) endoscopy is a diagnostic and therapeutic procedure accepted worldwide for some UGI diseases in children. With the advances and innovations in the field of pediatric endoscopy and equipment, UGI endoscopic procedures have been safely and effectively used in children with minor complications in experienced hands. In this review, we summarize the efficiency of UGI endoscopic procedures in pediatric surgery.

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INTRODUCTION

The anatomical area located above the junction of the duodenum and jejunum is described as the upper gastrointestinal (UGI) system. It includes the mouth, pharynx, esophagus, stomach and duodenum with the extra-hepatic pancreaticobiliary tree. Many congenital or acquired pathologies of the UGI system are encountered in pediatric surgical practice. Several diagnostic and therapeutic endoscopic interventions are required in some of these patients. After the introduction of flexible fiber optic endoscopy to pediatric gastroenterology in the 1970s, and through technological developments in the

Table 1 Most common indications of diagnostic upper gastrointestinal endoscopy

Caustic ingestion
Gastrointestinal bleeding
Dysphagia or odynophagia
Recurrent or epigastric abdominal pain
Failure to thrive or weight loss
Vomiting
Chronic or complicated GER
Diarrhea or malabsorption
Investigation for iron deficiency anemia
Inflammatory bowel disease

GER: Gastroesophageal reflux.

Table 2 Most common detected pathologies in upper gastrointestinal bleeding

Erosive esophagitis
Gastritis
Peptic ulcer disease
Esophageal varices
Duodenitis or duodenal ulcer
Mallory-Weiss tears
Gastric erosion
Dieulafoy's lesion
Angioectasia
Esophageal or gastric polyps

size and flexibility of endoscopes, UGI endoscopy can be performed even on premature infants from the first day of birth with smaller endoscopes[1-5]. Initially, endoscopy was used only for diagnostic study in children. With advances and innovations in the field of pediatric endoscopy and equipment, the frequency of therapeutic procedures such as removal of ingested foreign bodies, percutaneous endoscopic gastrostomy (PEG), ligation of esophageal varices, polypectomy, injection therapy, endoscopic retrograde cholangiopancreaticography (ERCP), and peroral endoscopic myotomy (POEM) has gradually increased in children.

DIAGNOSTIC ENDOSCOPY

Dyspepsia, UGI bleeding and abdominal pain are the most common indications for diagnostic UGI endoscopy in pediatric surgical practice[3,4,6-10]. The indications are summarized in Table 1[1-3]. Because endoscopy is performed easily and quickly, the number of patients undergoing negative endoscopy increases gradually, which causes increased economic burden. However, as a result of this practice several new diseases and pathologies of the UGI system in childhood have been described[10]. There is still no definitive description of dyspepsia. Epigastric pain, fullness, vomiting, regurgitation, nausea, abdominal discomfort, and bloating are commonly accepted as dyspeptic symptoms[11]. Guariso *et al*[11] reported that endoscopy is not necessary for all children with dyspeptic symptoms. They recommended endoscopy for patients with a family history of peptic ulcer or *Helicobacter pylori* infection, older than 10 years of age, with symptoms continuing for more than 6 mo or whose daily activities are affected. Various disorders such as gastritis, duodenitis, esophagitis, and peptic ulcer may cause recurrent or chronic abdominal pain in children. UGI endoscopy should be performed in children with intractable or unexplained abdominal pain. Multiple biopsies should be done randomly from the esophagus, stomach and duodenum during endoscopy, especially from the distal esophagus and antrum, even if these areas are macroscopically normal.

UGI bleeding is not uncommon and is usually a self-limited clinical condition. The causes of UGI bleeding are listed in Table 2[3,12-15]. UGI bleeding affected only 5% of patients who underwent UGI endoscopy[12]. Although causes vary among reports, excessive UGI bleeding commonly arises from esophageal varices, peptic ulcer, gastritis, esophagitis or esophageal ulcer[3,13-15]. Polyps, inflammatory disorders, Dieulafoy's lesion or vascular malformations such as angioectasia are less common in children[3,16-19]. The causes and sources of UGI bleeding are defined by endoscopy in 85%-90% of patients. Rates of misdiagnosis of bleeding of between 10% and 27% have been reported in different studies[15,20,21].

The diagnosis of gastroesophageal reflux disease (GERD) is commonly made by pH meter, barium meal test or scintigraphy. Endoscopy and esophageal biopsy are used for the diagnosis of complicated GERD, suspected but unproven or demonstrated GERD, or to exclude other diseases that can mimic GERD such as eosinophilic or infectious esophagitis and Crohn's disease[22,23]. Because normal endoscopic appearance of the esophageal mucosa does not exclude esophagitis, endoscopic biopsy should be done in all patients. The tonus of the lower esophageal sphincter and the location of the esophagogastric junction are also considered. El Mouzan *et al*[23] reported that esophageal pH monitoring was the most specific diagnostic study (91% specificity), whereas endoscopy was the most sensitive diagnostic tool (92% sensitivity) for GERD.

Caustic ingestion is another common clinical condition which requires UGI endoscopy in pediatric surgical practice. Different diagnostic trials such as radiocontrast esophagography, scintigraphy, and esophageal ultrasound have been conducted to diagnose caustic injuries. Several studies have reported that clinical signs are not always helpful in predicting the degree of injury[24-26]. Upper gastrointestinal system endoscopy is the most effective method for establishing the severity of injury and for planning treatment. Because the esophagus is weakest between days 7 and 21 after caustic injury and the frequency of endoscopic complications also usually increases during this period, endoscopy is recommended in the first 24-48 h of injury[24-26]. It is usually recommended to stop endoscopy at the first circumferential esophageal burn because of the increased risk of complications beyond this point[27]. This approach might cause a more severely burned esophagus or

stomach to be missed. We observed severe gastric injury in 18.4% of patients; gastric injury was more severe than esophageal injury in 3.4% of patients in our study[28]. Therefore we suggest complete upper GİS endoscopy if possible in children with caustic injuries[28]. UGI endoscopy revealed severe esophageal injury in 19.3% of our patients that did not have symptoms. In contrast, 59.7% of the patients with positive clinical symptoms had no or grade 1 esophageal injury. In these circumstances endoscopy prevents unnecessary hospitalization and also decreases complication rates[28].

DIAGNOSTIC ENDOSCOPY WITH THERAPEUTIC PROCEDURES

Massive UGI bleeding is a life-threatening condition and requires expeditious resuscitation and hemostatic therapy. Massive bleeding usually results from peptic ulcer, esophageal varices, Dieulafoy's lesion or vascular malformations[3,14,20]. Therapeutic interventions should be attempted at the same time as diagnostic endoscopy in the presence of active bleeding, non-bleeding visible vessels, or adherent cloth. Endoscopic therapies include adrenalin or alcohol injection, thermal coagulation, band ligation, tissue adhesives and mechanical clamping[3,4]. Similarly, diagnosis of polyposis and polypectomy can be made as successive procedures[3,6].

ERCP has been widely accepted as both a diagnostic and therapeutic tool for extrahepatic biliary and pancreatic diseases. The most common indication for ERCP, especially for its use as a treatment procedure in children, is biliary obstruction[29,30]. Complication rates of ERCP have been reported to be between 3.4% and 28.5%. The most common complications associated with ERCP are pancreatitis, hemorrhage, infection and perforation[30,31]. In joint diagnostic and therapeutic procedures such as ERCP, interventions to stop bleeding are usually performed by pediatric gastroenterologists. These procedures are not common in pediatric surgical practice.

THERAPEUTIC UGI ENDOSCOPY

Foreign body ingestion

Foreign body ingestions are usually encountered in small children under 5 years of age or older children. The elder children are usually with mental retardation. Most (98%) cases are reported as accidental events[32,33]. Coins are the most commonly ingested foreign body, which occurs in approximately 70% of cases[34]. However, toys, jewelry, magnets, and batteries are other commonly ingested foreign bodies[32]. Patients are asymptomatic 50% of the time; drooling, pain, refusal to feed, dysphagia, stridor, wheezing, and respiratory distress are the most common symptoms in the remaining 50% of patients[32,35,36]. Plain radiography is still the most used diagnostic modality. Barium meal study or computed tomography are indicated especially in cases of ingestion of a non-contrast object or for patients with complications[33,37]. The location of impaction usually relates to the age of the child and the size and shape of the foreign body. The esophagus, especially the upper esophageal sphincter, is the most common anatomical site for impaction of foreign bodies. The second and third most frequent anatomical sites of impaction are at the level of T4 where the distal aortic arch descends posterior to the esophagus, and the lower esophageal sphincter, respectively. Although 80%-90% of foreign bodies pass through the gastrointestinal system spontaneously, 10% or 20% of the remaining cases require endoscopic extraction. Only 1% of patients need surgery[37]. Foreign bodies detected in the stomach and intestines often tend to pass spontaneously[34]. The complication rates increase with pointed and sharp foreign bodies, button batteries, and magnets. Esophageal perforation has been detected in 2%-15% of patients with an esophageal foreign body in different studies[34]. Serious complications such as mucosal erosion, ulcer, esophageal or intestinal perforation, pneumothorax, pneumomediastinum, tracheoesophageal fistula and cervical abscess may be developed secondary to foreign body ingestion[36]. Removal of foreign bodies which are located in the esophagus is mandatory to prevent complications.

Button batteries, in particular, may lead to perforation secondary to the caustic injury or pressure effect. As a result, esophageal button batteries should be removed immediately. Ingestion of multiple magnets is another special condition, because if multiple magnets are ingested at different times, they may cling and cause intestinal perforation, peritonitis or enteroenteric fistula. For this reason, magnets should be removed as soon as they are identified[32].

The removal of the foreign bodies by endoscopy must be performed under general anesthesia with intubation to provide respiratory security. The method differs according to the shape and location of the foreign body. Use of McGill forceps is an easy procedure for foreign bodies located above the cricopharyngeal sphincter. Below this anatomical level, rigid or flexible endoscopy is required to remove foreign body impactions.

PEG

Several gastrostomy or enterostomy techniques have been described to establish long-term enteral feeding in children and adults. Stamm gastrostomy was the first surgical technique introduced for enteral nutrition. Laparoscopic gastrostomy is another method for insertion of a gastrostomy tube. Because it is less invasive and more cost-effective than surgical procedures, PEG has increasingly been used since it was described by Gauderer *et al*[38-41]. PEG is the most preferred technique especially for patients with neurological diseases[38]. However, Baker *et al*[40] revealed that there is increased risk of major complications of PEG compared to the laparoscopic gastrostomy[40]. The rate of complications

Table 3 Typical indications of percutaneous endoscopic gastrostomy

Inability to swallow
Neurological impairment
Multiple congenital malformation
Oropharyngeal dysmotility
Epidermolysis bullosa
Inadequate calorie intake
Cystic fibrosis
Congenital cardiac disease
Chronic respiratory failure
Special feeding requirements
Continuous enteral feeding
Oncologic disease
Genetic syndromes

can be reduced by an experienced endoscopist. Indications of PEG are summarized in Table 3[38,39].

Operative technique: The most preferred technique is the "pull" technique described by Gauderer[39,41]. Flexible endoscopy is performed using an appropriately sized endoscope. The stomach is insufflated. The optimal location for placement of the PEG is confirmed by both transillumination and finger indentation. A small incision less than 0.5 cm is made, then the stomach is cannulated with a needle or cannula. A thread is passed into the stomach through the cannula, grasped with a snare and pulled out of the mouth with a flexible endoscope. The PEG tube is connected to the thread and pulled from the mouth antegrade into the stomach. The bumper of the PEG tube is lubricated and manipulated to prevent esophageal damage. Finally, the position of the flange is confirmed by control endoscopy[38,39].

Replacement of PEG tube: Replacement of old, damaged or plugged PEG tubes is also performed by endoscopy. The bumper of the PEG catheter is removed endoscopically. A thread is passed into the stomach through the existing gastrostomy tunnel. Subsequent steps are identical to the initial insertion of the PEG tube.

Esophageal and pyloric dilation

UGI strictures are usually located at the esophageal level in children. Pyloric obstruction is encountered in fewer patients. The most common cause of benign esophageal stricture is ingestion of a caustic substance[42,43]. Esophageal strictures in children may be caused by congenital anomaly, foreign body ingestion, or be secondary to gastroesophageal reflux or esophageal surgery. However, of several possible surgical procedures, dilation with bougienage or balloon is the first choice of treatment for benign esophageal strictures in children[44,45]. Endoscopically or fluoroscopically guided bougienage or balloon dilation is recommended as a safe and effective treatment in children with benign esophageal stricture to reduce complication rates[44].

Pyloric stricture (PS) may be caused by peptic ulcer, granulomatous diseases and eosinophilic gastroenteritis, and caustic injury or unknown causes in children[46-48]. Diagnosis of PS is based on barium swallow. Endoscopic examination and biopsy of the UGI system should be performed to investigate the etiology of PS. Surgical correction is still the most common treatment in the majority of cases of PS[42]. However, there are some studies on endoscopic balloon dilation performed in children with PS. In these reports, success rates for balloon dilation have been reported between 16% and 80% with benign PS[49,50].

Technique: Endoscopy is performed under general anesthesia with tracheal intubation. After focusing on the narrowed esophagus or pylorus, a radiopaque guide wire is inserted under endoscopic guidance. A balloon catheter is passed over the guide wire and placed through the narrowed esophagus and pylorus. The location of the balloon is monitored endoscopically in pyloric dilation. Then the balloon is inflated with radiocontrast solution under fluoroscopy to the recommended level of pressure marked on each catheter. Inflation is performed for two minutes after expansion of the hourglass deformity of the stricture[42].

The balloon size is increased to the appropriate diameter as determined by the thumb rule for esophageal stricture. For PS, the preferred diameter of the balloon is 12-14 mm for infants and 15-18 mm for older children[42].

Miscellaneous procedures

In addition to the widespread use of endoscopy in diagnostic and therapeutic procedures, several reports presented as case reports or with limited patients include new therapeutic approaches for UGI diseases that are gradually increasing in popularity. Endoscopic treatments of duodenal duplication and duodenal web have recently been reported[51,52]. POEM has been described for achalasia in adults; clinical results of its use in children have been presented with small numbers of patients[53,54].

CONTRAINDICATIONS

Although endoscopy can be performed on children of any age from the first day of life to adolescents, it is contraindicated in patients with unstable airways, cardiovascular collapse, intestinal perforation or peritonitis[5]. Intestinal obstruction, neutropenia, severe thrombocytopenia, coagulopathy, recent gastrointestinal surgery, unstable cardiopulmonary diseases, and recent oral intake are accepted as relative contraindications[4,5].

ANTIBIOTIC PROPHYLAXIS

Antibiotic prophylaxis is not recommended for diagnostic endoscopy except for specific conditions, including congenital cardiac anomalies, cardiac surgery, neutropenia or ventriculoperitoneal shunt. However,

Table 4 Common complications of percutaneous endoscopic gastrostomy

Failure of replacement
Wound infection
Local erythema
Celulitis
Sepsis
Gastrointestinal bleeding
Gastric ulcer
Stomal leakage
Death
Gatrocolic fistula
Transient ileus
Gastroesophageal reflux
Peritonitis
Granulation tissue
Catheter migration
Hepatic injury
Aortogastric fistula
Subcutaneous emphysema

prophylactic antibiotic administration is suggested before diagnostic endoscopy with those clinical conditions and for all therapeutic endoscopic interventions such as insertion of PEG, endoscopic dilation, sclerotherapy, band ligation, and ERCP[5]. Ampicillin with sulbactam is the most commonly used antibiotic for this aim.

ANESTHESIA

Sedation with analgesia or general anesthesia is the accepted approach for endoscopy as for other interventional procedures in children. Sedation and general anesthesia facilitate endoscopic procedures and decrease the emotional stresses from separation from parents, analgesia and amnesia[4-9]. Detailed examination is recommended to choose an appropriate anesthetic modality and to reduce complications. The preferred anesthetic method and drugs should be decided by the endoscopist and anesthesiologist together[4,8]. Moderate sedation is the most preferred sedation regimen for endoscopy in children. Infants under seven months old are at higher risk because of obligatory nasal breathing; however, it has been reported that endoscopy is safe and uncomplicated with a trained practitioner even in neonates[1]. Under moderate sedation protective airway reflexes and spontaneous breathing remain active during endoscopy[5,9]. Midazolam, fentanyl, propofol and ketamine are the most commonly used anesthetic agents during endoscopy. The cardiovascular and respiratory systems of all patients should be monitored by electrocardiography and oxygen saturation. Endoscopy, especially in therapeutic interventions, should be performed under general anesthesia with endotracheal intubation in patients with poor general condition, severe respiratory disease or complex planned procedures.

COMPLICATIONS

UGI endoscopy and co-procedures are generally accepted as safe interventions in experienced hands. The complication rates reported are usually less than 2%-3% and decrease with age[55,56]. There are several complications associated with endoscopy or related procedures in the literature. Most are minor[55]. Complications are considered in two main groups. The first group is associated with anesthesia, such as delayed extubation, bronchospasm, and fever. Lee *et al*[13] reported minor complications in 1.5% of patients. The second group are complications associated with endoscopy and related procedures.

Complications after diagnostic endoscopy and endoscopic biopsy

UGI hemorrhage and duodenal hematoma may occur secondary to the endoscopy[13,57-59]. Lee *et al*[13] observed secondary bleeding following rubber banding or sclerotherapy in 3.4% of patients. Iqbal *et al*[60] reported bleeding, perforation and mucosal tears as iatrogenic complications in 6 of 9308 UGI endoscopy procedures (0.06%). A conservative approach is usually sufficient for improvement in patients without peritonitis[60].

Complications of PEG

Complications due to PEG insertion or tube are divided into major and minor complications, summarized in Table 4[38,39,61-65]. Hepatic injury secondary to the PEG placement was reported in one adult. Peristomal wound infection accounts for 30% of complications[64,66]. The risk of wound infection increases in patients with obesity, diabetes mellitus or malnutrition. Prophylactic antibiotic administration significantly reduces the risk of peristomal wound infection[64,66].

CONCLUSION

With an experienced practitioner, endoscopy is a safe and effective diagnostic and therapeutic procedure even for premature infants. Complications can easily be prevented.

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MINIREVIEWS

Hirschsprung's disease: Historical notes and pathological diagnosis on the occasion of the 100th anniversary of Dr. Harald Hirschsprung's death

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Conflict-of-interest statement: Dr. Sergi C is a "ad hoc" consultant of the World Health Organization (WHO)/International Agency for Research on Cancer (IARC) sitting in the panel as collaborator for the use of pesticides and cancer (IARC Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides) and Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone. Moreover, Dr. Sergi C. has received research funding from the Women and Children Research Institute, Saudi Cultural Bureau, and the Canada Foundation for Women's Health (CFWH) (Award 2009: CFWH General Research Grant Dr. L. Hornberger and Dr. C. Sergi), and has received fees for serving as grant reviewer for the Health and Medical Research Fund (HMRF), Hong Kong Special Administrative Region, and as consultant for Guidepoint.

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Abstract

Hirschsprung's disease (HSCR) or congenital megacolon is one of the differential diagnoses of chronic constipation mostly in infancy and may indeed represent a challenge for pediatricians, pediatric surgeons, and pediatric pathologists. The diagnosis relies clearly on the identification of the absence of ganglion cells at the plexuses (submucosus and myentericus) of the bowel wall. HSCR is usually located at the terminal (distal) rectum with potential pre-terminal or proximal extension to the less distal large bowel (sigmoid colon). Astonishingly, there is some evidence that Hindu surgeons of prehistoric India may have been exposed and had considerable knowledge about HSCR, but this disease is notoriously and eponymously named to Dr. Harald Hirschsprung (1830-1916), who brilliantly presented two infants with fatal constipation at the Berlin conference of the German Society of Pediatrics more than one century ago. Historical milestones and diagnosis of HSCR (originally called "Die Hirschsprungsche Krankheit") are reviewed. More than 100 years following his meticulous and broad description, HSCR is still a puzzling disease for both diagnosis and treatment. HSCR remains a critical area of clinical pediatrics and pediatric surgery and an intense area of investigation for both molecular and developmental biologists.

