

Challenges in Management of Irritable Bowel Syndrome in Children

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Irritable bowel syndrome (IBS) is a common cause of recurrent abdominal pain (RAP) in children and can be a debilitating experience for both child and family. Organic causes of RAP symptoms such as celiac and inflammatory bowel diseases should be excluded before a diagnosis of IBS is made. Treatment consists of dietary manipulation, drugs, and stress management.

Newer therapies may offer better control of symptoms with minimal side-effects. This article discusses the challenges faced by pediatricians in managing IBS and reviews management in the context of children from the Indian subcontinent.

Keywords: Irritable bowel syndrome; Management; Recurrent abdominal pain; Therapy.

Irritable bowel syndrome (IBS) was first mentioned as a concept in the Rocky Mountain Medical Journal in 1950 and so is a modern day epidemic. Recurrent abdominal pain (RAP), an important feature of IBS, was first described by Apley and Naish in 1958. Their criteria were 3 episodes of abdominal pain over 3 months, severe enough to affect the daily routine [1]. Irritable bowel syndrome (IBS), a common subtype of RAP in children [2], is one of the most common, non-infective gastrointestinal (GI) disorders in the Western world but is now increasingly recognized in adults in developing countries [1,3]. IBS has now been defined under the Rome III criteria as one of the functional gastrointestinal disorders [4]. This article has been written with the hope of stimulating interest in the epidemiology and treatment of IBS in children.

DEFINITION

IBS is a subtype of RAP with alteration of bowel habits (constipation, diarrhea or alternating constipation and diarrhea) [5]. IBS was defined by the current Rome III criteria for functional gastrointestinal disorders (FGIDs) including IBS, abdominal migraine and functional abdominal pain. For a clinical diagnosis of IBS the Rome III criteria need to be fulfilled [4].

As the age ranges of children seen in Pediatric practice varies in different countries, the prevalence of IBS may vary accordingly. Although the Rome III criteria require report of abdominal pain by the child, in practice younger children may present with typical symptoms of IBS such as alternating constipation and diarrhea with passage of mucus, loose stools with distress after meals

and constipation with out of proportion distress, relieved by defecation.

ETIOLOGY

The etiology of IBS remains undetermined [1]. Infection, inflammation, visceral hypersensitivity, allergy, or disordered gut motility may play a part [3]. Genetic predisposition and stress are also considered to compounding factors [3]. An infectious trigger for IBS, (infectious gastroenteritis more likely in developing countries) may also play a role. In developed countries, studies of bacterial gastrointestinal infections in adults suggested that around 25% continue to have longer lasting changes in bowel habit following an episode and that a small proportion develops IBS symptoms [6]. In a postal questionnaire survey of 576 individuals with a Salmonella or Campylobacter infection (between 2000-2009), nearly 10% of 189 individuals who responded to the questionnaire reported post-infectious IBS symptoms up to 10 years later [7]. Similar findings were also reported after an outbreak of gastroenteritis in children which was found to be associated with increased incidence of IBS [8].

A study in Norway showed that 7% of patients developed a post-infective FGID, mostly IBS, after a large waterborne outbreak of *Giardia intestinalis* infection [6, 9]. In a prospective study of 102 children with *Giardia lamblia* detected by ELISA in Russia, the prevalence of IBS was found to be 28% in girls and 17% in boys [10]. It is important to specifically ask for stool ELISA or microscopy for *Giardia* and treat with metronidazole if detected before making a diagnosis of

IBS [10]. Hence continuing symptoms after treatment of Giardiasis may reflect re-infection or the development of IBS symptoms. The incidence of post-infectious IBS in developing countries is not known; this would allow for a better description of risk factors for such children with IBS [6]. In developing countries, abdominal pain and diarrhea is often considered to be infectious in origin and the chances of a re-infection being high, pediatricians may not consider IBS at the top of their differential diagnosis. Moreover, IBS can have a waxing and waning course leading to its late detection and diagnosis [11].

There has been ongoing interest in finding a genetic association in IBS, more so because strong familial trends have been seen. So far, a positive association between IBS and an interleukin-10 polymorphism has been reported. Interestingly, patients with a mutation in a sodium channel gene (*SCN5A*) have been found more often report gastrointestinal symptoms, especially abdominal pain and may be contributory factor in IBS genetics [12]. Studies have also shown associations between migraine and IBS and a significant proportion of patients with IBS have frequent headaches [2,13].

