Leading Article

Constipation in children: New developments

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Functional constipation (FC) is a troublesome problem in children. It is characterized by reduced stool frequency, pain and difficulty in passing stools, stool withholding and faecal incontinence. It has been defined in many ways in the past, including the usage of a single symptom such as low bowel frequency or using symptoms complexes. However, since 1999, Rome criteria have been used to define FC in children. This Rome definition of FC is an evolving process and 2 iterations of Rome criteria have been in the field up to now[1,2]. The current definition (Rome IV) of FC is given in **box 1**[3]. Rome criteria use multiple clinical features to define FC rather than a single clinical feature such as low defaecation frequency or difficulty in passing stools.

Box 1: Rome IV criteria for functional constipation in children

Must include 2 or more of the following occurring at least once a week for a minimum of 1 month with insufficient criteria to diagnose irritable bowel syndrome

- Two or fewer defaecations in the toilet per week in a child of a developmental age of at least 4 years
- At least one episode of faecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel motions
- Presence of a large faecal mass in the rectum
- History of large diameter stool that can obstruct the toilet

After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

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Epidemiology

Data are emerging across the world to reiterate that FC is a more widespread problem than suspected. In the Asian region, the prevalence rates vary from 0.3% in Japan to 32% in Taiwan[4,5]. Several studies in Asia have also illustrated the magnitude of the problem. It is important to note that the growing economies in Asia have a higher prevalence of FC than some of the developed countries in the world[5,6]. In a developing country like Sri Lanka, the prevalence rates range from 7-15%, indicating that FC is a growing health problem[7,8]. More recent data from South America indicate that FC is a significant burden in this area as well. Prevalence of FC in Panama, Colombia, Ecuador and El Salvador is 15.9%, 13%, 11.8% and 10% respectively[9-12]. New data in the Western world show that FC is a growing problem in these countries too. A recently concluded study from the United States (US) reports the prevalence of constipation in children and adolescents as 13%[13]. Prevalence data from Italy showed that 17% of their school children are suffering from FC. The prevalence varies between 4.7 to 7.2% in Turkey[14,15]. Almost all these new studies have used standard Rome criteria (Paediatric Rome II or Rome III criteria) for diagnosis. These data suggest possible shifting of the epidemiological epicentre from the traditional Western world to the newly developed countries and some of the developing countries of the world.

Risk factors

The landscape of risk factors for FC is also changing. Obesity was considered to be a risk factor for FC in children. A study from the Netherlands has shown children with morbid obesity have prolonged colonic transit times. This would explain the higher prevalence of FC in children with obesity[16]. However, new emerging data from a school based survey from Colombia found no such association[10]. Child abuse is a major social welfare problem in the world. Both developed and developing countries have shown a high prevalence of child abuse. We studied the association between FC and major forms of child abuse in Sri Lanka. According to our findings, FC is clearly associated with physical, emotional and sexual

abuse in adolescents[17]. This study also revealed that children faced with abuse had more severe symptoms of FC[17]. A study from Hong Kong found another novel set of risk factors. These were, not having regular meals with parents, sleep deprivation and lack of physical activity, which were associated with FC in children[18]. These factors are becoming more common in modern society, especially in the developed and newly developing countries, perhaps rendering children more vulnerable to develop FC.

A systematic review by Phillip et al. has shown the importance of stressful life events as a risk factor for developing FC[19]. Bullying at school, failure in examinations, and separation from the best friend, are associated with FC[19]. In addition, frequent punishments at home and severe illness among a family member are reported as risk factors of developing FC[19]. Toilet training is a significant stressful period for both parents and young children alike. In this review and in other studies, it has been evident that punishment during the time of toilet training is associated with FC in children[20]. It is imperative to understand that toilet training is a delicate process and attention and understanding of parents play a key role in successful toilet training.

Dietary factors have also been shown to play a major role in the development of FC. Researchers have demonstrated that a low fibre diet predisposes children to develop FC[21]. Fast food consumption is a growing problem in the world and a study from China clearly illustrates increasing fast food consumption across all age groups in children[22]. Apart from its many other associated health problems, recent data show that consumption of fast food is emerging as a risk factor for the development of constipation in children[18].

Investigations

Evidence is emerging that conventional investigations do not help in the day to day management of patients with FC. Several investigators have shown a lack of sensitivity and specificity and low inter-observer and intra-observer reliability of plain abdominal x-rays and their scoring systems in investigating children with FC[23,24]. The recent guideline released by the North American and European Societies of Paediatric Gastroenterology, Hepatology and Nutrition has also reiterated the lack of evidence for doing an abdominal x-ray[25]. Emerging evidence shows that non-invasive ultrasonographic measurement of rectal diameter has a good correlation with the degree of faecal loading in the rectum[24,26,27]. Other conventional testing that most clinicians generally carry out in children with FC, such as thyroid function tests and tests for hypercalcaemia, have also proved to be not useful in finding organic diseases leading to constipation[25].