Key words: Constipation; Analysis; Rectum; Medicine; Biopsy; History

Core tip: Medical history is fascinating and, since its beginning, it was meant to enlighten scientific issues, booster the medical profession, and celebrate the traditions or tales of particular places. Harald Hirschsprung, who presented two infants with fatal constipation at the German Society of Pediatrics more than one century ago, is known in medicine for his eponym of intestinal aganglionosis. Events running before and after Dr. Hirschsprung's discovery may drive interest in medical students and doctors to review the diagnostic procedures of this intriguing disease and recognize the enormous input given from microscopy and pathology to this diagnosis.

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HIRSCHSPRUNG'S ANNIVERSARY

In 2016, a particular and noteworthy anniversary recurs that will probably have enormous impact to clinical pediatrics, pediatric surgery, and pediatric pathology. Dr. Harald Hirschsprung (1830-1916), a Danish pediatrician, first described Hirschsprung's disease or congenital megacolon about one and half century ago. He is notoriously acknowledged as the writer of the first description of two children who died of intestinal obstruction called "congenital megacolon", which is now known as Hirschsprung's disease (HSCR)[1]. Dr. Hirschsprung was working as pediatrician at Queen Louise Children's Hospital in Copenhagen, Denmark, when he came across this disease. He brilliantly reported two children in 1886 in occasion of the Berlin Conference of the German Society of Pediatrics.

WHEN THE SAGA BEGAN

Dr. Hirschsprung, who graduated with a degree in medicine in 1855, showed since his first steps into medical career a strong interest in pediatrics, becoming astoundingly the chief physician of the only children's hospital in Copenhagen just fifteen years later. The appointment as professor of pediatrics came in 1877 and Dr. Hirschsprung became director of a larger children's hospital in Copenhagen from 1979 until 1904, when he retired. The new children's hospital was magnificently named after Denmark's Queen Louise (The Queen Louise Hospital for Children). Dr. Hirschsprung was fond of anatomical variations, peculiar aspects of medicine, and intriguing diseases. He was a brilliant teacher with loyal and faithful students. Between 1880 and 1885, Hirschsprung came across two infants with similar clinical presentation. The first child had bowel problems that persisted soon after birth with absence of spontaneous bowel movements. Daily enemas and laxatives were necessary. The second case had similar bowel distensions with terminal bouts of diarrhea variably alternating with impossibility to evacuate. Notwithstanding the scarcity of information continuous therapy was applied, but, unfortunately, both children eventually died and a postmortem examination was performed. At the autopsy, the rectum was narrowed, but there were striking dilation of the bowel loops with some ulceration of the mucosa associated with thickening of the bowel wall[2,3]. In his publication, Dr. Hirschsprung summarized his findings and drew attention to the typical clinical presentation of both cases. In an opinion, which is worldwide shared, his meticulous and comprehensive description is not the first one to indicate details of this disease, but he provided a complete and excellent account of this entity in consideration of his clinical experience and practice in pediatrics[4]. The name "Hirschsprung's disease" came into widespread use shortly before the end of the 20th century and, in 1916, Hirschsprung himself added an additional 10 more cases before his death[5-8].

DIGGING INTO THE PRE-HIRSCHSPRUNG ERA

The examination of the scientific literature seems indicate that approximately 20 similar cases have been recorded between 1825 and 1888[9]. However, there is evidence that Hindu surgeons of prehistoric India had considerable knowledge about HSCR[10]. Sushruta's description of a disease called Baddha Gudodaram is extraordinarily analogous to that of HSCR. Semantically, it seems indicate "abdominal distension due to blocked rectum". According to Sushruta, Baddha Gudodaram is a type of disease caused by (functional) blockage of the ano-rectal canal. The affected child or, even, young adult may show rectum and distal colon stuffed with gas, "stones" (fecaliths), "hair" (undigested fibers), and, obviously, feces. In the child, there is an abdominal distension, which is characteristically seen between the heart and the umbilicus. Scanty stools are evacuated with greatest difficulty, and, eventually, it was reported that the patient might vomit feculent fluid. However, the pre-Hirschsprung era is not complete, if additional reports are not also mentioned. Indeed, Fredericus Ruysch, a Dutch anatomist in Amsterdam (Netherland) in 1691 described a 5-year-old girl with abdominal pain. It seems that the usual treatment to relieve pain was permanently inefficacious and the child continued to pass flatulence. No evacuation was practically possible and the child ultimately died[11]. Remarkably, Domenico Battini, an Italian physician of the 19th century described a child that he followed up for 10 years with severe constipation. The child died and the autopsy demonstrated severe dilatation of the colon[12]. The posthumously published

Italian contribution showed not only a very careful clinical evolution of the child, but also provided a detailed autopsy with examination of the abdominal viscera. Particular mention to the morphological alterations occurred in the large bowel were present in the original Italian publication. Through the examination of the reports, Fiori concludes that Dr. Battini, nearly one century before Hirschsprung, may have originally achieved its target in reporting an archetypal case of megacolon of congenital type. Distinctively, a number of characteristic features, including familiarity and the peculiar selective involvement of "neural layers" of the bowel, that later became characteristic of HSCR, were remarkably well postulated by Dr. Domenico Battini. To increase the controversy between Denmark and Italy as well as other countries, there may be a few more reports that need to be listed. In 1836, Ebers[13] reported a 17-year-old boy with a history of constipation since birth or, perhaps, as toddler, while Jacobi[14] had also described two neonates with intestinal obstruction in 1869. Fragmentary reports of children who died of severe constipation appeared also in the literature in the pre-Hirschsprung era[15,16]. In fact, Gee[17] reported the autopsy findings of a 4-year-old child with a "spasm" of the sigmoid colon without involving of the rectum in 1884, while Bristowe[18] described the outcome of a 8-year-old girl who died of mechanic ileus after longstanding severe constipation of the bowel. Dr. Hirschsprung died on April 11, 1916, but his supreme legacy to clinical pediatrics, pediatric surgery, and pediatric pathology is unmatched with contributions that go further than severe constipation in children or the disease harboring his name ("Hirschsprungsche Krankheit"). The Danish pediatrician observed and described in detail several diseases, including pyloric stenosis and intussusception. Dr. Hirschsprung indicated guidelines for management of a broad spectrum of pediatric diseases, including contributions in the area of teratology and clinical dysmorphology[4]. These contributions are now part of the didactic activity and scientific investigation of innumerable professors and researchers of Pediatrics, Pediatric Surgery, and Pediatric Pathology of the 21st century. His legacy to children is marvelous. He participated actively to the building of the children's hospital and his dedication to children was adamant and unbending. Queen Louise wanted the wall spaces above doors to harbor biblical quotations for the edification of the sick children, but Dr. Hirschsprung considered more appropriate to give the children an environment that could bring some quietness. In consideration of the sensibility of the children, he firmly refused the holy quotations and suggested colorful and beautiful wall decorations of animals and flowers, which in the end were well accepted by the Danish crown to be inserted in the wall spaces above doors.

BEYOND THE HIRSCHSPRUNG'S DISCOVERY

Recently, the interest has focused on the diagnosis of HSCR mainly because of the jeopardy of methods used to make the diagnosis and their accuracy. Being a genetic disease quite diverse, main topics on HSCR involve, indeed, the investigation of the best diagnostic marker for HSCR and changes that may take place during ganglion cell maturation. In the setting of the diagnosis, we recently published a systematic review on HSCR trying to identify the value of single methods to ascertain currently this diagnosis[19]. HSCR is now known as the most common cause of neonatal lower intestinal obstruction occurring in 1:5000 live birth newborns. HSCR involves in about three quarters of cases male children, and its incidence is variable according to ethnics. The caudal migration of the primordial neural crest cells starts at the upper end of the gut following progressively the vagal fibers distally. A delay or arrest in this migration induces failure of the neural crest cells to reach the distal bowel with consequent congenital abnormal nerve innervation of the bowel. There is a caudo-cranial severity, which means from the internal anal sphincter extending proximally for a variable length of gut. Pathophysiologically, there is a proximal intestine, which is dilated and progresses to an abrupt or, alternatively, gradual transition to a normal calibrated distal bowel. This distal intestinal segment shows typically a funnel like or cone shaped zone in between (the so-called "transition zone"). Moreover, there is a proximal muscle hypertrophy. This anatomic and prominent feature of the colon, located proximal to the aganglionic segment, represents undoubtedly an effort to overcome the partial obstruction. The bowel becomes distended with thickening of its wall, and the degree of dilatation and hypertrophy depends intricately upon both the time and degree of obstruction and obviously, indirectly, to the age of the patient. Clinical presentation settings include failure to pass meconium within the 24-h of life considering that 98% of newborns pass meconium in less than 24-h of age, neonatal intestinal obstruction syndrome (abdominal distension, refusal to feed, and vomiting of bilious type), and recurrent enterocolitis (mainly infants less than 3 mo of life), toxic megacolon, spontaneous perforation, and chronic constipation with persistent failure to thrive. Toxic megacolon includes fever, abdominal distension, bile stained vomiting, explosive diarrhea, dehydration, and shock. History includes failure to pass meconium, painless abdominal distension, and, obviously, constipation. Physical examinations of children with HSCR includes enlarged abdominal circumference with numerous fecal masses. Digital or post-evacuation examinations reveal hypertonic anal sphincter, typical empty rectum, and hard fecal mass. Radiology (plain abdominal X-ray both erect and supine as well as contrast enema) typically shows narrow distal segment, funnel-shaped dilatation characteristically localized at level of transition zone as well as marked dilatation of the proximal colon. Moreover, a poor emptying of barium throughout the colon in 24-h delayed films is also found. A differential diagnosis of "psychogenic" stool is requested and, in

Table 1 Differential diagnosis of chronic pseudo-obstruction of the child and young adult

Organic colorectal diseases	
Pseudotumors (*e.g.*, rectocele)	
Neoplasms (both benign and malignant epithelial and mesenchymal)	
Strictures (postinflammatory, postischemic, posttransplant, *etc.*)	
	Apostinflammatory (*e.g.*, Crohn's disease)
	Postischemic (*e.g.*, necrotizing enterocolitis)
	Graft *vs* host disease
	Others
Dysmetabolism	
Severe hypothyroidism	
Calcium imbalance (hypercalcemia)	
Potassium imbalance (hypokalemia)	
Diabetes mellitus (autonomic neuropathy)	
Autonomic Enteric Neuro-Myopathies	
Scleroderma or systemic sclerosis	
Amyloidosis or familial mediterranean Fever	
Sarcoidosis	
Central nervous system - pathologies	
Cerebral palsy	
Spinal cord injury	
Demyelinizating disease in youth (*e.g.*, multiple sclerosis)	
Iatrogenic Chronic Pseudo-Obstruction (drugs-related)	
	Anticholinergics, antidepressants (especially tricyclic antidepressants), antipsychotics, calcium-channel blockers, aluminum (antacids), narcotics and narcotic-related drugs

Drugs-related chronic pseudo-obstruction may have different and multiple etiologies and accidental intoxication should also be taken into account.

this latter case, the barium generally collects in the distal recto-sigmoid colon. Electromanometry shows absence of the recto-anal inhibitory reflex (RAIR) when the rectum is distended. RAIR is defined as the reflex of relaxation of the internal anal sphincter following rectal distension (balloon). RAIR (+) means normal, while lack of RAIR, RAIR (-), means HSCR. Bedside or outpatient procedures seem to give no complications. The test is unreliable if the gestational age plus post-natal age is less than 39 wk and birth weight is less than 2.7 kg. However, if, at neonatal age, electromanometry is useless, it represents a good screening tool in infancy and childhood. Ultrasonography is important to rule out associated anomalies and a genetic counselling may be considered appropriate according to the familiarity and the phenotype of the patients affected with HSCR. Rectal biopsy is the definitive diagnostic test showing absence of ganglion cells, presence of nerve hypertrophy, and increased acetyl-cholinesterase activity. It may include either a suction mucosal biopsy (at different levels) or a full thickness biopsy. Suction, transmural, and jumbo biopsies are the usual biopsies taken in an infant with severe constipation. It is a general opinion that pediatricians play a major role in diagnosing HSCR and dysmorphic features remain important landmarks that need to be identified first by clinical pediatricians and, later discussed with clinical geneticists. Typically, HSCR is clinically identified as a solitary gastro-intestinal anomaly in a full term, otherwise healthy newborn or infant, but associated anomalies do occur in about 1/5 of cases, including uro-genital system (11%), cardio-vascular system (6%), gastro-intestinal system (6%), and other systemic congenital defects (8%). In as many as 1/10 of children with HSCR, the condition of prematurity has been reported. Trisomy 21 syndrome (Down syndrome) occurs in approximately 1/20 of children with HSCR. Astoundingly, the work of the pathologists is impressive and their criteria for diagnosing HSCR are quite straightforward and easy to follow in classic cases as indicated above. Figure 1 shows mature and immature ganglion cells of the submucosus plexus of a rectal suction biopsy performed at 2 cm above the pectinate line in a 3-mo-old infant and a newborn with severe constipation. It is important to highlight that not all-severe constipation mean automatically HSCR. Table 1 indicates a differential diagnosis of chronic pseudo-obstruction of the child and young adult. Figures 2 and 3 show the absence of ganglion cells and the hypertrophy of nerve fibers in an infant with HSCR operated with pull-through procedure. Both the lack of ganglion cells and the hypertrophy of nerve fibers are pathologic landmarks of HSCR.

CONCLUSION

Several loci seem to be involved in HSCR. Nevertheless, the molecular-biologic basis of this intriguing gastro-intestinal disorder remains yet essentially unknown. In our working group at the Stollery Children's Hospital, we consider that the study of combined properties of modules linking functionally related genes may shed light on an efficient and effective platform of transcriptomics that can target rare diseases. A "Pathway-Based Analysis" may help to confirm a strong association bet-

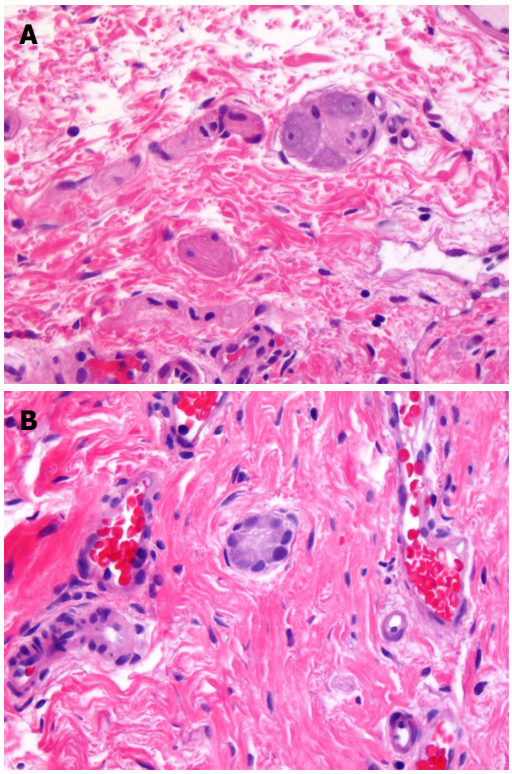

Figure 1 Mature ganglion cells (A) and immature ganglion cells (B). A: Mature ganglion cells; B: Immature ganglion cells (Hematoxylin and Eosin staining, magnification: 400 × for both photographs).

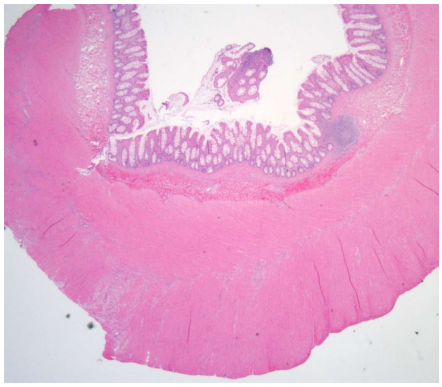

Figure 2 Hirschsprung's disease showing hypertrophy of nerve fibers.

ween genes and pathways related to signal transduction and its regulation of the enteric nervous system[20,21]. Most recently, some potential molecular markers, *e.g.*, targeting variations of *PTCH1* gene, have been reported to be useful for early diagnosis of HSCR in the Han Chinese population[22]. The *WNT8A* gene has also been involved in the susceptibility to HSCR and may play an important role in the occurrence and development of HSCR[23].

In summary, HSCR is still a disease with many unclear aspects. HSCR is due to migration failure of neural crest cells. Definitive anatomo-pathologic finding that identifies HSCR is the absence of ganglion cells in both the submucosal and myenteric plexuses. Thus,

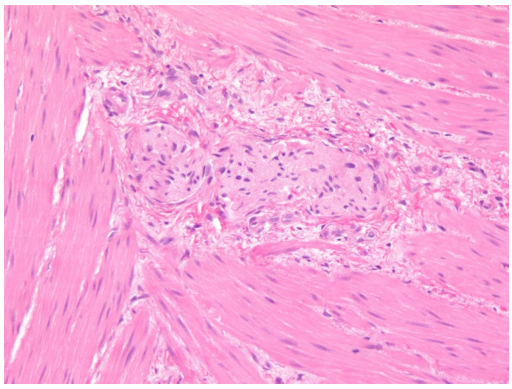

Figure 3 Hirschsprung's disease showing hypertrophy of nerve fibers and lack of ganglion cells.

rectal biopsy is definitive in most cases. In doubt, ancillary techniques may be applied, but a re-biopsy is the best choice[19]. If research is supported, signaling pathways may be identified that may play a diagnostic other than a mechanistic role. Despite genes and pathways identified in patients at the beginning of the 21st century there is still a lot to do investigating etiology, pathogenesis, and treatment modalities of this frightful disease.

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MINIREVIEWS

Acute encephalitis and encephalopathy associated with human parvovirus B19 infection in children

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Abstract

Reports of neurologic manifestations of human parvovirus B19 (B19) infection have been on the rise. Acute encephalitis and encephalopathy is the most common, accounting for 38.8% of total B19-associated neurological manifestations. To date, 34 children with B19 encephalitis and encephalopathy have been reported, which includes 21 encephalitis and 13 encephalopathy cases. Ten (29%) were immunocompromised and 17 (39%) had underlying diseases. Fever at the onset of disease and rash presented in 44.1% and 20.6% of patients, respectively. Neurological manifestations include alteration of consciousness occurred in all patients, seizures in 15 (44.1%) patients, and focal neurologic signs in 12 (35.3%) patients. Anemia and pleocytosis in cerebrospinal fluid (CSF) occurred in 56.3% and 48.1% of patients, respectively. Serum Anti-B19 IgM (82.6%) and CSF B19 DNA (90%) were positive in the majority of cases. Some patients were treated with intravenous immunoglobulins and/or steroids, although an accurate evaluation of the efficacy of these treatment modalities cannot be determined. Nineteen (57.6%) patients recovered completely, 11 (33.3%) patients had some neurological sequelae and 3 (8.8%) patients died. Although the precise pathogenesis underlying the development of B19 encephalitis and encephalopathy is unclear, direct B19 infection or NS1protein of B19 toxicity in the brain, and immune-mediated brain injuries have been proposed.

Key words: Encephalitis; Neurological manifestation; Human parvovirus B19; Encephalopathy; Pathogenesis; Complication

Core tip: Reports of acute encephalitis and encephalopathy associated with human parvovirus B19 (B19) infection have recently increased. B19 DNA has been detected in cerebrospinal fluid samples in approximately 4% patients with etiologically undiagnosed encephalitis. Some patients were treated with intravenous immunoglobulins and/or steroids. More than half of the patients with B19 encephalitis and encephalopathy recovered completely, but some patients developed severe neurological sequelae or died. Although the precise pathogenesis underlying the development of B19

encephalitis and encephalopathy is unclear, direct B19 infection or NS1 protein of B19 toxicity in the brain, and immune-mediated brain injuries have been proposed.

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INTRODUCTION

Human parvovirus B19 (B19) is a member of the erythrovirus genus in the family Parvoviridae[1], first discovered by Cossart *et al*[2] in 1975. B19 is a small, single-stranded DNA virus that binds the cellular receptor P antigen on erythrocytes[3]. The viral genome encodes only three proteins of known function, including nonstructural protein 1 (NS1), and two viral capsid proteins, viral protein 1 (VP1) and viral protein 2 (VP2)[1]. NS1 promotes multiple replicative functions and is cytotoxic to host cells[1]. Since Shneerson *et al*[4] reported the first symptomatic febrile patients with B19 infection in 1980, various clinical manifestations of B19 have been identified. These include erythema infectiosum (EI)[5], arthropathy, non-immune hydrops fetalis and congenital anemia, thrombocytopenia, hepatitis, myocarditis and neurologic diseases in healthy hosts, chronic pure red cell aplasia in immunodeficient hosts, and transient aplastic crisis in patients with increased red cell turnover[1,6]. Of these, neurologic manifestations of B19 infection have been increasingly reported, especially in children[7,8].