No direct co-relation between IBS and malnutrition has been described. However, it will not be surprising that children with IBS may suffer from nutritional deficiencies as post prandial abdominal pain may make them apprehensive to eat which can make their diet inadequate. It is therefore important that any exclusion diet is discussed with a dietician and adequate supplements are prescribed.

EPIDEMIOLOGY

IBS is now increasingly being recognized in younger children although majority of patients are diagnosed in their adolescent years [14,15]. In a community based study of 507 secondary school students in the USA who reported abdominal pain ($n=381$), IBS type symptoms were noted by 17% of high school and 8% of middle school students [14,15]. Recent adult studies have shown a lower range of prevalence of IBS in Iran and India; i.e., 5.8% and 4.2%, respectively; however, the values in other developed Asian countries are possibly similar to those seen in the Western countries [11,16]. Some questions therefore remain to be answered –

- Is there a significant difference in the incidence of IBS in developing and developed countries?
- Will the incidence of IBS increase by adoption of a Western lifestyle?
- Are predisposing factors different in developing and developed countries?

- Is the increasing stress on young children to achieve or family break-up responsible for IBS symptoms becoming evident at a younger age?

The answer is probably ‘yes’ to a certain extent to all the questions. In the absence of any other plausible explanation, infective pathology is often considered the trigger for the IBS, especially in developing countries [6, 8].

CLINICAL CLASSIFICATION

The diagnosis of the various FGIDs including IBS depends on a detailed clinical history. Children with abdominal pain and disordered bowel function are classified as IBS, which may be associated with diarrhea (IBSD), constipation (IBSC) or alternating diarrhea and constipation (IBSA). Those with epigastric pain are classified as functional dyspepsia. Abdominal migraine causes self-limiting episodes of severe abdominal pain interspersed with periods of no pain. During attacks of abdominal migraine, gastro-intestinal symptoms may be associated. If severe vomiting occurs at a regular interval interspersed with symptom free periods in between, these children are said to have cyclical vomiting syndrome [4]. The remaining children whose pattern of abdominal pain does not fall into the above groups are classified as functional abdominal pain. If other symptoms such as headache and limb pain are reported this is called functional abdominal pain syndrome. Amongst the latter group there are children with abdominal pain but no gastro-intestinal symptoms whose pain is made worse by exercise. Their pain is likely to be of musculoskeletal in origin and may represent the pediatric equivalent of adult abdominal wall pain.

Diagnosis: Ruling out Other Differential Diagnoses

The lack of definite laboratory or radiological investigations to diagnose IBS leads to a significant number of referrals to the pediatricians and pediatric gastroenterology services [5]. Diagnosing IBS however remains a challenge for the clinicians. A detailed history forms the most important discriminator to confirm a clinical suspicion of IBS. A family or personal history of cranial or abdominal migraine can often be found in association with IBS. Parents often describe their child as a ‘little worrier’ and an anxiety state is often present in association with IBS. It is important to explore psychological issues at school or home such as bullying, financial difficulties, divorce or parental separation, oncoming exams, etc. and these factors needs to be addressed at the earliest for a successful outcome in managing IBS symptoms. A history of recent gastrointestinal infection may indicate a starting point for

IBS [6]. The Rome III criteria should help the clinicians to make a positive diagnosis of IBS and avoid unnecessary surgery such as appendectomy.

It is also important to ask about (or elicit) red flag symptoms highlighted in **Box 1**.

The diagnosis of IBS should be made after exclusion of other organic causes such as inflammatory bowel disease (IBD), celiac disease, etc. As a minimum we suggest following investigations to rule out organic pathologies: serological screening for celiac disease, inflammatory markers (ESR, CRP likely to be raised in IBD), liver function tests (low albumin in IBD), full blood count. Constipation needs to be considered as it can present with hard feces (constipation) and may be associated with overflow spurious diarrhea mimicking alternating constipation and diarrhea pattern seen in IBSD. Especially in developing countries, it is also important that a stool sample is sent for microscopy and culture with specific request to look for ova, cyst and parasites (including *Giardia*). In the absence of 'red flags' (**Box 1**) a celiac screen will suffice in a Western (country) clinical setting. An algorithm for screening and rational investigations is highlighted in **Box 2**.