Novel high resolution anorectal and colonic manometry have revealed invaluable physiological understanding of colonic and anorectal function in FC. High resolution anorectal manometry (HRM) and 3-dimensional high resolution anorectal manometry have been in the field for a few years now. These investigations provide details of anorectal physiology and abnormalities in FC which could help in the management. In a study including 30 children with constipation, Ambartsumyan and coworkers found abnormalities such as asymmetric longitudinal and radial pressure distribution along the anterior, left posterior and right quadrants[28]. However, further studies are needed to clarify these findings and to understand their clinical utility for a practising paediatrician. High resolution colonic manometry is still in its infancy. One recent study by Wessel *et al*. has shown a reduction in postprandial retrograde cyclic propagating motor pattern (which is suggestive of the presence of a neuropathy), and increased number of pre-prandial long single motor pattern. High amplitude propagatory contractions (HAPCs) are rarely noted in children with FC during the post-prandial period but could be induced by bisacodyl infusion[29]. Compared to other studies, which were mainly concentrating on HAPCs alone, this study shows that other motor patterns in the colon are equally important in development of FC. These novel findings could shed light on the pathophysiology of intractable constipation and guide the therapeutic modalities in the future.

Faecal disimpaction

The majority of children with FC have faecal impaction. Disimpaction of the rectum loaded with faeces is considered an important step in managing children with FC. Contrary to traditional approaches such as soap sod enema, rectal suppositories and rectal medications like docusate sodium, mineral oil and glycerin enemas, oral medications have been found to be effective in evacuation of the rectum. High dose polyethylene glycol (PEG) (1-1.5g/kg/day) for 5-6 days is effective in most instances. In an elegant study Bekkali et al. noted that there is no significant difference between enemas and oral PEG in faecal loading in the rectum[30]. Given the fact that using rectal medications are painful and potentially traumatizing to the child, it is recommended to use oral medications in children with FC. Rectal medications are recommended when oral drugs fail to produce adequate results. We often use sedatives before administering rectal enemas or suppositories to minimize discomfort.

Dietary fibre

As we have pointed out previously, low fibre diets predispose children to develop FC. This became the basis of treating children with FC with dietary fibres. It is still a common practice in Sri Lanka to increase dietary fibre by the physician when they encounter a child with FC. Yang and Punati studied how paediatricians approach FC and how closely they follow the guidelines released by the North American Society of Paediatric Gastroenterology, Hepatology and Nutrition in 2006. The majority of paediatricians, residents and trainees who participated in this study have indicated that their approach to FC without faecal incontinence would be increasing fluid consumption (92.1%), increasing dietary fibre (89.5%), and increasing juices (71.2%). However, there is no evidence that any of these interventions help in relieving symptoms of FC[31]. Several studies have proved dietary fibre is no more effective than a placebo in treating children with FC[32,33]. More recent evidence and guideline from both North American and European Societies of Paediatric Gastroenterology, Hepatology and Nutrition also indicate the lack of efficacy of increasing fibre consumption in children with FC, who are taking normal daily requirement of fibre (age in years +5 grams)[25,34]. Therefore, it is important that paediatricians inquire and quantify the amount of dietary fibre intake in children presenting with features of FC and only increase fibre in the diet if it is determined that the child's diet is inadequate in fibre.

Probiotics

Probiotics are live micro-organisms (bacteria and fungi) that offer a wide range of health benefits to humans. Utility of probiotics in the treatment of functional gastrointestinal diseases has been widely discussed[35]. The basis for using probiotics in FC is derived from a study that demonstrated children with FC had abnormally low bacteroides and high firmicutes[36]. Abnormalities in the gut microbiome is thought to alter gas production in the gut, especially methane that could delay the colonic transit time[37]. Several studies have been published using a number of probiotic strains in children with FC such as *lactobacillus rhamnosus*, *lactobacillus casei*, *lactobacillus reuteri*, *bifidobacterium longum*, and *bifidobacterium lactis*[34]. A recent systematic review noted that the evidence for using probiotics in children with FC is still weak[34]. The future of using probiotics in children with FC or other functional gastrointestinal diseases depends not on randomly selecting probiotic strains in trials, but on studying and identifying abnormalities in the microbiome of children with FGDs and tailoring the treatments accordingly. However, this remains a rather difficult task.

Conventional medications

Osmotic laxatives have become the major therapeutic modality in the maintenance phase. A Cochrane review comparing lactulose with PEG has shown that PEG is superior to lactulose in terms of improving stool frequency, softening stools, and relief from abdominal pain[38]. Stimulant laxatives are rarely needed in the maintenance phase and the NICE guideline recommends to use them only when there is a poor response to osmotic laxatives[39].