B19-associated neurologic manifestations include encephalitis, encephalopathy, meningitis, cerebellar ataxia, transverse myelitis, stroke, and peripheral neuropathy[7,8]. Of these, encephalitis and encephalopathy are the most common with 38.8% of total B19-associated neurological manifestations[8]. Furthermore, recent reports reveal that specific forms of encephalopathy also are associated with B19 infection, which include chorea encephalopathy[9-11], mild encephalitis/encephalopathy with reversible splenial lesion (MERS)[12] and posterior reversible encephalopathy syndrome (PRES)[13]. The following is a review of B19 associated encephalitis and encephalopathy (B19 encephalitis and encephalopathy) in children.

DEFINITION OF B19 ENCEPHALITIS AND ENCEPHALOPATHY

Because encephalitis is defined as inflammation of the brain parenchyma, pathologic examination of brain tissue (brain biopsy) is necessary for its diagnosis. However, brain biopsy is rarely done premortem with its potential risk for patients[14]. In this review, we used the Pillai encephalitis definitions[15], as follows. Encephalopathy was defined as an altered or reduced level of consciousness and a change in personality or behavior or confusion lasting ≥ 24 h. Encephalitis was defined as an acute encephalopathy with 2 or more of the following: fever ≥ 38 ℃, seizures or focal neurologic signs, cerebrospinal fluid (CSF) pleocytosis (≥ 5 white blood cells/μL), electroencephalographic (EEG) findings consistent with encephalitis, and neuroimaging suggestive of encephalitis[15]. B19 infection was based on the detection of either B19 DNA or anti-B19 IgM specific antibodies in serum or CSF[8]. Two patients with encephalitis and encephalopathy without laboratory tests confirming B19 infection were included in this review on the basis of clinical presentation of EI[16,17].

EPIDEMIOLOGY

Balfour *et al*[16] reported an 8-year-old boy who developed encephalitis associated with EI in 1970. Seven years later, Breese *et al*[17] reported a 9-mo-old boy with severe encephalopathy during the course of EI who developed permanent neurologic sequelae. In the era of molecular and serological diagnostics for B19 infection, cases of encephalopathy and B19 DNA in sera and in CSF are accruing[18,19]. To date, 34 patients less than 19 years of age with B19 encephalitis or encephalopathy have been reported (Table 1)[9-11,16-31]. This includes 21 patients with encephalitis, five with encephalopathy, four with chorea encephalopathy, three with MERS and one with PRES. Eleven patients have been reported from United Kingdom, eight from Japan, six from Jamaica, three from United States, two from Italy, two from Brazil, one from Germany and one from Turkey. The age of patients ranges from 1 to 15 years (mean of 6.7 years, median of 7 years). Fifteen patients were male, and the male to female ratio was 0.79. 24 (71%) were immunocompetent individuals, and 10 were immunodeficient. Seventeen (39%) patients had underlying diseases, including sickle cell disease, hereditary spherocytosis (HS), congenital heart diseases, acute lymphocytic leukemia, Crigler-Najar syndrome, Cockayne syndrome, Turner syndrome, and post-renal transplantation for nephropathic cystinosis[12,23-26,28,29]. One patient suffered from ulcerative colitis eight years after B19 encephalopathy[20].

Although the prevalence of B19 infection for all encephalitis and encephalopathy is unknown, two studies reported that B19 DNA has been detected in CSF samples in 2 of 43 (4.7%) and 7 of 162 (4.3%) patients with etiologically undiagnosed encephalitis[22,23].

CLINICAL MANIFESTATIONS

Fever at the onset of diseases presented in 15 of 34 (44.1%) patients (Table 2). Rash was reported in seven (20.6%) patients[13,16,17,19,21,29,31]. Rash developed before the onset of CNS manifestations in two patients, simultaneously with the onset in two patients, and

Table 1 Basic characteristics of children with B19 encephalitis and encephalopathy

Case No.	Ref.	Age	Gender	Diagnosis	Underlying disorders	Immunodeficiency
1	[16]	8 yr	M	Encephalitis		-
2	[17]	9 mo	M	Encephalitis		-
3	[19,20]	5 yr	F	Encephalitis		-
4	[23,24]	2 mo	F	Encephalitis		-
5	[23,24]	2 yr	M	Encephalitis	Acute lymphocytic leukemia	+
6	[23,24]	2 yr	F	Encephalitis		-
7	[23,24]	6 yr	F	Encephalitis	Cockayne syndrome	+
8	[23,24]	9 yr	M	Encephalitis		-
9	[23,24]	13 yr	F	Encephalitis	Crigler-Najar syndrome	-
10	[23,34]	13 yr	M	Encephalitis		-
11	[23,34]	15 yr	F	Encephalitis		-
12	[23,24]	1 d	F	Encephalitis	Necrotizing enterocolitis Patent ductus arteriosus Respiratory distress syndrome	+
13	[23,24]	1 d	F	Encephalitis	Ventricular septal defect Atrial septal defect Patent ductus arteriosus Turner syndrome Obstructive jaundice	+
14	[25]	8 yr	F	Encephalitis	Sickle cell disease Nephrotic syndrome	+
15	[25]	8 yr	M	Encephalitis	Sickle cell disease Nephrotic syndrome	+
16	[25]	12 yr	F	Encephalitis	Sickle cell disease Aplastic crisis	+
17	[25]	14 yr	M	Encephalitis	Sickle cell disease Aplastic crisis	+
18	[27]	10 yr	F	Encephalitis		-
19	[28]	9 yr	M	Encephalitis	Nephropathic cystinosis Renal transplant	+
20	[30]	4 yr	F	Encephalitis		-
21	[31]	5 yr	F	Encephalitis and cerebellitis		-
22	[18]	8 yr	F	Encephalopathy		-
23	[19]	5 yr	F	Encephalopathy		-
24	[21]	5 yr	M	Encephalopathy		-
25	[22]	4 yr	M	Encephalopathy	Prader-Willi syndrome	-
26	[26]	13 yr	F	Encephalopathy	Sβ + thalassemia	+
27	[9]	8 yr	F	Chorea encephalopathy		-
28	[10]	1 yr	M	Chorea encephalopathy		-
29	[11]	1 yr	M	Chorea encephalopathy		-
30	[11]	1 yr	F	Chorea encephalopathy		-
31	[29]	9 yr	F	MERS	Hereditary spherocytosis	-
32	[12]	11 yr	M	MERS	Hereditary spherocytosis	-
33	[12]	10 yr	M	MERS	Hereditary spherocytosis	-
34	[13]	9 yr	F	PRES	Acute glomerulonephritis	-

MERS: Clinically mild encephalitis/encephalopathy with reversible splenial lesion; PRES: Posterior reversible encephalopathy syndrome; F: Female; M: Male.

after the onset in three patients. All patients with rash had normal immune function. Three (8.8%) patients complained of arthralgia.

Acute kidney injury occurred in three patients with sickle cell disease, and in one patient with Cockayne syndrome as a part of multiple organ failure[23-25]. Patients experiencing acute B19 infection sometimes develop renal complications[32,33]. These include acute glomerulonephritis, thrombotic microangiopathy and Henoch-Schönlein purpura nephritis, probably due to direct cytopathic effects on glomerular epithelial cells and endothelial cells, and an immune complex mediated mechanism[32,33].

One of the neurological manifestations was a reduced level of consciousness, which occurred in all patients. Seizures developed in 15 (44.1%) patients and two had statue epilepticus[19,27]. Twelve (35.3%) patients exhibited focal neurologic signs (Table 2), which included neurogenic bladder, chorea, loss of vision, ataxia, dysarthria, hemiparesis, and focal seizures[9-11,13,16,22,23,25,30,31].

LABORATORY DATA

B19 infection causes various blood diseases and cytopenias affecting several blood cell lineages, such as red cell aplasia, pancytopenia and hemophagocytic lymphohistiocytosis (HLH)[34]. In patients with B19 encephalitis and encephalopathy, anemia developed in

Table 2 Clinical manifestations of children with B19 encephalitis and encephalopathy

Case No.	B19 related symptoms			Neurological manifestations			Complications	Sequelae or death
	Fever	Rash	Arthralgia	Unconsciousness	Seizure	Focal neurologic signs		
1	+	+	+	+	-	+Neurogenic bladder		Left weakness and clonus
2	+	-	-	+	+	-		Psychomotor retardation
3	+	+	-	+	+	-	Status epilepticus	Epilepsy Mental retardation
4	+	-	-	+	+	-		-
5	+	-	-	+	-	-		Cognitive deficit
6	+	-	-	+	-	+Ataxia		-
7	-	-	-	+	-	-	Multiple organ failure Acute renal failure	Died
8	-	-	-	+	+	-		Cognitive deficit Epilepsy
9	-	-	-	+	-	-		Not determined
10	-	-	-	+	-	+ Right hemiparesis Ataxia		-
11	-	-	-	+	-	-		Cognitive deficit
12	-	-	-	+	-	-		Died
13	-	-	-	+	-	-		Died
14	-	-	-	+	+	+ Right hemiparesis Transient blindness	Acute renal failure Aplastic crisis Acute chest syndrome	-
15	-	-	-	+	+	+ Cortical blindness	Acute renal failure Aplastic crisis Acute chest syndrome	-
16	+	-	-	+	+	+ Focal seizures	Acute renal failure Acute chest syndrome	-
17	+	-	-	+	+	-		-
18	+	-	-	+	+	-	Status epilepticus	Epilepsy
19	-	-	+	+	+	-		-
20	+	-	-	+	+	+ Cerebellar syndrome		Cerebellar syndrome
21	+	+	-	+	+	-		Cerebellar syndrome
22	-	-	+	+	+	-		-
23	-	+	-	+	+	-		-
24	-	-	-	+	-	-	Pancytopenia Liver dysfunction	-
25	-	-	-	+	-	-		Spastic quadriplegia
26	+	-	-	+	-	-	Aplastic crisis	-
27	-	-	-	+	-	+ Chorea		-
28	-	-	-	+	-	+ Chorea		-
29	-	-	-	+	+	+ Left hemiparesis Athetosis		-
30	-	-	-	+	+	+ Left hemiparesis Choreo-athetosis		Global developmental delay
31	+	+	-	+	-	-	Aplastic crisis Pancytopenia	-
32	+	-	-	+	-	-	Aplastic crisis HLH Pancytopenia	-
33	+	-	-	+	-	-	Aplastic crisis HLH Pancytopenia	-
34	+	+	-	+	+	+ Loss of vision	Transient SLE symptoms Hypertension	-

HLH: Hemophagocytic lymphohistiocytosis; SLE: Systemic lupus erythematosus.

18 of 32 (56.3%) patients (Table 3). Aplastic crisis was recorded in five patients with sickle cell disease and three patients with HS. Pancytopenia and HLH occurred in 4 patients and 2 patients, respectively.

CSF examination showed pleocytosis in 13 of 27 (48.1%) patients and increased protein levels in 8 of 20 (40%) patients (Table 3).

Anti-B19 IgM antibodies and B19 DNA were detected in the sera of 19 out of 23 (82.6%) patients and 12 out of 20 (60%) patients, respectively. Anti-B19 IgM antibodies and B19 DNA were detected in the CSF of two out of 11 (18.2%) patients and 18 out of 20 (90%) patients, respectively (Table 3). These results suggest that serum anti-B19 IgM and CSF B19 DNA examinations are useful tools for diagnosing of B19 infection in patients with encephalitis and encephalopathy.

Table 3 Laboratory data and treatment of children with B19 encephalitis and encephalopathy

Case No.	Anemia	Serum B19 markers			CSF B19 markers			CSF		IVIG and/or steroids
		IgM	IgG	DNA	IgM	IgG	DNA	Pleocytosis	Increased protein	
1	-							+	-	-
2	-							-	+	-
3	-	+	+	+			-	+	+	-
4		-	-	-	-	-	+	-		IVIG
5					+	-	-	-	-	-
6	+				-	-	+	-	-	-
7	-				-	-	+			-
8	+	+	-	+	-	-	+			-
9	-						+			-
10	-						+	-		-
11	-						+	+		-
12	+	+	-	+	+	-	+			-
13	+	-	-	-	-	-	+			-
14	+	+	+	+				+		-
15	+	+	+	+				+		-
16	+	+	+	+				+		-
17	+	+	+	+				+		-
18	-	+	-		-	-		+	+	IVIG and steroids
19	+	+		+				+	+	-
20	-	-	-	+	-	-	+	+	-	IVIG and steroids
21	-	+	+	+			+	+	+	Steroids
22	+	+		+			+	-		-
23	-	+	+	+			+	-	+	-
24	+	+	+	+			+	-	+	-
25	-	+	+	+	-	-	+	+	+	-
26	+	+	+	-	-	-		-	-	Steroids
27	+			+			+	-	-	-
28	-	+	+				+	-	-	IVIG and steroids
29	-	+	-							-
30	+	+	-					+	-	-
31	+	-	+	+			+	-	-	Steroids
32	+							-	-	IVIG
33	+							-	-	IVIG
34	+	+	+	+			+	-	-	-

IVIG: Intravenous immunoglobulin; CSF: Cerebrospinal fluid.

IMAGING STUDIES AND EEG

Six of 13 (46.2%) patients had abnormal brain computed tomography findings, which included an enlarged ventricle, brain edema, frontal and occipital vasogenic swelling, and lesions in right parietal, temporal or occipital areas[13,22,23,25]. Brain magnetic resonance images showed abnormal findings in 10 of 15 (66.7%) patients. These findings included high signal intensity in the white matter[13,23,26,30], basal ganglia, and cerebellum in T2 weighted images, high signal intensity in the splenial lesion of corpus callosum in diffusion-weighted images or T2 weighted images, and enlarged ventricles[12,23,26,29,31].

EEG revealed abnormal findings in 15 of 19 (78.9%) patients, which included diffuse or focal slowing of the background activity, encephalopathic changes or epileptic abnormality[10,12,16,17,24,26,27,29,30].

TREATMENT

As discussed elsewhere, direct B19 infection or NS1 toxicity in the brain, and immune-mediated brain injuries have been proposed as pathogenic causes that result in the development of B19 encephalitis and encephalopathy[7,8,35]. Some patients with B19 encephalitis and encephalopathy were treated with intravenous immunoglobulin (IVIG) and/or steroids (Table 3). IVIG and steroids are often used in post-infectious or immune-mediated encephalitis as immuno-modulatory therapies[36]. In addition, IVIG is used for many clinical conditions associated with B19 infection such as chronic anemia, because immunoglobulin preparations are a good source of neutralizating antibodies against B19[6].

Both IVIG and steroids were administrated to three patients[10,25,30], two of them showing neurologic sequelae (epilepsy and cerebellar syndrome). Three patients were treated with IVIG only, and they all recovered completely. Steroids only were administered to two patients, one of whom exhibited neurological sequelae (cerebellar syndrome)[12,23,26,31]. Since there have been only a few reports of B19 encephalitis and encephalopathy with IVIG and/or steroids, an accurate evaluation of the efficacy of these treatment cannot be determined. However, due to the lack of other effective treatments for B19 encephalitis and encephalopathy, Barah *et al*[8] recommended that treatment of severe cases might benefit from a combined regimen of IVIG and steroids.

OUTCOME

Nineteen of 33 (57.6%) patients recovered completely from neurologic disturbances, whereas 11 (33.3%) patients had some neurological sequelae and three (8.8%) patients died (Table 2). Patients with B19 encephalitis had worse prognosis (8 of 20 patients had neurological sequelae, and 3 patients died) than patients with B19 encephalopathy, MERS or PRES (2 of 13 patients had neurological sequelae, and no patient died). Neurological sequelae included psychomotor retardation[11,17,19], cognitive deficit, epilepsy, cerebellar syndrome, hemiparesis and spastic quadriplegia[16,19,22,23,27,30,31]. All of the patients that died were immunodeficient (two neonates and one patient with Cockayne syndrome)[23].

SPECIFIC FORMS OF B19 ENCEPHALOPATHY

Recent reports have revealed that specific forms of encephalopathy are associated with B19 infection, which include chorea encephalopathy, MERS and PRES[9-13].

Chorea encephalopathy

Chorea encephalopathy is characterized extrapyramidal features in the context of self-limiting neurological illness with CSF oligoclonal IgG bands, probably caused by immune-mediated (possibly autoantibody) pathogenic mechanisms[37]. Four patients with B19 associated chorea encephalopathy have been reported to date[9-11]. Grillo *et al*[38] pointed out the clinical similarity between chorea encephalopathy and anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, which is an autoimmune encephalitis caused by autoantibodies against the NR1 subunit of NMDAR[39], and suggested that some cases of anti-NMDAR encephalitis could be triggered by B19.

Clinically mild encephalitis/encephalopathy with reversible splenial lesion

Clinically MERS is clinically mild encephalitis/encephalopathy characterized by an MRI finding of a reversible lesion with reduced diffusion in the corpus callosum, first proposed by Tada *et al*[40] in 2004. Delirious behavior, impaired consciousness and seizure often occur as neurological symptoms, all of which completely recover within a month[41]. Although a majority of patients with MERS are associated with viruses or bacteria[41], some cases of Kawasaki disease associated with MERS have been reported[42]. The precise pathogenesis of MERS is unknown, intramyelinic edema, interstitial edema in tightly packed fibers and transient inflammatory infiltrate have been postulated[41].

Three patients with B19-associated MERS have been reported[12,29]. Oshima *et al*[29] reported a 9-year-old girl with HS developed MERS and aplastic crisis. They followed the plasma and CSF concentrations of B19 by real-time polymerase chain reaction and found that the symptoms of encephalopathy had occurred at the peak viral load, suggesting that B19 MERS might occur as a result of direct B19 invasion. Suzuki *et al*[12] also reported that two brothers with HS developed B19 MERS and HLH. HLH is due to dysregulated lymphocyte activation, which leads to macrophage hyperactivation and over-expression of pro-inflammatory cytokines, including IL-6[43]. HLH has been reported in 28 patients with B19 infection, most of whom had HS as an underlying disease[43]. Moreover, increased IL-6 levels in CSF have been reported in patients with MERS[44,45]. These findings suggest that B19-induced IL-6 overproduction may lead to MERS and HLH in patients with HS[12].

PRES

PRES is characterized clinically by headaches, impaired consciousness, visual disturbances and seizures, and radiologically by posterior (parieto-occipital) imaging changes predominantly occurring in the sub-cortical white matter[46]. Although the pathophysiology underlying the development of PRES is multifactorial, hypertension plays a major role in the development of PRES through disruption of autoregulation in cerebral blood vessels[46].

Cugler *et al*[13] reported a 9-year-old girl with severe acute glomerulonephritis and PRES associated with B19 infection mimicking systemic lupus erythematosus. Only adequate control of blood pressure and diet led to complete resolution of the patient's symptoms.

PATHOGENIC MECHANISMS

Although the precise pathogenesis underlying the development of B19 encephalitis and encephalopathy is unclear, direct B19 infection or NS1 toxicity in the brain, and immune-mediated brain injuries that include cytokine dysregulation and autoantibody production directed against brain antigens, have been proposed[7,8,35].

Direct B19 infection or NS1 toxicity

Only erythroid progenitor cells are permissive for B19 replication because these cells have both high concentrations of P blood type antigen, the receptor for B19[3] and $\alpha5\beta1$ integrin, the co-receptor for B19[47]. P antigen is also expressed on other cell types including megakaryocytes, granulocytes, lung, heart, liver, kidney, endothelium, and vascular smooth muscle[48]. However, P antigen is necessary for B19 binding but not sufficient for virus entry into cell, which requires $\alpha5\beta1$ integrin as a cellular co-receptor[47]. Because non-erythroid progenitor cells with P antigen do not have $\alpha5\beta1$ integrin, B19 can bind, but cannot infect them. However, the NS1 exerts a cytotoxic effect on the cells it binds without any B19 replication or virion accumulation[49,50]. Therefore, NS1 may directly damage the cerebrovascular endothelium during B19 infection.