MANAGEMENT

Once a diagnosis of IBS has been agreed the next daunting task a clinician faces is how best to manage the symptoms. The aim for any therapeutic intervention in IBS is to improve the quality of life, make the child pain free and regulate the stool consistency and frequency. The first step is to explain the diagnosis, suggest strategies to cope with stress, and reassure that there is nothing seriously wrong [18].

The complex interplay of biopsychosocial factors that may be involved in the development of IBS in children highlights the need for a multidisciplinary management approach [18]. Before commencing an

Box 1: RED FLAGS IN DIAGNOSING IBS

- Confirmed weight loss
- Symptoms persistent or worse at night (child wakes up with pain)
- Unexplained anemia
- Bleeding per rectum
- Severe diarrhea and/or vomiting
- Delayed puberty
- Unexplained fever
- Strong family history of inflammatory bowel disease

intervention, the expected benefits of the therapy need to be explained. Available therapeutic interventions are as follows:

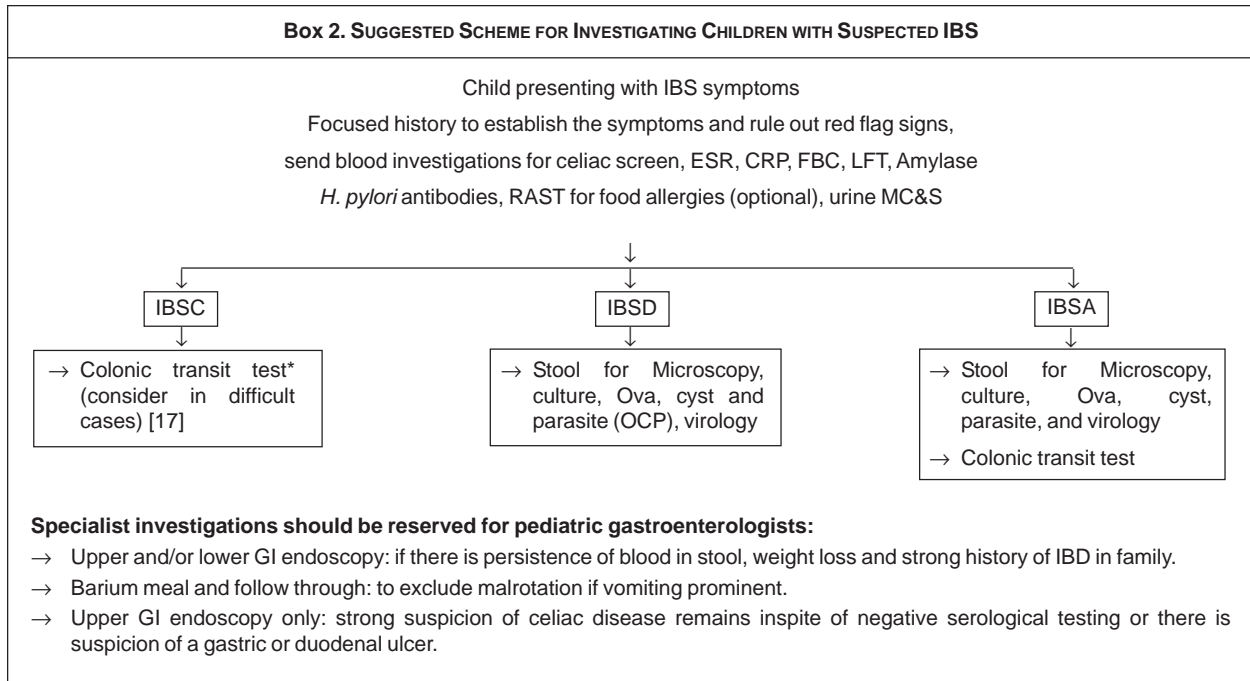
Placebo response: There are only a few placebo controlled studies. A recent multicentre double-blind, randomized controlled trial (RCT) [19, 20] of low-dose amitriptyline with placebo in treating children with pain-related FGIDs for 4 weeks showed no significant difference in the effectiveness of amitriptyline and placebo therapy.