Novel pharmacological agents

Prucalopride is a selective, high affinity 5HT4 agonist which enhances the colonic motility. Although initial studies in adults have shown promising results, a recently published long term observational study did not show any significant improvement in the bowel frequency. However, a more recent analysis of 6 phase 3 trials and 4 randomized control trials in adults has shown that prucalopride increases spontaneous bowel movements (more than 3 per week) in adults with constipation[40]. Yet for all that, the only available randomized controlled trial of use of prucalopride in children did not show any improvement of spontaneous bowel movements [41].

Lubiprostone is a prostaglandin E1 derivative that activates the chloride channel subtype 2, thereby increasing secretion of chloride rich fluid into the colon to soften stools. According to an open labelled pilot study conducted in 127 children, lubiprostone significantly improves bowel movements[42]. Results of a multicentre randomized placebo-controlled trial involving children in Europe and the US will be available in the near future.

Other drugs

Linaclotide is another novel drug that has already been evaluated in adults. It is a synthetic peptide that activates luminal guanylin receptors in the intestine, which enhance fluid secretion into the gut lumen and thereby soften stools. Several studies have demonstrated positive effects of linaclotide on improving bowel motion in adults with constipation[43,44]. Yet again, there are no studies involving children to recommend use of linaclotide in paediatric practice.

Elobixibat is a potent inhibitor of ileal bile acid transporters. It therefore can increase the bile acid content in the colon which in turn increases the fluid secretion and motility of the colon[45]. One randomized, double-blind, placebo-controlled trial in adult females has shown some promising results including significant acceleration of colonic transit time[46].

Electrical stimulation therapy

Transcutaneous electrical stimulation (TES) using interferential current has been used in the management of urinary incontinence[47]. It has been noted that patients develop diarrhoea as a side effect of this treatment. Using this concept, a group of researchers from Melbourne, Australia developed a protocol of TES for children with slow transit constipation. The protocol uses 4 electrodes (2 anterior and 2 posterior). They are connected in such a manner that the apparatus delivers a crossing current[48]. Using this technique, the group has conducted several studies. A randomized, controlled trial using 46 children has shown a significant increase in colonic transit compared to placebo stimulation[49]. In the long term follow up, a significant proportion of these children had improved to the degree that they were able to stop laxative treatment[50]. TES has also increased defaecation frequency to a normal range and reduced faecal soiling and abdominal pain. A physiological study using colonic manometry with TES has demonstrated a significant increase of frequency of antegrade propagatory contractions as well[51]. Currently, the researchers are testing the possibility of delivering TES at home and soon it will be available to children with slow transit constipation.

Sacral neuromodulation

In sacral neuromodulation, two electrodes are placed at the anterior ramus of the sacral nerve roots 3 and 4. These electrodes are connected to a pulse generator implanted to the lateral buttock. The pulse generator, when switched on, delivers an electrical impulse to stimulate the sacral nerves which in turn stimulates the colon and the rectum. Although several open label and observational studies have shown promising results, in a large randomized, double blind, placebo controlled, two phase trial involving 59 patients with refractory slow transit constipation, primary outcome measures did not differ between suprasensory and sham stimulation. There were no significant changes in the quality of life score at 3 weeks of intervention[52]. However, long term effects of this trial are yet to be published.

Surgical options

Surgery has been suggested as an option for intractable constipation in children. Siminas and Losty have systematically reviewed the surgical management of FC in children[53]. The surgical options could broadly be classified under 4 themes; anal and pelvic floor procedures, antegrade continent enemas and other colonic irrigation methods, colonic and rectal resections and formation of permanent stoma. Administration of botulinum toxin to the external anal sphincter is an acceptable therapeutic modality in children with FC due to external anal sphincter dys-synergia. Antegrade continent enemas have also been a treatment modality for children with intractable FC. The methods of inserting the tube to irrigate the colon vary from open surgical insertion to laparoscopic insertion of a caecostomy button. The published studies are mostly case series and no firm conclusions can be drawn from these studies[53]. Resection of the dilated rectum and the sigmoid colon is helpful in children with severe long standing constipation. Other surgical methods such as total colectomy and ileo-anal anastomosis and formation of permanent stoma are rarely used in children.

Future projection

We are certain that the future for children with FC would be a brighter one. In the next few weeks the Rome IV criteria will be widely available to clinicians and the diagnosis would yet again be standardized and will be used in both clinical and research fields for the next decade. New studies to identify the epidemiology and risk factors of FC in children living away from the traditional "western" world are being carried out giving broader understanding of the distribution of the disease. Culture independent microbiological methods are giving more understanding of the changes in the gut microbiota in children with FC which will help to understand and individualize probiotic therapy. Colonic and rectal manometry with high resolution catheters with 3- dimension pressure plots will also be able to identify abnormal motor patters in the whole colon or in segments which will be able to help in guiding both medical and surgical therapies. An array of novel drugs is constantly being developed to treat constipation in adults. Although the initial clinical trials are not very encouraging, novel therapeutic agents such as prucalopride, lubiprostome and alvimopan will undergo more trials including their usage in more diverse populations of children. These drugs will eventually be tested in trials and add to our armoury to treat childhood constipation more effectively.

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