B19 DNA has been detected in the brain of two intrauterine deceased fetuses in mothers with recent B19 infection[51,52]. Hobbs *et al*[53,54] reported that B19

DNA was detected in 42% of dorsolateral prefrontal cortex and in 100% of cerebella, of postmortem samples taken from 104 subjects without recent acute B19 infection. Manning *et al*[55] also reported that B19 DNA was detected in 69% of frontal or occipital lobe of postmortem brain tissue samples taken from 29 subjects without recent acute B19 infection.

Although B19 DNA was frequently detected in the CSF of children with B19 acute encephalitis and encephalopathy, B19 detection in the brain has never been reported in children[35]. Kerr *et al*[24] reported that postmortem brain tissue from a child with B19 acute encephalitis was negative for B19 in using *in situ* hybridization method. Skaff *et al*[56] also reported negative immunohistochemistry results for detecting B19 in brain biopsy tissue taken from an immunocompetent adult patient with B19 encephalitis. Meanwhile, B19 DNA was detected in brain biopsy tissues taken from adult patients with B19 encephalitis by PCR[57,58]. There is still controversy regarding whether B19 has direct infection or NS1 toxicity in the brain cells or not[59].

Cytokines dysregulation

B19 infection induces cytokine dysregulation. Wagner *et al*[60] studied concentrations of interleukin (IL)-1β, and IL-6 concentrations and interferon (INF)-γ messenger RNA (mRNA) in peripheral blood mononuclear cells (PBMC) from patients with acute B19 infection and reported that these cytokine genes were activated in PBMC, suggesting systemic monocyte and T cell activation. Moffatt *et al*[61] demonstrated that IL-6 production caused by the B19 NS1 protein was mediated by an NF-κB binding site in the IL-6 promotor region. Kerr *et al*[62,63] reported that serum IL-6, tumor necrosis factor (TNF)-α, IL-1β, IL-4, IL-8, INF-γ, macrophage chemoattractant protein-1(MCP-1), granulocyte-monocyte colony stimulating factor (GM-CSF) levels were increased during acute B19 infection.

Kerr *et al*[24] reported that increased levels of TNF-α, INF-γ, IL-6, INF-γ, GM-CSF and MPC-1 in the serum and CSF of patients with B19 encephalitis and suggested that over-production of inflammatory cytokines might play a role in B19 encephalitis.

Autoantibody production

B19 infection often develops clinical features similar to autoimmune disease and has been associated with the production of antibodies against self-antigens, including nuclear antigens, rheumatoid factor, neutrophils cytoplasmic antigens, and phospholipids[64,65]. Molecular similarities between host and B19 proteins and the induction of inflammatory cytokine production encourage the development of autoimmune reactions during B19 infection[64,65]. B19 chorea encephalitis has been suggested to be caused by autoimmune reactions against brain autoantigens[38].

CONCLUSION

Acute B19 encephalitis and encephalopathy are the most common B19-associated neurological manifestations. Some patients were immunocompromised or had underlying diseases. Impaired consciousness, seizures and focal neurologic signs are the main neurological features. Serum Anti-B19 IgM and CSF B19 DNA examinations are useful tools for diagnosing B19 infection in patients with B19 encephalitis and encephalopathy. Two studies reported that B19 DNA has been detected in CSF samples in approximately 4% of patients with etiologically undiagnosed encephalitis. Serum Anti-B19 IgM and CSF B19 DNA should be examined in patients with etiologically undiagnosed encephalitis and encephalopathy. Some patients with B19 encephalitis and encephalopathy were treated with IVIG and/or steroids; however, an accurate evaluation of the efficacy of these treatment modalities cannot be determined. Although more than half of B19 encephalitis and encephalopathy patients recovered completely, some patients developed severe neurological sequelae or died. While the precise pathogenesis underlying the development of B19 encephalitis and encephalopathy is unclear, direct B19 infection or NS1 toxicity in the brain, and immune-mediated brain injuries have been proposed.

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MINIREVIEWS

Use of corticosteroids during acute phase of Kawasaki disease

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Abstract

In spite of initial intravenous immunoglobulin (IVIG) treatment, a significant number of patients are unresponsive to it and are at a higher risk for coronary artery lesions. Corticosteroids have been used as a secondary drug or used in combination with IVIG. Three options of using corticosteroids for the treatment of patients during the acute phase of Kawasaki disease, have been considered. The first is their use exclusively for patients unresponsive to IVIG treatment. The second is their use in combination with IVIG as the routine first line therapy for all patients. The last is the use in the combination as the first line therapy for selected patients at a high risk being unresponsive to initial IVIG. However, it is uncertain that the corticosteroids as the second line treatment are better than the additional IVIG in patients unresponsive to initial IVIG. The combination of corticosteroids and IVIG as the routine first line therapy also have not enough evidences. The last option of using corticosteroids - the combination of corticosteroids and IVIG in patients at high risk of unresponsiveness, is a properly reasonable treatment strategy. However, there have been no globally standardized predictive models for the unresponsiveness to initial IVIG treatment. Therefore, future investigations to determine the best predictive model are necessary.

Key words: Kawasaki disease; Methylprednisolone; Corticosteroids; Coronary aneurysm; Immunoglobulins; Prednisolone; Fever

Core tip: In spite of initial intravenous immunoglobulin (IVIG) treatment, a significant number of patients are unresponsive to it and are at a higher risk for coronary artery lesions. Corticosteroids have been used as a secondary drug or used in combination with IVIG. There are several options of using corticosteroids for the treatment of patients with Kawasaki disease during the acute phase. A thorough review of the use of corticosteroids in acute phase Kawasaki disease was performed in this paper.

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INTRODUCTION

Kawasaki disease is an acute, self-limited systemic type of vasculitis which occurs predominantly in young children. Kawasaki[1] firstly reported it in 1967, and it is now acknowledged as a common acquired heart disease of children in many developed countries. The etiology of Kawasaki disease is currently unknown. It is a reasonable open hypothesis that Kawasaki disease is caused by an unidentified microorganism that induces striking immune perturbations in genetically susceptible individuals. Although the efforts to find a causative microorganism have failed[2-4], the suspicion of an association between some unidentified microorganism and Kawasaki disease remains[4-7]. Investigations to identify a genetic susceptibility locus in Kawasaki disease also have been performed recently[8-10]. Several institutes had cooperated and reported a result regarding the genetic susceptibility of Kawasaki disease[11]. A recent review[12] further explains the related genetic studies. The standard first line therapies during the acute phase are an intravenous infusion of immunoglobulin (IVIG) and the administration of a high dose of aspirin[13]. Corticosteroids were used as the first line therapy before Kato *et al*[14] suggested the possibility of an aggravation of coronary artery lesions caused by them. Another report[15] to the contrary was quieted because the strong therapeutic efficacy of IVIG was reported in 1984[16]. More than 10 years after the introduction of IVIG, there were reports of the successful therapeutic application of corticosteroids for children with Kawasaki disease unresponsive to initial IVIG treatment in whom neither significant aggravation of coronary artery lesions nor other adverse effects were found after the administration of corticosteroids[17-19]. In addition, a question about the study by Kato *et al*[14], in which an information about randomization methods was not provided, was raised[17-19].

According to the guidelines of American Heart Association (AHA) in 2004, corticosteroids treatment could be recommended for children in whom $\geqslant$ 2 infusions of IVIG have been ineffective in alleviating the fever and acute inflammation[13]. However, corticosteroids have been occasionally used more early as the second line therapy for patients unresponsive to initial IVIG treatment, as the routine first line therapy in combination with IVIG, or as the first line therapy in combination with IVIG for selected Kawasaki disease patients at a high risk of unresponsiveness to initial IVIG.

THE EXCLUSIVE USE OF CORTICOSTEROIDS IN PATIENTS UNRESPONSIVE TO IVIG TREATMENT

The best second line therapeutic methods for patients unresponsive to initial IVIG treatment is still uncertain. In an investigation of 5633 patients with Kawasaki disease in the United States, methylprednisolone was used as the second line therapy in 196 patients (27.1%) among the 722 patients unresponsive to initial IVIG[20]. IVIG was the second line drug of choice in 466 patients (64.5%) in this investigation. A nationwide survey in Japan showed that steroids were used exclusively in 2.0% of hospitals and that they were used with additional IVIG in 5.1% of hospitals as the second line therapy for patients unresponsive to initial IVIG[21]. Additional IVIG exclusive administration was the second line treatment of choice in 464 hospitals (44.1%) and a combination of additional IVIG and another drug was selected in another 26% of hospitals in this survey. Therefore, the most common second line treatment is additional IVIG administration currently.

Despite initial IVIG treatment, 6.8%-38.3% of patients are unresponsive to it[22-36] and are at a higher risk for coronary artery lesions[30-33,37]. A study based on the United States national database showed that the resistance rate to initial IVIG therapy was 16.3% (hospital range 8.0%-26.8%)[36]. Authors suggested that highly variable rates among pediatric hospitals are possibly associated with variable diagnostic and treatment patterns at individual hospitals[36]. The rate of resistance to second additional IVIG only treatment was 22.2%-48.6%[18,22,24-26,38], and was not lower than that to initial IVIG treatment. Therefore, a consideration of another therapeutic option in patients unresponsive to the initial IVIG treatment is reasonable, and corticosteroids have been considered as an alternative treatment. Several reports of the use of corticosteroids as a treatment in Kawasaki disease patients unresponsive to initial IVIG treatment are presented in Table 1. In these studies, 164-411 patients with Kawasaki disease were observed, and the rate of unresponsiveness to initial IVIG was 13.4%-18.0%. The definition of unresponsiveness is varied by institute. Persistent fever was used commonly as the definition, but the cut-off level of body temperature, the duration of observation for recrudescent fever, and whether or not the CRP level was used were different for each institute. The duration of observation for recrudescent fever is 36 h according to the definition of the AHA[13], and 24 h was suggested in the recent Japanese guideline[39]. Intravenous methylprednisolone pulse therapy for 3 d was applied in all studies[22-26,40]. The dose was 30 mg/kg per day in most of studies[22-24,26,40], except in one[25]. Oral administration of prednisolone was followed after pulse therapy in 3 studies[22,24,26]. In these studies[22-25,40], a comparative analysis between corticosteroid therapy and additional IVIG treatment was performed and showed no significant difference with respect to the occurrence of coronary artery aneurysms. The frequencies of adverse effects of corticosteroids seemed to be relatively higher in reports by Miura *et al*[26,40]. They defined hypothermia as < 35.0 ℃; bradycardia as a heart rate less than the second percentile of the normal standard; hypertension as a systolic/diastolic blood pressure > 95th percentile of normal standard; hyperglycemia as a fasting blood glucose > 6.99 mmol/L; and hyponatremia as a serum Na^+ level < 135 mmol/L[26]. Although any serious adverse

Table 1 Re-treatment with corticosteroids or additional intravenous immunoglobulin in Kawasaki disease patients unresponsive to initial intravenous immunoglobulin

Ref.	No. of patients with KD	Definition of unresponsiveness: BT, obs period, other	No. of patients unresponsive to initial IVIG	Stage of CS Tx	Regimen	No. of patients re-Tx	Tx day after fever onset[1]	No. of patients with response	No. of patients with CAA	No. of patients with adverse effects
[22]	411	36 h after IVIG	63	2nd line	IVMP 30 mg/kg per day, 3 d Followed Pd	44	7 (6-8)	34	5	Hypertension 5, hypothermia 3, bradycardia 3, transient paralysis 1
					IVIG 1-2 g/kg	19	8 (5-11)	12	2	
[40]	NA	≥ 37.5 ℃, 48 h after IVIG	22	2nd line	IVMP 30 mg/kg per day, 3 d	11	NA	NA	2	Hypertension 10, hypothermia 1, bradycardia 9, hyperglycemia 6, aPTT↓ 3
					IVIG 2 g/kg	11	NA	NA	3	
[23]	164	≥ 37.5 ℃, 36-48 h after IVIG CRP↓ ≤ 50%	27	2nd line	IVMP 30 mg/kg per day, 3 d	13	7 ± 1.3	NA	0	Bradycardia 2
					IVIG 2 g/kg	14	8 ± 2.4	NA	3	
[24]	237	≥ 38 ℃, 36 h after IVIG 37.5 ℃-38 ℃ and CRP ↓ ≤ 50%	41	2nd line	IVMP 30 mg/kg per day, 3 d Followed Pd	14	7 (7-9)	7	5	Gastrointestinal bleeding 1
					IVIG 2 g/kg	27	8 (5-14)	21	7	
[25]	262	≥ 37.5 ℃, 48 h after IVIG CRP↓ ≤ 50%	35	3rd line	IVMP 20 mg/kg per day, 3 d	9	NA	NA	7	NA
					IVIG 1 g/kg	8	NA	NA	5	
[26]	412	48 h after IVIG	74	3rd line	IVMP 30 mg/kg per day, 3 d Followed Pd	21	8 (IQR 8-9)	21	2	Hypertension 17, hypothermia 3, bradycardia 17, hyperglycemia 7, serum Na↓ 4

[1]Median (range), median (IQR), or mean ± SD. IVIG: Intravenous immunoglobulin; KD: Kawasaki disease; BT: Body temperature; obs: Observation; Tx: Treatment; CS: Corticosteroids; CAA: Coronary artery aneurysm; NA: Not available; IVMP: Intravenous methylprednisolone pulse; Pd: Oral prednisolone; IQR: Interquartile range.

Table 2 Risk scoring systems for the selection of patients expected to have unresponsiveness to initial intravenous immunoglobulin treatment

	Cut-off	Points
Kobayashi score (≥ 4-5 points)[51,54,55]		
Age	≤ 12 mo	1
Days of illness at initial treatment	≤ 4	2
Platelet count	≤ 300×10^3/mm^3	1
Neutrophil	≥ 80%	2
CRP	≥ 10 mg/dL	1
AST	≥ 100 IU/L	2
Sodium	≤ 133 mmol/L	2
Egami score (≥ 3 points)[52]		
Age	≤ 6 mo	1
Days of illness at initial treatment	≤ 4	1
Platelet count	≤ 300×10^3/mm^3	1
CRP	≥ 8 mg/dL	1
ALT	≥ 80 IU/L	2
Sano score (≥ 2 points)[53]		
CRP	≥ 7 mg/dL	1
AST	≥ 200 IU/L	1
Total bilirubin	≥ 0.9 mg/dL	1

IVIG: Intravenous immunoglobulin; CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

effects of corticosteroids inducing irreversible organ damage have not been reported in these studies[22-26,40], a close monitoring of vital signs, blood glucose level, and serum electrolytes level and supportive administration of medications – heparin infusion (15-20 units/kg per hour) and H2 blocker are needed in Kawasaki disease patients receiving corticosteroids. Meanwhile, a high incidence of adrenal suppression which had resolved within 6 mo was reported in patients treated with corticosteroids[41]. In the view of the reduction of fever, corticosteroids seem to be more effective than IVIG[23,25,42]. However, Furukawa *et al*[22] warned of a tendency for recrudescent fever in patients unresponsive to corticosteroids, which could potentially delay the therapeutic decision-making process. Although Miura *et al*[26] suggested increasing the dose of oral prednisolone following third line pulse therapy for the patients with recrudescent fever, whether this strategy could be applied to second line therapy is currently unclear. In addition, the usefulness of corticosteroids in the view of their medical cost is controversial[23-25], and this issue may be dependent on the therapeutic strategy of an institute and on the health system of a society.

Table 3 Clinical and laboratory variables associated with the unresponsiveness to initial intravenous immunoglobulin treatment

	Risk factors	Ref.
Age	≤ 6-12 mo	[51,52,58]
Sex	Male	[33,61]
Duration of fever	Long duration	[58,69]
Days of illness at initial treatment	≤ 4	[31,33,51,52,58,60,71]
Recurrent Kawasaki disease	Recurrent case	[33]
Principal features/symptoms	Early appearance	[72]
	Polymorphous exanthema	[60]
	Lymphadenopathy	[32]
Other physical findings	Changes around anus	[60]
Brand of IVIG	β-propiolactone	[65,66]
Neutrophil	≥ 80%, or increased	[51,58,60,69,72]
Band form	≥ 20%, or increased	[31,34]
Hemoglobin	Anemia by age, < 10 g/dL	[31,59]
Eosinophil count	High level – good response	[68]
Platelet count	≤ $300 \times 10^3/mm^3$, or decreased	[51,52,58,72]
	≥ $530 \times 10^3/mm^3$	[32]
ESR	≥ 75 mm/h, or increased	[32,37]
CRP	≥ 7-10 mg/dL, or increased	[51-53,58-60,69]
Albumin	Lower than normal	[34,61,67]
ALT	≥ 80-84 IU/L	[52,62]
AST	≥ 100-200 IU/L, or increased	[51,53,61,72]
Total bilirubin	≥ 0.9 mg/dL, or increased	[53,62,72]
γGlutamyl transferase	≥ 60 IU/L	[31]
Lactate dehydrogenase	> 590 IU/L	[59]
Sodium	≤ 133 mmol/L	[51]
Imaging studies	Sonographic GB abnormalities	[70]

IVIG: Intravenous immunoglobulin; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; NT-proBNP: N-terminal fragment of B-type natriuretic peptide; GB: Gall bladder.

There has been no confirmative evidence of a better usefulness of corticosteroids as the second line treatment compared to additional IVIG. The combination of corticosteroids and additional IVIG as the second line therapy needs further study to confirm its efficacy, in spite of small group study[43] supporting it. By the way, this combination has been tried more frequently as the first line treatment instead.

THE USE OF CORTICOSTEROIDS IN COMBINATION WITH IVIG AS THE ROUTINE FIRST LINE TREATMENT

By about the year 2000, the combination of corticosteroids and IVIG as the first line therapy was reported shortening the duration of fever and/or reducing the severity of systemic inflammation[44-46]. Okada *et al*[46] reported that the levels of cytokines were lower, the duration of fever was shorter, and the C-reactive protein level decreased more quickly in the patient group who underwent the combination treatment than in the patient group who underwent IVIG treatment only. This result implicates a more rapid reduction of inflammatory reactions in the combination treatment. Wooditch *et al*[47] reported that the inclusion of corticosteroids in aspirin-containing regimens with or without IVIG for the first line treatment of Kawasaki disease reduces the incidence of coronary aneurysms in their meta-analysis. In addition, Inoue *et al*[48] reported that the combination of corticosteroids and IVIG as the first line therapy improved the clinical course and coronary artery outcome in their multicenter prospective study with 178 patients. However, the result of a multicenter randomized double-blind placebo-controlled study by Newburger *et al*[49], in which a single dose of methylprednisolone (30 mg/kg) was administrated did not agree with the result by Inoue *et al*[48] The result of another study of 216 patients in which dexamethasone (0.3 mg/kg per day for 3 d) was combined with IVIG showed no significant difference of coronary outcomes between groups[50]. Therefore, it is less likely that the administration of corticosteroids in combination with IVIG as the routine first line therapy in all Kawasaki disease patients reduces coronary artery lesions. However, further studies to determine the most appropriate regimen of corticosteroids should be needed, because the duration of the administration of corticosteroids (prednisolone was selected) including the period of tapering seems to be longer in studies which reported the efficacy of the combination therapy[45,46,48].

THE USE OF CORTICOSTEROIDS IN COMBINATION WITH IVIG AS THE FIRST LINE TREATMENT IN SELECTED PATIENTS

Another strategy of a use of corticosteroids in Kawasaki

disease patients is their administration in combination with IVIG in selected patients who are expected to be unresponsive to initial IVIG treatment. Three risk scoring systems for the selection of patients were proposed in Japan (Table 2)[51-53]. The cut-off level of the sum of points in the Kobayashi scoring was changed from ⩾ 4 points[51] to ⩾ 5 points[39,54,55]. The sensitivity and the specificity for predicting initial IVIG unresponsiveness were 86% and 68% in the Kobayashi scoring model, 78% and 76% in the Egami scoring model, and 77% and 86% in the Sano scoring model, respectively, according to the reports by their respective creators[51-53]. There were following reports showing the efficacy of these three scoring systems[54-57]. The other predictive scoring systems have had no subsequent studies to show their usefulness, or are based on a small number of subjects[31,58-60]. Kobayashi *et al*[51] suggested four different points of their study from the study by Newburger *et al*[49]: the time to start a treatment was 2 d earlier in their study, a the longer duration of the administration of corticosteroids, the selection of patients with a high risk of unresponsiveness to initial IVIG treatment, and the ethnic homogeneity of their subjects[54]. The selection criteria of patients at a high risk have been the most hot issue until recently. The efficacy of the Japanese scoring systems has been tested in other institutes. However, satisfactory results have not been achieved, and an especially low sensitivity has been reported[43,60-63]. The sensitivity and the specificity of the Kobayashi scoring system were 33%-60% and 35%-87%[43,60-63], those of the Egami scoring system were 21.4%-57% and 77%-86.6%[60-62], and those of the Sano scoring system were 40%-60% and 85%-90%[61,62], respectively. These results suggest refinement of the Japanese scoring systems is needed before they can be used effectively. In addition, one recent study whose subjects were patients with incomplete Kawasaki disease, showed that the proportion of patients identified as being at high-risk for IVIG resistance using three Japanese scoring systems were not significantly different between the IVIG resistance group and the IVIG responsive group[64].

Many clinical/laboratory variables have been reported as the predictors of the unresponsiveness to initial IVIG treatment (Table 3)[31-34,37,51-53,58-62,65-73]. The diversity of predictors might be one reason of the low sensitivity of the proposed risk scoring systems. The biomarkers and the genetic variants also have been investigated as the predictors. However, there has been no report in which any aggressive therapy prevented coronary artery lesions in patients at high risk of unresponsiveness predicted by biomarkers and genetic variants. For more information about studies of biomarkers and genetic variants, two recent reviews are informative[74,75].

More-aggressive initial treatment for patients at a high risk of IVIG unresponsiveness after risk stratification using a predictive model has been recommended in the recently updated guidelines for the medical treatment of acute Kawasaki disease in Japan[39]. Future investigations to determine the best predictive model to use are necessary.

CONCLUSION

It is uncertain that the corticosteroids as the second line treatment are better than the additional treatment of IVIG in Kawasaki disease patients unresponsive to initial IVIG. It is also uncertain that the combination of corticosteroids and IVIG is better than the initial IVIG only treatment as the routine first line therapy during the acute phase. The therapeutic strategy that an aggressive treatment including the combination of corticosteroids and IVIG is needed in patients at high risk of unresponsiveness to initial IVIG treatment, is properly reasonable. Future investigations to determine the best predictive model for the unresponsiveness are necessary.

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Limitations of urease test in diagnosis of pediatric *Helicobacter pylori* infection

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Abstract

The diagnosis of *Helicobacter pylori* (*H. pylori*) infection is usually based on the results of urease test and histology. The urease test known as a simple and cheap method does not need special skills to perform or to read the result. The time needed for the test to turn positive depends on the concentration of bacteria, and the accuracy is up to the density of *H. pylori* density in the biopsy sample, which is generally lower in children than adolescents and adults. Therefore, there are debates about the sensitivity of the urease test in children. The reason for lower sensitivity of the urease test in children was not identified, but might be related to the low density and patchy distribution of bacteria. In this review, we discuss the limitations of the urease test in children according to age, histology, number of biopsy samples, and biopsy site. In children under 5 years old, the differences in positivity rate when the urease test used one or three biopsy samples, and samples from the antrum or the gastric body, were larger than those in children aged 5-15 years. Thus, three or more biopsy samples from both the antrum and body would improve the sensitivity of *H. pylori* infection diagnosis in children under 5 years old.

Key words: *Helicobacter pylori* infection; Urease test; Children

Core tip: The diagnosis of *Helicobacter pylori* (*H. pylori*) infection is usually based on the findings of histology and the results of the urease test. However, the sensitivity of urease test in children was lower compared to adults. The lower sensitivity of urease test of children might be related to the low density and patchy distribution of bacteria. In urease test, three or more biopsy samples

from both the antrum and body would improve the sensitivity of *H. pylori* infection diagnosis in children under 5 years old.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is the main pathogen of acute and chronic gastritis, peptic ulcer disease, and gastric cancer[1,2]. Although primary *H. pylori* infection occurs during early childhood, most adults eventually become *H. pylori* carriers in developing countries[3,4]. In children, abdominal pain is the most common symptom in *H. pylori* infection[5]. Whether or not *H. pylori*-infected children with recurrent abdominal pain should be treated did not reach consensus[6]. However, a positive family history of gastric cancer is one of the risk factors of adulthood gastric cancer in children with *H. pylori* infection[7]. Thus, a reliable diagnostic test to detect *H. pylori* infection in children is required. The most reliable diagnostic method of *H. pylori* infection in children is endoscopy with gastric biopsy[8].

The diagnosis of *H. pylori* infection is usually based on the findings of histology and the results of the urease test[9]. Histology plays an important role in detecting *H. pylori* and also indicates the degree of chronic and active inflammation in the stomach[10]. The urease test known as a simple and cheap method does not need special skills to perform or to read the result. The urease test uses phenol red, which changes from yellow to pink or red as the pH increases. *H. pylori* can stay alive in the human stomach and activate its own cytoplasmic urease, converting urea into carbon dioxide and ammonia and increasing the pH of the surrounding environment[11]. Buffered urease tests need at least 10^5 organisms so as to produce a positive result[12]. Therefore, the urease test may be negative, if biopsy samples in which the histology reveals only one or two bacteria in the entire section[13]. The time needed for the test to show a positive result depends on the concentration of bacteria[14], and the accuracy of the urease test primarily is up to the density of *H. pylori* in the gastric sample. Generally the *H. pylori* density is found to be lower in children than adolescents and adults[15]. The time of the urease test turns positive is up to the concentration of bacteria and the temperature. Most commercially available urease tests will turn positive within 2-3 h but it is best to hold those that appear negative for 24 h regardless of age[14]. The urease enzyme activity of *H. pylori* at the diagnosis also affects the urease test. Acid suppression by proton pump inhibitor is a well-known cause of the false negative result of urease test[14].

However, there is currently a debate about the sensitivity of the urease test in children without consideration of the urease enzyme activities. A review of the literature about *H. pylori* diagnostic tests in children from 1999-2009 suggested that prompt urease tests have better sensitivity than histology to detect the occurrence of *H. pylori*[16]. In 1590 pediatric patients from 1989 to 2009, urease tests had lower sensitivity (83.4%) and comparable specificity (99.0%) with histology[17]. The reason for this lower sensitivity in children was not identified, but it might be related to the low density and patchy distribution of bacteria[15,18]. In this review, we discuss the limitations of the urease test in children based on the literature reporting on pediatric patients.

AGE OF CHILDREN

Age is another factor influencing the sensitivity of the urease test[17,19,20]. The age ranges of the children in different studies were wide, and varied from $\leqslant$ 15 to $\leqslant$ 18 years of age[5-8]. In children, a low density of *H. pylori* has been reported[15,21], which can be attributable to sampling errors such as very low numbers of *H. pylori* in the tissue samples or patchy distribution of the organism in the stomach's mucosa[22]. Among 530 children infected with *H. pylori*, the urease test was positive in 442, and the rate of urease tests was positively associated with the children aged 5 years old and above compared with those below 5 years old[17]. The false negative rate for the urease test was 16.6% in these children, mostly found in those below 5 years old[17]. In our previous studies, we divided pediatric patients into three age groups: 0-4 years, 5-9 years, and 10-15 years[19,20]. The positivity rate of the urease test increased with each increasing age group, with the lowest rate in the 0-4 years group and highest in the 10-15 years group (Figure 1)[20]. We then compared the time points at which the positive reaction produced, dividing these into 0-1 h, 1-6 h, 6-24 h, and 24-48 h. This was considered within each of 4 age groups: 0-4 years, 5-9 years, 10-14 years, and 20-29 years[20]. Positive results occurred within 1 h in the older age groups, 10-15 years and 20-29 years. Conversely, most positive results occurred at 6-24 h in the 0-4 years group using body biopsy specimens (Figure 1)[20]. This result suggested that a low degree of *H. pylori* colonization in gastric biopsy samples might be more frequent in children under 5 years old.

HISTOPATHOLOGICAL GRADES AND THE POSITIVITY RATE OF THE UREASE TEST

H. pylori infection causes chronic inflammation in stomach mucosa. Histology has been regarded as the golden compass for *H. pylori* detection[9], as it can detect the bacteria as well as the severity of inflammation. However, just as a positive urease test requires approximately 10^5 *H. pylori* in the biopsy sample[12],

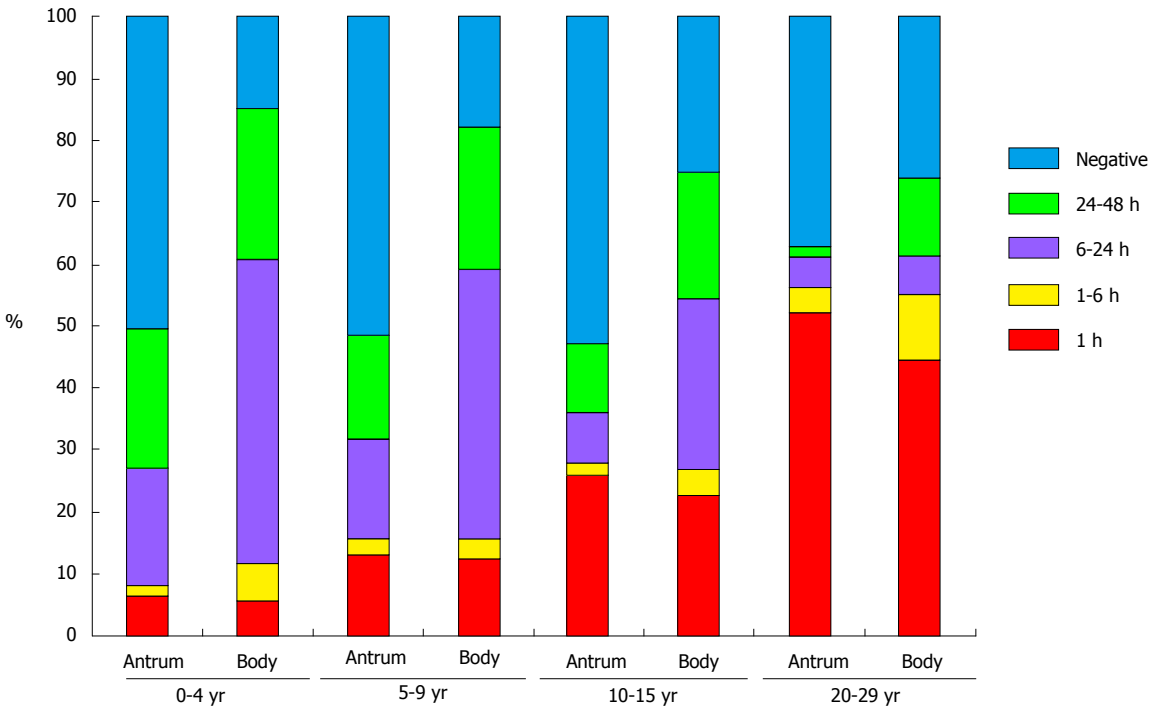

Figure 1 The positivity rate and positive timing of the urease test both in the antrum and body according to age. The positivity rate of the urease test in the antrum was higher in 20-29 years group than that in other three age groups, and the positivity rate of the urease test in the body decreased with increasing age ($P < 0.0001$). The highest positivity timing was within 1 h in the 20-29 years group, and within 6-24 h in children ($P < 0.0001$)[20].

Table 1 The studies about the positivity rate of urease test by comparing to biopsy sites and biopsy numbers

Ref.	Published year	No. subjects	Mean age (yr)	Comparison	Positivity rate of urease test (%)
Siddique *et al*[24]	2008	100 adults	36.1	One biopsy	52
				Two biopsies	68
				Three biopsies	76
				Four biopsies	96
Seo *et al*[19]	2014	255 children	NA	One biopsy	32.2
				Three biopsies	40.1
Moon *et al*[25]	2012	214 adults	53.6	Antrum	58.9
				body	62.1
				Antrum + body	69.2
Lan *et al*[26]	2012	164 adults	NA	Antrum	83.3
				Antrum + corpus	100

NA: Not available.

histopathological results are limited by the distribution and density of the bacteria in the sample. Therefore, the patchy distribution and low density *of H. pylori* in gastric mucosa in children might be related to the absence of bacteria in some histopathological findings. Nevertheless, the positive urease test is highly correlated with the density of bacteria, the severity of chronic gastritis, and the presence of active gastritis, as determined by histopathology[15,17].

When histopathological evaluations found severe degrees of chronic and active gastritis, or *H. pylori* infiltration, the urease tests revealed a quick change of color, indicating positive results in samples from both the antrum and gastric body, regardless of age, compared with those from milder histopathological grades[20]. In 38 children, aged 2-18 years, the accuracy of the rapid urease test was 95% for samples determined to be positive by histology[23]. The accuracy of the urease test is up to the density of *H. pylori* in the gastric sample. However the *H. pylori* density is overall lower in children than in adolescents and adults[15]. Therefore, both histology and a urease test should be performed in children for diagnosis of *H. pylori* infection.

EFFECT OF THE NUMBER OF GASTRIC BIOPSY SPECIMENS

Two or more numbers of gastric biopsies improve the sensitivity and saves the time for the positive result for diagnosis of urease test[19,24]. There were several studies comparing positivity rate of urease test according to the biopsy numbers diagnosis (Table 1): three were

adults studies and one was children study. In children, the positivity rate of the urease test was higher in three biopsy samples than single biopsy sample, in the same child[19]. The discrepancy between positivity rates of the urease test utilizing one *vs* three biopsy samples was elevated in children below 5 years old[21]. Thus, when the urease test is performed on three or more biopsy samples, it is possibly a more accurate diagnostic modality.

In adults, the positivity rate of urease test also increased with using two to four biopsy specimens than a single biopsy specimen[24]. The discrepancy rates of one and two or more biopsy specimens were higher in adults (10.3%, 16.7% and 16%) than in children (7.9%) (Table 1)[19,24-26]. In adults, the time for positive urease test was faster in united test (1.69 h for antrum and body) than in separate test (3.58 h for body or antrum) on average[25]. In children, it is reported to be a low degree of *H. pylori* colonization and more patchy distribution of *H. pylori*[21]. Thus, when the urease test is performed on three or more biopsy samples, it may be a more accurate diagnostic modality.

EFFECT OF BIOPSY SITE ON UREASE TEST RESULTS

Most patients were taken of biopsy specimens from the antrum, as one biopsy from the gastric angle for urease test had the maximum probability for detecting *H. pylori* infection[27]. The use of an additional biopsy from the gastric body can improve the detection rate of *H. pylori* (Table 1)[20,25,26]. In our previous study[20], the discrepancy of urease test results was bigger between the antrum and body in children compared with that in adults, and the most difference was found in the samples that showed a positive color change late in testing, from 6-24 h (Figure 1). In our study, no difference was observed between the speed of a positive reaction in samples from the antrum and from the body in adults[20]. But the time of positive test was 3.58 h for the separate test and 1.69 h for the united test on average[25]. The colonization degree was remarkably lower in the body compared with the antrum[21]. In our previous study, the histopathologic findings of the antrum and body revealed similar degrees of chronic and active gastritis and infiltration of bacteria in children, the positivity rate of the urease test was higher in samples from the body than from the antrum[20]. This result was similar to the study of Korean adults, where the positivity rate of urease test in body was higher than in antrum (Table 1)[25]. In adults, the sensitivity of urease test decreased along with the degree of gastritis with atrophy increasing from 100% in normal, 97% in mild, 91% in moderate to 66% in severe[26]. However additional corpus biopsy resulted in increased sensitivity to 16.67% compared to single antrum biopsy (Table 1)[26]. This might also be related to the patchy distribution of *H. pylori* and low density of the organism in body. There has been a continuing debate about the optimum site and number of gastric biopsies for the diagnosis of *H. pylori*.

CONCLUSION

Early diagnosis of *H. pylori* infection is crucial for symptomatic children with a family history of gastric cancer. In children, endoscopic examination and biopsy for histology and urease test is still the most reliable method for diagnosis of *H. pylori* infection. The difference in the positivity rate of the urease test between using one or three biopsy samples, or using biopsy samples from the antrum or body, were larger in children aged 0-5 years than 5-15 years. Use of three or more biopsy samples from both the antrum and body would improve the sensitivity of *H. pylori* detection in children.

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ORIGINAL ARTICLE

Retrospective Study

Coeliac disease in children in Christchurch, New Zealand: Presentation and patterns from 2000-2010

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Author contributions: All the authors equally contributed to this work.

Institutional review board statement: This conduct of this retrospective study was approved by the Upper South A Regional Ethics Committee, New Zealand (URA/11/EXP/044).

Informed consent statement: Given the nature of the study (retrospective review of patient charts, with no direct patient contact), specific informed consent was not required (as per the approval of the Regional Ethics Committee).

Conflict-of-interest statement: None of the authors have any conflicts of interest to declare relevant to this study.

Data sharing statement: Not applicable.

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Abstract

AIM: To evaluate the presentation patterns of a cohort of children diagnosed with coeliac disease (CD) at Christchurch Hospital, New Zealand.

METHODS: Children aged 16 years or less diagnosed with CD at Christchurch Hospital, Christchurch, New Zealand, over the 11 year period between 2000 and 2010 were identified retrospectively. Diagnosis of CD was based upon standard histological criteria of endoscopically-obtained duodenal biopsies. Overlapping search methods were used to identify all relevant diagnoses within the time period. Endoscopy reports and histology findings were reviewed to confirm diagnosis. The numbers of diagnoses per year were calculated and changes in annual rates over the study period were delineated. Available records were reviewed to ascertain presenting symptoms, baseline anthropometry and the indication for referral for each child. In addition, the results of relevant investigations prior to diagnosis were accessed and reviewed. These key investigations included the results of coeliac serology testing (including tissue transglutaminase and endomysial antibodies) as well as the results of tests measuring levels of micronutrients, such as iron. In addition, the histological findings of concurrent biopsies in the oesophagus and stomach were reviewed.

RESULTS: Over the 11 year study period, 263 children were diagnosed with CD at this New Zealand paediatric facility. Children were diagnosed from late infancy to 16.9 years: the largest subgroup of children (n = 111) were diagnosed between 5 and 12 years of age. The numbers of children diagnosed each year increased from 13 per year to 31 per year over the 11 years (P = 0.0095).

Preschool children (aged less than 5 years) were more likely to have low weight, and to have diarrhoea and abdominal pain prior to diagnosis. Older children (over 5 years of age) most commonly presented with abdominal pain. Fifty-six (21.6%) of the 263 children were diagnosed following screening in high risk groups, with 38 of these children having no symptoms at diagnosis. Mean weight Z scores were lower in children aged less than five years than children aged 5-12 years or older children (-0.4096 ± 1.24, *vs* 0.1196 ± 0.966 *vs* 0.0901 ± 1.14 respectively: $P = 0.0033$).

CONCLUSION: Increasing numbers of children were diagnosed with CD in this New Zealand centre over this time, with varied presentations and symptoms.

Key words: Coeliac disease; Children; Screening; Small bowel biopsy; Antibodies

Core tip: Coeliac disease (CD) is increasingly diagnosed throughout childhood. Physicians must be aware of the varied presentations of CD in children and consider this diagnosis accordingly.

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INTRODUCTION

Coeliac disease (CD) is an autoimmune disease of the small bowel, triggered by dietary exposure to gluten in genetically susceptible individuals[1]. Ingestion of gluten provokes immune-mediated damage to the small intestinal mucosa. Following diagnosis of CD the optimal management currently involves a life-long gluten-free diet (GFD)[2].

Although traditionally felt to be a disease of infancy, presenting with classical symptoms of malabsorption (diarrhoea, abdominal bloating and failure to thrive), it is now clear that CD can develop at any age whilst on a gluten-containing diet[3]. A number of recent reports have documented increasing variability in presentation patterns with more patients presenting with non-specific complaints such as iron deficiency anaemia or lethargy[4-6]. In addition, more individuals are now identified consequent to active screening in groups at higher risk of CD (such as those with positive family history) and a number of these patients may be asymptomatic at diagnosis[7]. Although strategies such as active screening recognise more individuals with CD, it is felt that for every person diagnosed there are still many individuals who are undiagnosed in the community[8-10].

CD is now recognised as a common disease, with prevalence estimated to be at least 1: 100[7]. Locally, a population-based study performed in Christchurch, New Zealand, suggested a prevalence of one in 82 individuals[11]. In addition, a subsequent hospital-based study conducted in the same region demonstrated increasing numbers diagnosed each year over the last years of the twentieth century[12]. The primary aims of this retrospective study were to determine the rates of diagnosis and the presentation patterns of paediatric-onset CD at Christchurch Hospital in the first decade of the 21st century.

MATERIALS AND METHODS

Population

Children aged 16 years or less (defined as diagnosis before their seventeenth birthday) diagnosed with CD at Christchurch Hospital, Christchurch, New Zealand between January 1st 2000 and December 31st 2010 were identified retrospectively. Christchurch Hospital is the sole secondary-level public hospital for the Canterbury region and also provides tertiary paediatric services for surrounding regions. The study population did not include children diagnosed outside Christchurch Hospital.

The Department of Pathology database was searched for the keywords "coeliac disease", "celiac disease" and "gluten sensitive enteropathy". This search returned histology reports of patients who had been investigated for and/or diagnosed with CD. Records available from the Dietetics Department were also reviewed to identify children referred for dietetic education prior to commencement of a GFD. Each patient's hospital records (hard-copy and electronic) was also retrieved and reviewed for the purpose of the study.

The duodenal biopsies taken at Christchurch Public Hospital from 2000-2010 were all analysed by the same medical laboratory, although by different pathologists. Lesions consistent with Marsh-Oberhuber criteria (including increased intraepithelial lymphocytes, partial to complete villous atrophy, crypt hyperplasia and increased lymphocytes in the lamina propria) were considered to be diagnostic[13]. The histological findings in other areas of the upper gastrointestinal tract were also reviewed.

Clinical features

Relevant background features, such as presenting signs and symptoms, risk group status, and anthropometry were extracted from hospital clinical records and where available, GP referral letters and blood test results. In the event of missing data, the patients' last known GP was contacted and asked to provide relevant results and notes where available.

Endoscopy and pathology reports were reviewed. The results of serological tests [anti-gliadin (AGA), anti-

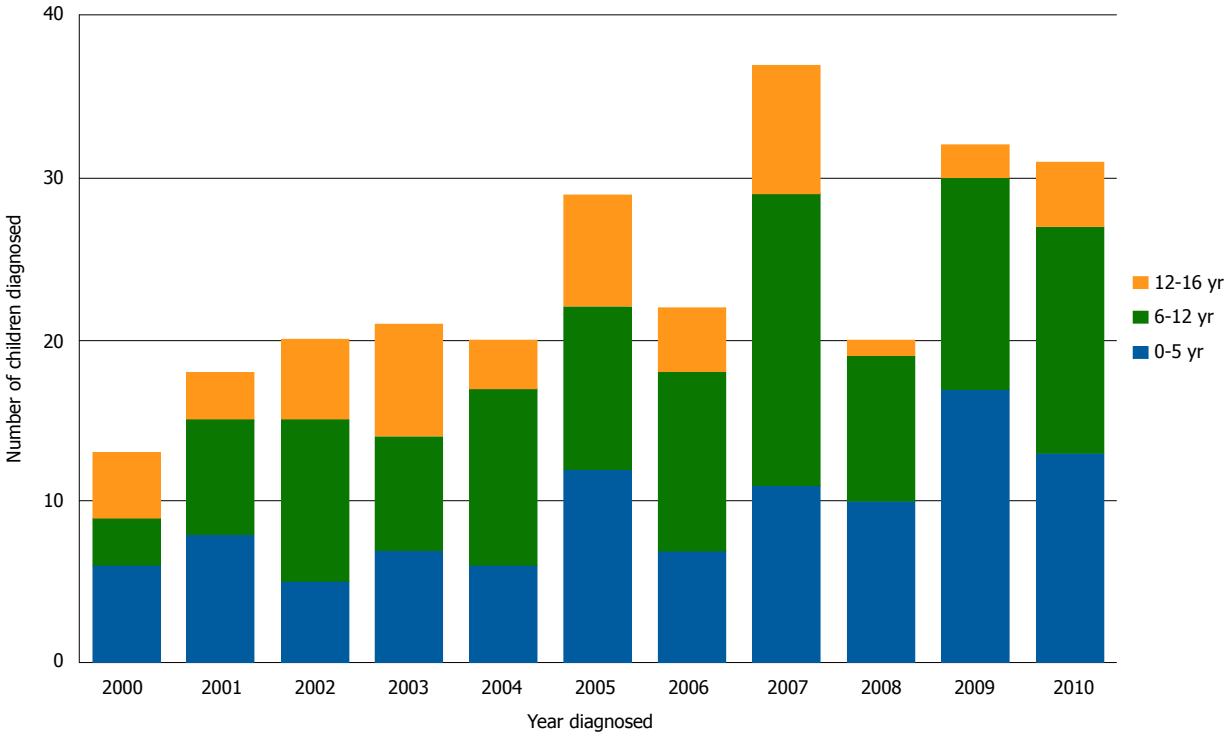

Figure 1 Age distribution of 263 children diagnosed with coeliac disease in Christchurch, New Zealand, between 2000 and 2010.

endomysial antibodies (EMA), tissue transglutaminase (tTG) and deaminated gliadin peptide (DGP)] were obtained. The results of other tests conducted prior to diagnosis (haemoglobin level, iron studies, total IgA level and HLA DQ2/DQ8 status) were also noted where available. Patients were classified as iron deficient in the presence of one or more of the following: serum ferritin levels below normal reference range in the absence of an elevated C-reactive protein; transferrin saturation or serum iron levels below the normal reference range; total iron binding capacity and serum transferrin receptor levels above the normal reference range. Iron deficiency anaemia was defined as a microcytic hypochromic anaemia, with evidence of low iron stores as stated above.

Statistical analysis

Descriptive analyses were executed using Microsoft Excel 14.0.0. Weight and height Z scores were calculated using an online calculator employing data from the National Health and Nutrition Evaluation Survey - (http://www.emmes.com/study/ped/resources/htwtcalc.htm). Statistical analyses were performed using GraphPad InStat 3.0 (GraphPad Software, Inc., La Jolla, CA). One-way analysis of variance (ANOVA), *t* tests and chi-square tests were utilised for data analysis. Statistical significance was defined as a *P* value below 0.05.

RESULTS

Study population

A total of 263 children were diagnosed with CD over the time period. The median age of the study population was 7.88 years (range 0.8-16.9 years) and 169 (64%) were female. Two hundred and sixteen children were aged less than 12 years whilst 26 were aged less than 2 years of age. The largest number of children (42.3%) was aged between 6 and 12 years at diagnosis.

The gender and age distribution of the group did not vary over the study period. However, the numbers of children diagnosed each year increased from 13 in 2000 to 31 in 2010 ($P = 0.009$) (Figure 1).

At least one risk factor for CD was seen in 140 (53.4%) of the 263 children. Positive family history ($n = 92$), Trisomy 21 ($n = 15$) and type 1 diabetes mellitus (T1DM) ($n = 22$) were seen most commonly, whilst other risk groups included Turner's syndrome, autoimmune thyroid disease and William's Syndrome ($n = 11$). Two risk factors, such as positive family history and T1DM, were seen in 7 children. Diagnosis was made after screening in 56 (21%) children: 38 of whom were reported to be asymptomatic. One patient was found to have CD at the time of upper gastrointestinal endoscopy for suspected eosinophilic oesophagitis.

Presenting features

Details of presenting features were available for 260 of the 263 children. Thirty-eight of these 260 children had no reported symptoms at the time of diagnosis. Abdominal pain (44.2%) and diarrhoea (38.9%) were the most commonly reported symptoms in the 222 children presenting with symptoms (Table 1). Most children presented with a combination of intestinal and extra-intestinal symptoms. Whilst diarrhoea (51.5%)

Table 1 Presenting symptoms or signs in 263 children diagnosed with coeliac disease in Christchurch, New Zealand *n* (%)

	Presenting sign or symptom	Children
Gastrointestinal	Abdominal pain	115 (43.6)
	Diarrhoea	101 (38.3)
	Bloating (± increased flatus)	60 (22.7)
	Nausea and vomiting	42 (15.9)
	Constipation	17 (6.4)
Nutritional	Iron deficiency (± anaemia)	84 (31.8)
	Poor weight gains/wasting	65 (24.6)
	Weight loss	27 (10.2)
	Micronutrient deficiency	25 (9.5)
	Short stature	10 (3.8)
Extra-gastrointestinal	Lethargy	36 (13.6)
	Poor health/recurrent infections	12 (4.6)
	Irritability/low mood	11 (4.2)
	Headaches	6 (2.3)
	Pubertal delay	3 (1.1)
	Poor sleep	2 (0.8)
	Neuropsychiatric symptoms	1 (0.4)
Asymptomatic	Identified following screening	38 (14.4)

The presenting features prior to diagnosis were noted. Some children had more than one presenting feature.

and failure to thrive (46.6%) predominated in the children aged less than 5 years of age, abdominal pain was the most common symptom in older children (P = 0.0032).

Growth parameters at diagnosis of CD

Weight measurements were available for 229 of the 263 children, and height measurements available for 184 of the children. Overall, the mean Z score (± SD) for weight was -0.12 ± 0.22, whilst that for height was -0.24 ± 0.31. The children aged less than five years had a lower mean weight z score (-0.4096 ± 1.24) than the children aged 5-12 years (0.1196 ± 0.966) and the older group (0.0901 ± 1.14) (P = 0.0033, ANOVA). There were no differences in the mean height z scores for the three age groupings (Table 2).

Eighteen (7.8%) of the patients had a weight score more than 2 SD below the mean (wasting), and 15 (8.2%) had a height score more than 2 SD below the mean (stunting). More of the children with wasting were aged less than 5 years of age than older than this age (13 *vs* 5; P = 0.005). Stunting was not different across the age ranges (data not shown). Five children (2%) had a weight score more than 2 SD above the mean (overweight). Only three children (1.6%) had a height score more than 2 SD above the mean.

Results of serological tests prior to diagnosis

The results of serological tests were available in 261 children. AGA testing (IgA and IgG) was completed only prior to 2008: IgG AGA was positive in 82.4% of 193 children, whilst IgA AGA was positive in 50.8% of 185 children. EMA testing was positive in 177 (87.6%) of the 202 who had been tested for this antibody. tTG serology was positive in 183 (89.3%) of the 205 children who had been tested. Sixteen children had DGP testing (all since 2008): IgG DGP was positive in 75% and IgA DGP positive in 62.5% of this group.

Twelve children were negative for IgA-based tests (EMA, tTG and AGA): three of these children were IgA deficient. These three children all tested positive for IgG AGA and one was also IgG tTG positive.

Table 2 Nutritional parameters in children diagnosed with coeliac disease, stratified by age

Age group (yr)	Weight Z score (± SD)	Height Z score (± SD)	Iron deficiency (*n*)	Other deficiency (*n*)
0-5	-0.4096 ± 1.24	-0.4210 ± 1.102	41	9
6-12	0.1196 ± 0.966	-0.914 ± 1.125	25	8
> 12	0.0901 ± 1.14	-0.229 ± 1.347	21	7

Children aged less than five years of age had lower weight Z scores than the other groups (P = 0.0033), but there were no differences in height Z scores between the groups. Other deficiencies included those with low levels of folate, vitamin B12, vitamin A, vitamin D, vitamin E or vitamin K.

Results of other investigations completed at diagnosis

Full blood count results were available in 178 children: 25 (14.0%) of these children were found to have a haemoglobin level below the normal reference range, and 12 (6.7%) had microcytosis. Four of the 25 anaemic children did not have assessment of iron status at the time of diagnosis: two were documented as having iron deficiency anaemia in their referral letters to hospital whilst the other two children had normocytic normochromic anaemia.

Iron status was assessed in 153 children: 84 (54.9%) of these children were iron deficient (Table 2). Measurement of other micronutrients was completed only in a small number of children: 24 were found to have deficiency of folate, vitamin B12, vitamin A, vitamin D, vitamin E, and/or vitamin K (Table 2). Genetic testing for HLA DQ2/DQ8 was not routinely undertaken during this period: only 28 children had undergone this investigation, all of whom had positive results. Detailed analysis of this HLA marker was therefore not conducted.

Histological findings

Duodenal biopsies were evaluated by pathologists and diagnosed according to Marsh-Oberhuber criteria[13]. Almost all the children diagnosed with CD also had concurrent biopsies of the oesophagus and the stomach taken during gastroscopy. Distinct abnormalities were seen in 86 children, with some children having more than one other finding. Common findings included reflux oesophagitis (seen in 21 children) and lymphocytic gastritis (n = 16) (Table 3).

DISCUSSION

This retrospective study showed progressive increases in the number of children diagnosed with CD each year

Table 3 Oesophageal and gastric findings in 263 children diagnosed with coeliac disease

	Histological diagnosis	Number of patients	Percentage of patients (%)
Oesophageal findings	Reflux oesophagitis	21	7.9
	Eosinophilic oesophagitis	4	1.5
	Candida oesophagitis	1	0.4
	Non-specific oesophagitis	21	7.9
Gastric findings	Lymphocytic gastritis	16	6.1
	Non-specific gastritis	30	11.4
	Reactive gastritis (bile reflux)	11	4.2
	Active chronic gastritis (*H. pylori*)	1	0.4
	Gastric metaplasia	1	0.4

Eighty-six of the 263 children diagnosed with coeliac disease were found to have one or more oesophageal or gastric findings on review of endoscopic biopsies. *H. pylori*: *Helicobacter pylori*.

in this single New Zealand location over the 11 years of observation. Presenting symptoms varied widely in this group, and a substantial number of children were diagnosed following screening assessments in high risk groups. Preschool children were more likely to have nutritional impairment than older children. Although this study was not designed to define population-specific rates of CD, the results clearly emphasise that CD is an increasingly important condition in New Zealand children.

A prospective population-based study has previously documented that CD is common in adults in this region of New Zealand, with rates of 1:82[11], equivalent to prevalence studies in several other countries[7]. A further study documented increasing rates of diagnosis in children and adults from the same region over the last three decades of the 20th century[12]. That prospective study documented the diagnosis of CD in 62 children aged between 0 and 12 years of age, with increasing numbers in the last years of the 30 year period. In contrast, 216 children aged less than 12 years were diagnosed within the 11 year period of the current study, emphasising the increasing numbers of diagnoses in the same region of New Zealand.

Cumulative incidence rates in children (0-12 years old) in previous New Zealand studies have been low in comparison to corresponding adult rates: 0.10/1000 in Wellington[14], 0.35/1000 in Otago[15] and 0.40/1000 in Canterbury[12]. More recently the prevalence of childhood CD was ascertained in the New Zealand Asthma and Allergy Cohort[16]. This birth-cohort was established between 1997 and 2001, with infants recruited in two New Zealand centres (Christchurch and Wellington). The parents of 916 children in this cohort were asked in 2009 about doctor-diagnosed CD. Nine children were identified, giving a prevalence of 1%. However, this parental report was not validated by detailed review of each patient's medical history.

This pattern of increasing numbers of young children diagnosed with CD in New Zealand may be related in part to enhanced awareness of CD and more recognition of groups at higher risk of developing this condition. Advances in serological tests and diagnostic approaches may be additional factors[17]. Environmental factors, such as infant breast-feeding practices, age at introduction of gluten, and the amount of gluten in the diet, could also be relevant to changes in rates of CD in recent years[18]. It is unlikely, however, that genetic risk will have altered over a period of just a few decades. There may also be a true rise in incidence of CD. Studies from Finland, in particular, indicate a true increase in the incidence of CD over time, with most recent rates estimated to be 2.4%[19]. In the New Zealand setting, deregulation of the New Zealand wheat industry and changes in infant feeding practices could be potential drivers of such a rise in incidence[11]. The retrospective nature of the current study did not allow any clarification of environmental risk factors, such as breast feeding, or of other details including family history of CD.

The current study clearly demonstrated that CD can be diagnosed at any age through childhood, with pain being a predominant presenting symptom, especially in older children. Overall, significant nutritional impairments were not commonly seen, with less than 10% percent being malnourished at diagnosis. However, nutritional impairment was more likely in preschool children than in those of school age. Unfortunately, the presentation patterns and nutritional state of the children diagnosed at the same centre in the preceding three decades were not documented[12]. However, the reduced number of children diagnosed prior to their second birthday in the second cohort compared to the earlier group (12% *vs* 21%) suggests less frequent presentation with classical malabsorptive symptoms.

Previous reports over the last decade from elsewhere in New Zealand[4] and Australia[5,20] also demonstrate similar findings in presentation patterns. Internationally, similar observations have been made, with less preschool children presenting with classical malabsorptive symptoms, and more with gastrointestinal or non-gastrointestinal symptoms[6].

A number of children in the current study had been diagnosed with CD following screening within a high risk group and more than two thirds of the children identified by screening were asymptomatic. Groups at highest risk of CD include those with a first degree family member, children with T1DM and Down syndrome (Trisomy 21)[7]. Children with a first degree family history of CD comprise the largest high risk group in the children diagnosed with CD in the current study. The increased identification of children following focused screening is noted elsewhere also[5,20].

The use of specific serological tests has evolved over the period of the current study. Whereas AGA and EMA were utilised in the last thirty years of the 20th century[12], tTG and EMA were the predominant tests utilised in the current cohort. AGA tests were available for part of the period, whilst DGP were utilised only in the latter years. In this setting, EMA and tTG were

positive in the majority of those children tested.

The recently published European guidelines for the diagnosis of CD include a provision for the diagnosis of CD without obtaining duodenal biopsies[21]. The current study does not permit a detailed assessment of the validity of this protocol to the New Zealand setting. However, a number of children in the current cohort would not have reached diagnostic criteria without completion of duodenal biopsies. Furthermore, less than 15% of the current cohort had estimation of HLA DQ2/DQ8. Whilst best considered as a test to provide risk stratification (negative gene testing reflecting essentially no risk of developing CD), HLA testing is also included in the ESPGHAN guidelines as a requirement for considering diagnosis without duodenal biopsies[21].

A number of the current cohort had additional histological findings present in the upper gut. Whilst the presence of lymphocytic gastritis is well-recognised as a component of CD, the recognition of oesophageal findings is of interest. Several paediatric cohorts have shown an association between CD and eosinophilic oesophagitis[22-24]. Although the reason for this link is as yet unclear[25], it does further illustrate the evolving patterns of CD in children.

The limitations of this study relate principally to its retrospective nature. This limited the availability of all required data, with incomplete data across some key areas. This study did not consider children seen and diagnosed in the private sector, and consequently cannot be considered population-based. However, the small number of additional children diagnosed in the private sector would likely serve to further increase the total numbers diagnosed over time. The included population was seen and diagnosed within a single hospital setting over an 11 year period, and follows directly from an earlier assessment of CD in the same setting[12]. Together, these two datasets cover 41 years of children diagnosed with CD in Christchurch, New Zealand.

In conclusion, these data reflect a large increase in number of children and adolescents diagnosed with CD at this single New Zealand tertiary centre. Common to other reports, the presentation patterns of CD in children are many and varied. Practitioners must consider the diagnosis of CD in children seen with a variety of symptoms. The increased emphasis upon screening in groups at higher risk of CD is likely to lead to even more children diagnosed without symptoms.

COMMENTS

Background

Coeliac disease (CD) may present at any age after commencement of a gluten containing diet. Increasing rates of the diagnosis of CD was previously noted in the Christchurch region over the last three decades of the 20th century. The current study focused on the first 11 years of the 21st century and ascertained annual rates of diagnosis over this time.

Research frontiers

CD may present throughout childhood, with a variety of symptoms. Increasing numbers of children are diagnosed after screening in groups at greater risk of developing CD. Such children may not have any symptoms at the time of screening or diagnosis.

Innovations and breakthroughs

Different symptom patterns may be seen in children of varying age. Screening for CD in children at increased risk of CD (such as those with a first degree family member) may lead to earlier diagnosis and avoid nutritional or other consequences of CD.

Applications

Physicians assessing children must be aware of the myriad different possible presentation patterns of CD. Early investigation in those with possible CD should be undertaken to avoid long term morbidity and adverse outcomes.

Terminology

Genetic risk for the development of CD is attributed to particular *HLA* genes. Serological tests for CD include tissue transglutaminase antibodies (tTG: measured by immunoassay) and endomysial antibodies (EMA: assessed by immunofluorescence).

Peer-review

Increasing numbers of children were diagnosed with CD after screening exercises: a number of these children have no symptoms at the time of diagnosis. Assessment of HLA genetic status was completed in few of the children included in this retrospective study of CD. Consequently, few conclusions could be made about the relevance of these findings.

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ORIGINAL ARTICLE

Retrospective Study

Use of laparoscopy as the initial surgical approach of impalpable testes: 10-year experience

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Informed consent statement: As anonymized administrative and clinical data were used for this study, specific written consent was not required to use patient information stored in hospital databases.

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Data sharing statement: No additional data are available.

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Abstract

AIM: To review the experience in the management of impalpable testes using laparoscopy as the initial approach and the need for inguinal exploration.

METHODS: From January 2004 to June 2014, 339 patients with undescended testes underwent operation in our institute. Fifty patients (15%) had impalpable testes. All children with impalpable testes underwent initial laparoscopy. A retrospective review was conducted on this group of patients and the outcome was analyzed.

RESULTS: Forty children had unilateral impalpable testis. Ten children had bilateral impalpable testes. Thirty-one children (78%) in the unilateral group underwent subsequent inguinal exploration while 4 children (40%) in the bilateral group underwent inguinal exploration ($P < 0.05$). Orchidopexy was performed in 16 children (40%) in the unilateral group and 9 children (90%) in the bilateral group ($P < 0.05$). Regarding the 24 children with unilateral impalpable testis and underwent orchidectomy for testicular nubbin ($n = 19$) or atrophic testes ($n = 2$) or has vanishing testes ($n = 3$); contralateral testicular hypertrophy was noticed in 10 (41%). No intra-operative complication was encountered. Two children after staged Fowler-Stephens

procedure and 1 child after inguinal orchidopexy had atrophic testes.

CONCLUSION: The use of laparoscopy in children with impalpable testes is a safe procedure and can guide the need for subsequent inguinal exploration. Children with unilateral impalpable testis were associated with an increased need for inguinal exploration after laparoscopy. Orchidopexies could be performed successfully in 90% of children with bilateral impalpable testes.

Key words: Laparoscopy; Impalpable; Testis; Inguinal

Core tip: Among over 300 children with undescended testis underwent operation, 15% of children had impalpable testis. The review studies the use of laparoscopy as the initial management of children with impalpable testes. Compared with children with bilateral impalpable testes, children with unilateral impalpable testis had an increased need for subsequent inguinal exploration and a lower incidence of successful orchidopexy. Laparoscopy is a safe procedure with no intra-operative complication encountered in this study.

Chan KWE, Lee KH, Wong HYV, Tsui SYB, Wong YS, Pang KYK, Mou JWC, Tam YH. Use of laparoscopy as the initial surgical approach of impalpable testes: 10-year experience. *World J Clin Pediatr* 2015; 4(4): 155-159 Available from: URL: http://www.wjgnet.com/2219-2808/full/v4/i4/155.htm DOI: http://dx.doi.org/10.5409/wjcp.v4.i4.155

INTRODUCTION

Cryptorchidism is a common pediatric surgical condition that affected 2%-5% of new born[1]. If left untreated, cryptorchidism poses risk in malignancy and infertility[1-4]. In a child with a palpable testis at inguinal region, orchidopexy is recommended to be performed at 6-12 mo-of-age if spontaneous descend of the testis does not occurred by 6 mo-of-age[3]. On the other hand, in a child with an impalpable testis, ultrasonography of the inguinal canal is required locate the testis in pre-operative evaluation[4].

In the era of minimally invasive surgery, laparoscopy was advocated as the initial surgical approach in children with impalpable testes[5-8]. Laparoscopy can confirm the presence or absence of intra-abdominal testes and can direct the subsequent approach. However, others suggested that inguinal or scrotal exploration should be used as the initial approach in children with unilateral impalpable testis[9-11].

In our institute, all children with impalpable testes underwent initial laparoscopy. This study aimed to study the outcome of children using this approach.

MATERIALS AND METHODS

From January 2004 to June 2014, 339 boys with undescended testes underwent operation in our institute. Fifty children (15%) had impalpable testes. Impalpable testis was defined as the testis was not palpable under general anesthesia. The median age for children at the time of operation with impalpable testis was 26 mo (range: 8-192 mo). They all underwent laparoscopy as the initial procedure.

Operative procedure

All patients were examined again under general anesthesia and confirmed the diagnosis of impalpable testes. A sub-umbilical incision was made and a 5 mm 30 degree laparoscope was used. If the testis was identified intra-abdominally (Figure 1), two 3 or 5 mm ports were inserted over the abdomen; either one-stage laparoscopic or two-staged laparoscopic Fowler-Stephens orchidopexy was performed. If a blind ended vas was located away from the deep ring, the testis was defined vanished. If both vas and testicular vessels entered into the deep ring (Figure 2), an inguinal exploration was then performed. Inguinal orchidopexy was performed for normal looking testis. If a testicular nubbin or an atrophic testis was identified, it would be excised and sent for histological examination. For peeping testis, orchidopexy was performed by either inguinal or laparoscopic approach, depending on the surgeon's preference.

The age of the patients, the laterality of the testes, the presence of any contralateral testicular hypertrophy on physical examination, the laparoscopic findings and the need for inguinal exploration, the incidence of orchidopexy and any intraoperative and post-operative complication were reviewed.

Statistical analysis

Statistical analysis was accomplished using the SPSS program for Windows 21.0 (SPSS, Chicago, Illinois, United States). Fisher exact test was used to compare the categorical data. $P < 0.05$ was considered statistically significant. The statistical methods of this study were reviewed by Yuk Him Tam from the Prince of Wales Hospital.

RESULTS

Forty children had unilateral impalpable testis. Ten children had bilateral impalpable testes. Orchidopexy was performed in 16 children (40%) in the unilateral group and 9 children (90%) in the bilateral group ($P < 0.05$) (Figures 3 and 4).

Unilateral group

Regarding the 16 children who underwent orchidopexy, 12 children underwent inguinal orchidopexy (5 peeping testes), 3 children underwent Fowler-Stephens operation (1 peeping testis) and 1 child underwent laparoscopic

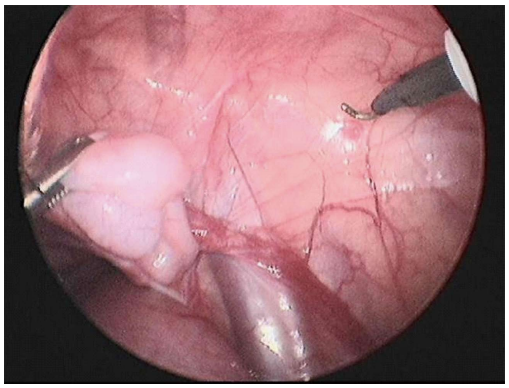

Figure 1 Laparoscopic view of a right undescended testis.

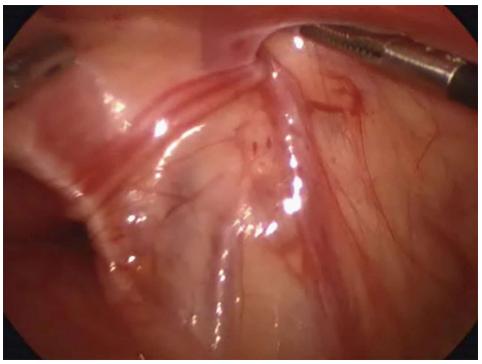

Figure 2 Vas deferens and vessel enter into the right deep ring, a groin exploration is required.

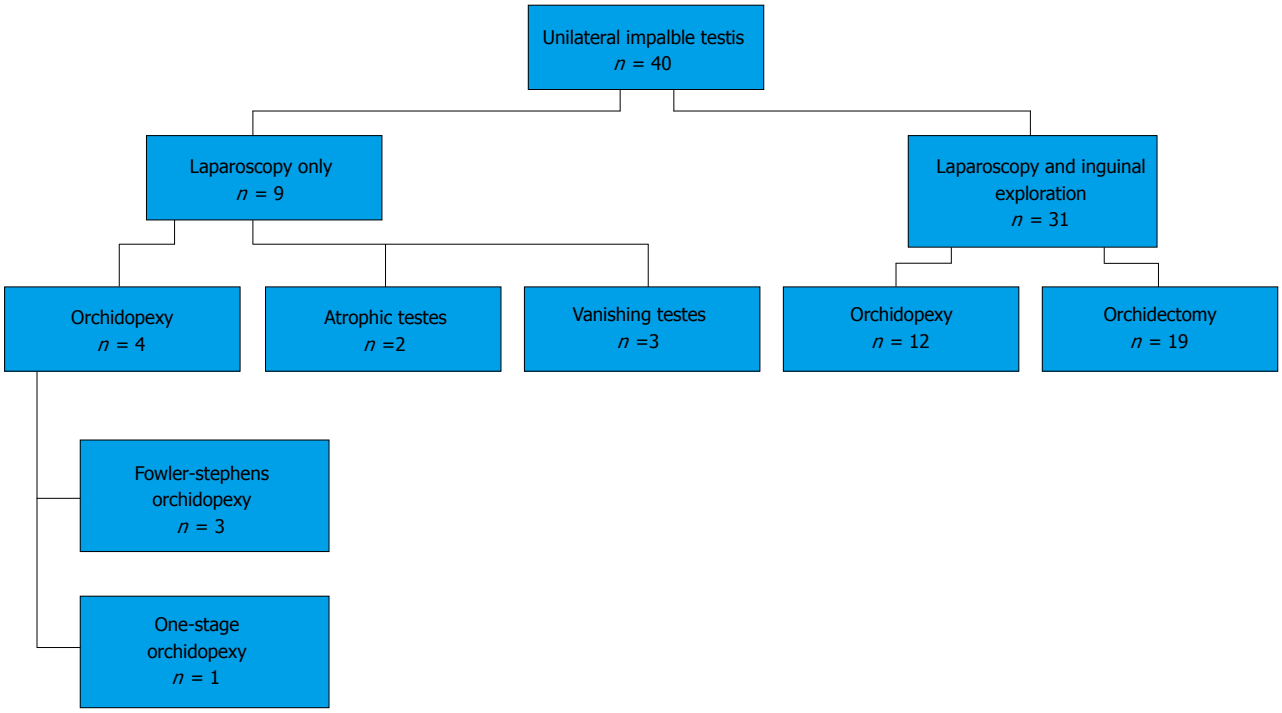

Figure 3 A flow chart showing the management of children with unilateral impalpable testis.

Table 1 The association of the need for inguinal exploration and orchidopexy in children with unilateral or bilateral impalpable testes

		Unilateral impalpable testis *n* = 40	Bilateral impalpable testis *n* = 10	*P* value
Inguinal exploration	Required	31	4	0.03
	Not required	9	6	
Orchidopexy	Performed	16	9	0.005
	Not performed	24	1	

one stage orchidopexy. Twenty-one children have "orchidectomy" performed for the testicular nubbin (*n* = 19) or atrophic testis (*n* = 2). Three children had vanishing testes. Out of the 24 children who underwent orchidectomy or has vanishing testes, contralateral testicular hypertrophy was noticed in 10 children (41%). Children with left impalpable testis has a lower rate of orchidopexy (L: 35%, 9/17, R: 50%, 7/7), However the difference did not reach statistical significant (Figure 3, Tables 1 and 2).

Bilateral group

Orchidopexy were performed in 18 testes (90%). Inguinal orchidopexy was performed in 7 testes. Fowler–

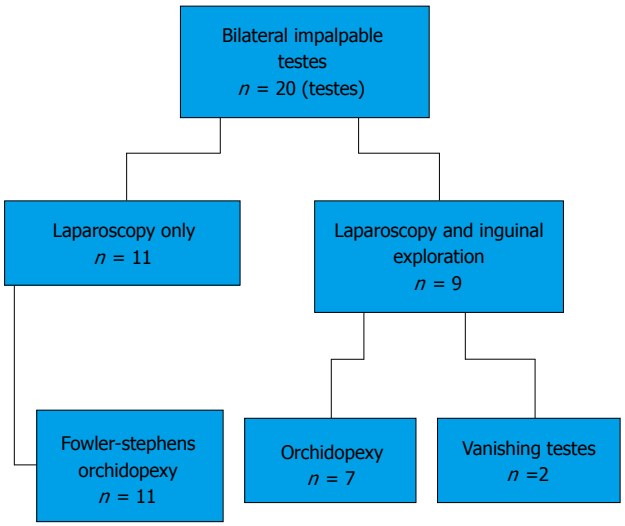

Figure 4 A flow chart showing the management of children with bilateral impalpable testes.

Stephens procedure was performed in 11 testes. One child had bilateral vanishing testes upon inguinal exploration (Figure 4).

Inguinal exploration

Thirty-one children (78%) in the unilateral group underwent subsequent inguinal exploration while only 4 children (40%) in the bilateral group underwent groin exploration ($P < 0.05$). In the unilateral group, children with left impalpable testis had a higher need for inguinal exploration (L: 85%, 22/26, R: 64%, 9/14) but the difference did not reach statistical significance (Tables 1 and 2).

Outcome

No intraoperative complication was encountered. Histological examination showed absence of testicular tissue in all the nubbins. Benign testicular tissues were identified in the 2 atrophic testes. The mean follow up was 53 mo (range 10 to 198 mo). Testicular atrophy was noticed in 2 children after 2nd stage Fowler-Stephen procedure and 1 child after inguinal orchidopexy.

DISCUSSION

There is ongoing debate on the best initial approach for impalpable testis. Our study showed in children with unilateral impalpable testis, 78% of children required an inguinal incision. In reports which used laparoscopy as the initial approach for impalpable testes, the need for inguinal or scrotal exploration for unilateral impalpable testis ranged from 38% to 85%[12,13]. Ethnic, geographic and genetic reasons may account for the difference in the incidence of intra-abdominal testes in children with impalpable testes[13-15]. Although a high proportion of children with unilateral impalpable testes required an inguinal incision, initial laparoscopy directed the subsequent approach without any intraoperative complication encountered in this study.

Table 2 The association of the need for inguinal exploration and orchidopexy with the laterality of testes in children with unilateral impalpable testis

		Left *n* = 26	Right *n* = 14	*P* value
Inguinal exploration	Required	22	9	0.14
	Not required	4	5	
Orchidopexy	Performed	9	7	0.27
	Not performed	17	7	

Regarding the laterality of the unilateral impalpable testis, the testis was more commonly located on the left side (65%). Eighty-five percent of children with left impalpable testis had inguinal exploration while only 64% of children with right impalpable testis had inguinal exploration. Park *et al*[16] had similar finding in their study but other studies did not report the laterality of the testes[7,8]. In children with bilateral impalpable testes, only 40% of children in this study required additional inguinal exploration. Sixty-five percent (13/20) of testes can be managed by laparoscopy alone, including 2 vanishing testes.

Fifty three percent of children with unilateral impalpable testis underwent orchidectomy. Majority of children had either a testicular nubbin or a vanishing testis. Intrauterine loss was the postulated etiology in children with unilateral impalpable testis[17]. Studies showed if contralateral testicular size larger than 1.8 cm predict testicular loss on the symptomatic side[11,17]. In this study, we used subjective manual assessment, which may not be as accurate as the measurement by ultrasonography. Although only 41% of children with unilateral testicular loss showed contralateral testicular hypertrophy, this physical finding can provide additional information in pre-operative counseling.

Germ cell was reported to be present in up to 16% of the testicular nubbin specimen[18]. In this study, pathological study of the testicular nubbin did not detect any testicular tissue. We think it is still a reasonable approach the removed the nubbin in order to confirm the histology.

The success rate after laparoscopic assisted orchidopexy was 87% (13/15). There were reports studying the success rate of different laparoscopic approaches including one-stage laparoscopic repair, one-stage Fowler-Stephens or two-stage Fowler-Stephens repair[19-21]. The assessment on the feasibility of one stage laparoscopic repair may be difficult. Two-stage Fowler-Stephens orchidopexy may be the treatment of choice for all intra-abdominal testes, if there was any doubt in decision of the laparoscopic approach intra-operatively[22].

One of the limitations of this study is on the decision of surgical approach in peeping testis. Five out of 6 peeping testes were managed by inguinal orchidopexy. Both inguinal and laparoscopic approaches were eff-

ective in the management of peeping testis[23]. Our approach increased the number of inguinal exploration in this study.

COMMENTS

Background

In the era of minimally invasive surgery, laparoscopy was advocated as the initial approach in children with impalpable testes. Laparoscopy can confirm the presence or absence of intra-abdominal testes and can direct the subsequent approach.

Research frontiers

Controversies still exist on the best initial approach in the management of impalpable testis. Others suggested that inguinal or scrotal exploration should be used as the initial approach in children with unilateral impalpable testis.

Innovations and breakthroughs

This study showed in children with unilateral impalpable testis, 78% of children required an inguinal incision. Orchidopexies could be performed successfully in 90% of children with bilateral impalpable testes.

Applications

Laparoscopy is a safe procedure with no intra-operative complication encountered in this study. A prospective study is needed to study the best initial approach in unilateral impalpable testis.

Terminology

Cryptorchidism: Impalpable testis or undescended testis. Impalpable testis: The testis is not palpable in scrotum or at groin after general anesthesia. First stage Fowler-Stephens operation: Division of the testicular vessels which aids the development of collateral vessels along the vas deferens. Second stage Fowler-Stephens operation: Mobilization of the testis into the scrotum.

Peer-review

This is a retrospective study of 50 children with impalpable testes who have been managed by laparoscopy as the initial treatment and perhaps the initial diagnostic procedure as well. The paper is well written and the messages are clear.

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Inflammatory fibroid polyps in children: A new case report and a systematic review of the pediatric literature

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Author contributions: Righetti L, Parolini F, Cengia P and Boroni G conceptualized and designed the study, designed the data collection instruments, drafted the initial manuscript, reviewed and revised the manuscript; Cheli M, Sonzogni A and Alberti D conceptualized the study and critically reviewed the manuscript; all the authors approved the final manuscript as submitted.

Conflict-of-interest statement: We hereby declare that the following information relevant to this article are true to the best of our knowledge: The above mentioned manuscript has not been published, accepted for publication or under editorial review for publication elsewhere and it won't be submitted to any other journal while under consideration for publication in your Journal; we have no financial relationship relevant to this article to disclose; there isn't any conflict of interest relevant to this article; all authors participated in the concept and design, analysis and interpretation of data, drafting and revising the manuscript, and they have approved the manuscript as submitted.

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Abstract

AIM: To study that inflammatory fibroid polyps (IFPs) in children are extremely uncommon tumors that may occur throughout the gastrointestinal tract.

METHODS: A systematic review of the pediatric literature and a report of a new case of IFP is also presented. The PubMed database was searched for original studies on pediatric IFPs since 1960, according to "Preferred reporting items for systematic reviews and meta-analyses" guidelines for systematic reviews.

RESULTS: Five studies were finally enclosed, encompassing 6 children with IFPs (mean age 64 mo). Tumors were located in the stomach (2 patients), in the small bowel (2 patients), in the rectum (1 patient) and in the colon (1 patient). Open surgery was performed in all patients and complete excision of the mass was achieved in all cases. All patients are alive and free of symptom. Authors described a further case of a 3-year-

old boy with a large duodenal IFP, in whom the tumor was removed by "en block resection". The presence of IFP throughout the gastrointestinal tract and its variable clinical appearances make it difficult to diagnose. An accurate pre-operative assessment is fundamental in order to differentiate IFP from other more aggressive gastrointestinal tumor, enabling unnecessary demolitive surgery.

CONCLUSION: When complete resection of the IFP is achieved, the prognosis is excellent.

Key words: Inflammatory fibroid polyp; Duodenum; Ultrasound endoscopy; Children; Surgery

Core tip: We present a new case of inflammatory fibroid polyp (IFP) occurring in a 3-year-old child who, to the best of our knowledge, is the first reported case of duodenal IFP in childhood. Below is a detailed systematic review of the literature on paediatric IFPs, focusing on etiopatogenesis, clinical presentation, diagnostic assessment and treatment.

Righetti L, Parolini F, Cengia P, Boroni G, Cheli M, Sonzogni A, Alberti D. Inflammatory fibroid polyps in children: A new case report and a systematic review of the pediatric literature. *World J Clin Pediatr* 2015; 4(4): 160-166 Available from: URL: http://www.wjgnet.com/2219-2808/full/v4/i4/160.htm DOI: http://dx.doi.org/10.5409/wjcp.v4.i4.160

INTRODUCTION

Inflammatory fibroid polyp (IFP) is an uncommon benign lesion that may occur throughout the gastrointestinal tract, even if stomach is the most affected site[1,2]. IFP natural history is unknown but rapid growth of the lesion within few months has been reported. IFP is found in all age groups but its typical presentation is in the 5th to 7th decade of life[2]; occurrence in children is extremely rare, with only 6 reported cases[3-7]. We present a new case of IFP occurring in a 3-year-old child who the best of our knowledge is the first reported case of duodenal IFP in childhood. A detailed systematic review of the literature on pediatric IFPs, focusing on ethiopatogenesis, clinical presentation, diagnostic assessment and treatment is then provided. A 3-year-old boy was referred to our Centre because of asthenia and anorexia. Physical examination was unremarkable. Blood test revealed a microcytic hypochromic anemia and eosinophilia; stools were positive both for heme and Enterobius Vermicularis. Upper GI endoscopy showed a 3.7 cm peduncolated mass of the duodenum. Contrast enhanced Abdominal MRI detected homogeneous enhancement of the mass after contrast (Figure 1). The tumor was close to the pancreatic head, but the common bile duct and the papilla major were spared. Endoscopic ultrasound (EUS), showed an hypoechoic mass located into the submucosa (echo-layer 3), not completely separated from the muscularis propria (echo-layer 4). In some EUS scans, the lesion showed features suggesting origin from the muscular layer, thus mimicking gastrointestinal stromal tumors (GIST) features (Figure 2). Cytological analysis of EUS fine needle aspiration (FNA) was compatible with diagnosis of leiomyoma. At laparotomy the mass deformed the postero-lateral wall of the proximal duodenum; the sero-muscular wall at tumor level was longitudinally severed but the lack of a cleavage with the submucosa did not allow local tumor excision. Intraoperative histological examination showed mesenchymal spindle cells proliferation with an inflammatory eosinophilic infiltrate, without morphological features suggesting malignancy. The tumor was completely removed by partial en block duodenectomy (Figure 3), followed by a duodenal inverted Y plasty. Histological findings were compatible with diagnosis of IFP: stromal looking cells with marked inflammatory eosinophilic infiltrates was evident, with no presence of mitosis or necrotic areas (Figure 4). The lesion was immunoistochemically reactive to vimentin (Figure 4) and CD34, and negative to citocheratins AE1-AE3 and CAM-5.2, LCA, CD20, CD3, ALK1, CD21, CD23, CD35, CD117, S100, CD1a, muscular markers (desmin, smooth and striated muscle), neuro-endocrine markers (cromagranin, sinaptofisin, CD56), D2-40, EMA, Mieloperossidase, CD99, GFAP. Proliferative index Ki67 was 2%. *H. pylori* research was negative. The postoperative course was unremarkable, and the patient was discharged home on post-operative day-7. Radio-allergo-absorbent test 6 mo later was positive for cow's milk protein allergy. At 4-year-follow-up the child is doing well.

MATERIALS AND METHODS

Data sources and study selection

For this systematic review we adhered to Preferred reporting items for systematic reviews and meta-analyses guidelines[8,9]. The PubMed database was searched for studies on IFP that were published since 1960. The date of the last search was December 2014. Inclusion criteria were English articles that reported original data on IFPs in pediatric setting. Eligible study designs were case report, case series and review. We omitted reports in which titles or abstracts indicated that they were on adult population (> 18 years) and they not clearly reported the method of diagnosis and treatment. We then evaluated the full text of the passed articles. Titles and abstracts of identified publications were checked and reviewed against the predefined inclusion criteria, and afterward, the full text articles was similarly

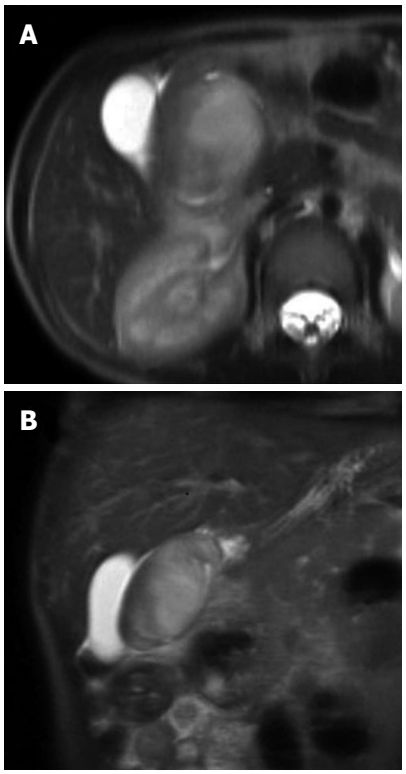

Figure 1 T2- weighted magnetic resonance image in axial (A) and coronal (B) scans, showing the solid mass arising from the duodenum.

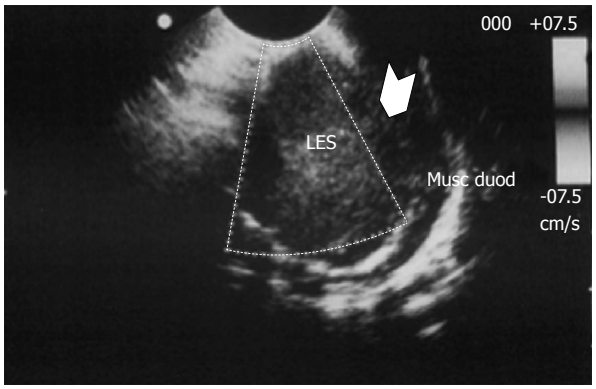

Figure 2 Endoscopic ultrasound showed an homogeneous, hypoechoic mass of 36 mm located into the echo-layer 3 (submucosa), but not completely separated from the muscularis propria (echo-layer 4); in some endoscopic ultrasound scans, the lesion showed features suggesting origin from the muscular layer, thus mimicking gastrointestinal stromal tumors features. The wall of the lesion was homogeneous and the external part showed hyperechoic spots, suggestive of microcalcifications.

assessed for eligibility.

Data extraction and quality assessment

Two independent authors extracted information related to the study. Methodological quality of the studies was assessed with the level of evidence and the strength of guideline recommendations in diagnosis scales[8]. For each study, data were extracted for age at presentation, sex, clinical presentation, size and location, diagnostic assessment, treatment, pathological examination and outcome.

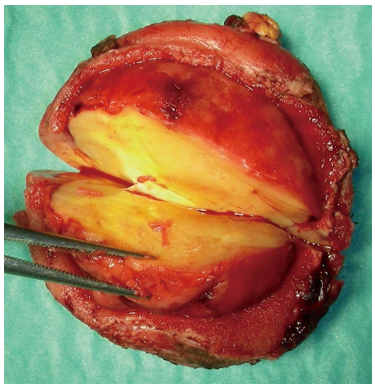

Figure 3 Gross examination: Firm round yellowish mass without necrosis and with an overlying area of mucosal ulceration.

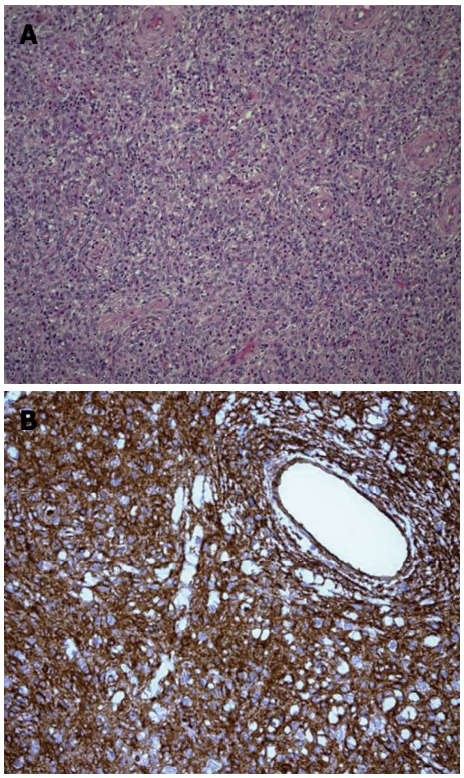

Figure 4 Stromal looking cells has no presence of mitosis or necrotic areas and the lesion was immunoistochemically reactive to vimentin. A: Stromal looking cells intermixed with marked inflammatory infiltrates rich in eosinophils granulocytes (40 ×); B: Marked immunohistochemical positivity to vimentin.

RESULTS

Description of studies

The initial PubMed search yielded 126 potentially relevant articles. Finally, 5 eligible articles met all the inclusion criteria and were enclosed in the review, encompassing a total of 6 cases. All reviewed studies were case reports (classes of evidence Ⅲ and rating scales of evidence E)[8].

Table 1 Demographics, clinical characteristics, diagnostic tools and treatment of inflammatory fibroid polyp in children

Ref.	Sex	Age (yr)	Clinical/laboratory	Diagnostic tools	Location	Size (cm)	Morphology	Treatment	Histology/immunohistochemistry	Follow-up
Samter *et al*[3]	Male	4	Acute abdomen	X-ray	Transverse colon	3.5 × 3.5 × 3	Peduncolated	Resection of transverse colon (7 cm), including a perforated diverticulum proximal to an obstructive intraluminal polyp	Granulation tissue containing an infiltrate of plasma cells Europhiles, lymphocytes and eosinophils; the predominant cells were stellate and spindle-shaped cells with plump vesicular nuclei an even chromatin distribution; numerous blood vessels	Alive and free from disease
Samter *et al*[3]	Female	8	Vomiting, diarrhea, cherry colored stools, palpable mass in RLQ1, hypochromic anemia	X-ray	Jejunum	5 × 3.7 × 3	Sessile	Resection of jejunum (12 cm)	Closely packed collagen fibers, and spindle-shaped cells with vesicular nuclei; inflammatory infiltrated composed by neutrophils, lymphocytes and eosinophils	Alive and free from disease
Persoff *et al*[4]	Male	3	Intermittent crampy abdominal pain and vomiting	X-ray Upper gastrointestinal series	Ileum	3	Peduncolated	Resection of ileum, including an ileo-ileal intussusception on intraluminal polyp	Proliferating edematous fibro vascular tissue diffusely infiltrated with inflammatory cells, many of with eosinophils, that involved all layers of the bowel wall except the mucosa	Alive and free from disease
Pollice *et al*[5]	Male	8	Recurrent enterorrhagy, anemia	Colonoscopy	Rectum	3 × 1.5	Sessile	Resection of rectum (7 cm)	Fibrous connective tissue with collagenous fibers arranged in large bundles; the inflammatory infiltrates consisted mainly of plasma cells and lymphocytes; numerous thin walled capillaries, sometimes dilated	Alive and free from disease
Schroeder *et al*[6]	Female	5	Epigastric pain, weakness, splenomegaly, hypocromic anemia	Ultrasound, CT	Stomach	Several cm	Endoexophytic	Subtotal gastrectomy	Not reported	Alive and free from disease
Chongsrisawat *et al*[7]	Female	4	Fever, arthralgia and severe anemia (Hb 3.9 g/dL)	Upper gastrointestinal series	Stomach	5 × 8	Sessile	Partial gastrectomy	Proliferative fibroblast and blood vessels admixed with mixed inflammatory cell infiltrated in stroma	Alive and free from disease
Our patient	Male	3	Asthenia, anorexia, hypochromic anemia, eoshinophylia	Upper GI endoscopy MRI EUS with FNA	Duodenum	3.7	Sessile	Partial "*en bloc*" with the tumor duodenectomy	Inflammatory infiltrates rich in eosinophils and stromal spindle-shaped cells, with no evidence of mitosis and necrotic areas	Alive and free from disease

CT: Computed tomography; GI: Glycemic index; MRI: Magnetic resonance imaging; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration.

Systematic review

In this series, IFPs affected both sex equally. Mean age of presentation was 64 (SD 2.16) mo, with a different distribution throughout the GI tract: in 2 patients (33%) IFP arose in the stomach, in 2 (33%) in the small bowel, and in remaining 2 patients, one IFP was in the rectum and one in the colon. In 2 patients (33%) the polyp was pedunculated, in 2 (33%) was sessile, and endoexophytic in the remaining 2 (Table 1).

Abdominal pain is the most common referred symptom, although physical examination was generally unremarkable in this series, except for in an 8-year-old girl who displayed a palpable mass in right lower quadrant[3]. Chronic anemia was the most common sign, present in 4 patients (67%). Recurrent enterhorragy and vomiting were also frequent. Chongsrisawat *et al*[7] reported a 4-year-old girl with atypical presentation, with chronic fever, arthralgia of knees and ankles, iron deficiency anemia, and hypoalbuminemia. One patient presented intermittent crampy abdominal pain and vomiting, and ileo-ileal intussusception was subsequently diagnosed[4]. Samter *et al*[3]

reported one case of peritonitis caused by perforation of colonic IFP.

Considering the diagnostic assessment, peripheral blood eosinophilia was never reported in this series. Although abdominal X-ray may provide some clue of the disease, gastrointestinal endoscopy and EUS was the preferred method for IFP diagnosis in adult population.

Most of the studies in adult population agreed that complete resection is the treatment of choice for IFPs. Nevertheless in this pediatric series all the masses were larger than 3 cm of diameter, and no endoscopic polypectomy was performed (Table 1). Open surgery was performed in all patients, and complete excision of the mass was achieved in all cases (Table 1). The 2 patients with gastric IFP underwent partial gastrectomy. The patients with IFP arising in the small bowel underwent resection and primary anastomosis. The patient with colonic IFP underwent colonic resection and primary colo-colonic anastomosis[7]. The remnant patient underwent resection (7 cm) of the rectum. All but one studies[6] reported data on pathological examination. A variable grade of inflammatory infiltrate was evident in all patients, while eosinophilic infiltrate was present in three (50%). At follow-up all patients are alive and present no symptom recurrence.

DISCUSSION

Demographics and tumor location

IFP was firstly described by Vanek[1] in 1949. Although at least 1000 IFP cases have been reported in literature, only 6 cases have been described in pediatric patients (Table 1)[3-7]. Both sexes appear equally affected. Mean age of presentation was 5 ± 2 years (range 3-8), IFPs were about equally distributed throughout the GI tract: 29% respectively into the stomach, small bowel and colon-rectum and 13% into the duodenum. That differs from adults in whom 70% of cases were found in the stomach[2-8].

Clinical characteristics

IFPs present in a variety of ways depending on their size, location and adjacencies. Polyps in the stomach usually cause pyloric obstruction, while IFPs located on the small bowel cause chronic episodes of colicky abdominal pain, lower gastrointestinal bleeding, anemia and intermittent episodes of intestinal bowel intussusceptions[1-3]. In pediatric population the most frequent symptom was asthenia and anemia related to the mass bleeding, but they are unspecific findings[1-5]. Rupture of colonic IFP has been described in a 4-year-old boy[3]. Physical examination is generally not conclusive (Table 1).

Etiopathogenesis

Etiopathogenesis of IFPs is still largely unknown. An allergic hypothesis has been firstly proposed, on the base on eosinophilic infiltrate[1]. The role of parasite or chronic *H. Pylori* infection has been also reported[8-11]. Although IFPs have been regarded as inflammatory and reactive phenomenon occurring in response to unknown irritants or allergic factors[1], recent data show that the spindle cells express platelet-derived growth factor receptor alpha (PDGFRA), and the majority of IFP harbor activating PDGFRA mutations configuring IFPs as true mesenchymal tumors[12].

Diagnosis

Peripheral blood eosinophilia has been reported in adults[10,11], this finding was also observed in our patient, but it was never described in the other children of the series (Table 1). Ultrasonography (US) and computed tomography scan are usually requested; however, they fail to differentiate IFP from other more common lesions[4]. At GI Tract Endoscopy IFPs are seen as protruding intraluminal masses with a smooth and often ulcerated mucosa. As most IFPs are submucosal lesions, it is almost impossible to obtain a completely diagnostic endoscopic biopsy. EUS is the gold standard for diagnosis of IFPs in adults. The tumour presented as a hypoechogenic and homogeneous mass, located within the second or third sonographic layer of the GI tract wall, with an intact fourth layer. Ours was the first case in which EUS was performed in a child with IFP. However, EUS findings in our patient were wrongly suggestive of leiomyoma rather than IFP, due to the strong adherence of the proliferating mass to the muscular layer. These findings led us to perform FNA in order to confirm clinical suspicion and to rule out a GIST; unfortunately, as reported in the literature, the result of biopsy was non-diagnostic.

Histopathology

The striking features of IFPs are the characteristic arrangement of fibrous and vascular elements ("perivascular onion skinning") associated with marked inflammatory eosinophilic infiltrate[2,8]. IFPs were suggested to show different appearance according to the different part of GI tract from which they arise. Gastric IFPs seem to arise at the base of the lamina propria, extending through and disrupting the muscularis mucosa. Ileal IFPs are intramural proliferations that push against the muscularis mucosae, eventually disrupting it and extending into the mucosa often ulcerating it. They obliterate the submucosa and muscularis propria often invading the mesentery. Gastric IFPs have less stromal edema and therefore they appear more solid in comparison with the ileal ones. Furthermore, gastric IFPs typically have also a prominent perivascular orientation of the different cells and eosinophils infiltration is more prominent than in ileal IFPs[13]. For duodenal IFPs it has been suggested they display the same histological feature of gastric IFPs; they arise in the lower layer of the lamina propria, causing splitting fraying and atrophy of the muscle wall layer[14,15]. That was observed also in our case in which the tumor was composed of stromal looking cells,

embedded in a mixed matrix intermixed with marked inflammatory infiltrates extremely rich in eosinophils granulocytes. Nevertheless, in IFPs the degree of eosinophilic infiltration is variable and of doubtful significance. The different histological patterns and the variable degree of stromal eosinophilic infiltration have been correlated with the evolutive stages of the lesion. Both IFPs of the GI tract and the eosinophilic gastroenteritis have been also considerate as variants of the same disease[10,11]. Immunohistochemical investigations give little help in the diagnosis of IFPs, mainly by excluding mesenchymal and myogenic tumors that should be considered in differential diagnosis[8-10].

Treatment

Complete resection is the treatment of choice for IFPs, in order to relieve symptoms and resolve diagnostic uncertainty. In adults, accessible pedunculated IFPs can be removed by endoscopy (endoscopic submucosal dissection is required), since most of the polyps are smaller than 2 cm[13,16-18]. This is uncommon in children in whom all polyps were larger than 2 cm, making endoscopic polypectomy impracticable, as in our case. As IFPs arise from the submucosa and may be sessile, endoscopic resection may result in perforation or incomplete resection in larger lesions. Surgeons should be aware of the existence of this rare benign entity, which may mimic spindle cell tumours such as GIST, leiomyoma, leiomyosarcoma and schwannoma[2-17]. EUS with fine needle biopsy might improve the accuracy of the preoperative diagnosis of duodenal IFPs, enabling local "*en bloc* resection" and avoiding unnecessary pancreatoduodenectomy[18]. According to the limited pediatric experience, when complete excision of the tumour is achieved, the prognosis is excellent. Unlike adults patients with IFPs, recurrence or metastazisation in children was never reported.

COMMENTS

Background

Inflammatory fibroid polyp (IFP) is an uncommon benign lesion that may occur throughout the gastrointestinal tract, even if stomach is the most affected site. IFP natural history is unknown but rapid growth of the lesion within few months has been reported.

Research frontiers

IFP is found in all age groups but its typical presentation is in the 5th to 7th decade of life; occurrence in children is extremely rare, with only 6 reported cases.

Innovations and breakthroughs

The authors present a new case of IFP occurring in a 3-year-old child who the best of their knowledge is the first reported case of duodenal IFP in childhood. A detailed systematic review of the literature on pediatric IFPi is then provided.

Applications

The study provide a detailed systematic review of the literature on pediatric IFPs, focusing on ethiopatogenesis, clinical presentation, diagnostic assessment and treatment.

Terminology

IFP was firstly described by Vanek in 1949. Etiopathogenesis of IFPs is still largely unknown. An allergic hypothesis has been firstly proposed, on the base on eosinophilic infiltrate. The role of parasite or chronic *H. pylori* infection has been also reported. Now IFP is considered a benign reactive phenomenon similar to granulomata, occurring in response to unknown irritant or allergic factors. Recently mutations in platelet-derived growth factor receptor alpha have been identified in adult patients with IFP.

Peer-review

The manuscript is well written and very interesting.

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