Another meta-analysis which compared RCTs in children with IBS with no treatment, placebo and active intervention demonstrated that both spontaneous improvement and the effect of placebo were instrumental in contributing to the therapeutic effect observed in the patients receiving active compounds [21]. Studies have also demonstrated that a strong patient-clinician relationship is necessary and the support provided along with positive reinforcement provided by the clinician will confer a successful placebo response [19].

Psychological interventions: Many children with IBS receive psychological interventions [22]. A Cochrane review which included six trials conducted in children aged between 5 to 18 years with RAP comparing cognitive behavioral therapy (CBT) with standard therapies such as dietary interventions, pharmacological interventions, etc. concluded that CBT may be a useful intervention for children with RAP and IBS [22]. However, the evidence remains weak and bigger RCTs are necessary to establish this as a standard therapeutic intervention.

Some studies have shown that hypnotherapy may produce a beneficial effect in children with IBS for at least five years. It is believed that hypnotherapy normalizes altered visceral sensation, reduces colonic phasic contractions and reverses the patients' negative thoughts about their condition. A recent systemic review found that all trials demonstrated statistically significant improvement in abdominal pain scores in children in hypnotherapy group [23]. The authors recommended hypnotherapy as the first line in the management of children with IBS [23]. Behavioral therapies are beset by unavailability of therapists and the need for a number of sessions.

Pharmacological interventions: There is a weak evidence that pharmacological agents may provide relief from symptoms [24]. Functional abdominal pain and IBS are considered to be a state of dysregulation within the enteric and the central nervous systems, resulting in alterations in sensation, motility, and possibly, immune



system function. Pharmacological interventions for FGIDs should therefore be based on the understanding of bidirectional brain gut interactions, the “brain-gut axis.” [25].

Antispasmodic agents can be used when diarrhea is the predominant symptom in IBS to attenuate heightened baseline and postprandial contractility [26]. Mebeverine is licensed in the UK and is generally well tolerated; and can be used on an as required basis before meals. Other classes of antispasmodic such as calcium channel blockers have not shown any consistent benefit in IBS and are licensed for children in only a few countries [27]. In a recent study clinical recovery was seen in 94.9% of children treated with trimebutine maleate at the end of 3 weeks when compared to the non-medicated group where spontaneous recovery was seen in only 20.5% children [28]. Children in this study predominantly had IBS with constipation.

Antidepressants have shown some benefit in treating children with IBS symptoms [15,20]. In a study of 98 children who took amitriptyline for FGID; 77 patients responded to the treatment for an average of 10.7 months and this effectiveness persisted [29]. Selective Serotonin Reuptake Inhibitors (SSRIs) are widely used for treating anxiety, depression, and somatization disorders. Four RCTs of SSRIs in IBS showed that a standard dose of an SSRI led to a significant improvement in health related quality of life in patients (adults) with chronic or treatment resistant IBS.

Fiber, including bran, ispaghula husk, methylcellulose and sterculia, is sometimes used in children with constipation predominant IBS. However, only 10% of patients are improved by such agents, and insoluble fiber has been shown in a placebo controlled RCT to have no effect on pain and to exacerbate flatulence and bloating [30]. The traditional use of a high fibre diet may not be well tolerated by children [18,31].

Stimulant laxatives are associated with increased abdominal pain and tachyphylaxis [32]. If a long term treatment is considered necessary, polyethylene glycol (PEG) based laxative therapy may be a better option for treating IBSC [32].

Anti-diarrheal agents have a limited role and may be tried in children with diarrhea predominant IBS symptoms (IBSD). Loperamide, an opiate analogue, acts by stimulating inhibitory presynaptic receptors in the enteric nervous system resulting in inhibition of peristalsis and intestinal secretion. Studies in adults have found loperamide to be effective in reducing diarrhea in IBS patients but not symptoms of abdominal pain [33].

Serotonin (5-HT) acts through the 5-HT₃ and 5-HT₄ receptors and plays a significant role in the control of gastrointestinal motility, sensation, and secretion. Recent observations suggest that plasma 5-HT concentrations are reduced in IBS patients with constipation, but are raised in those with diarrhea, especially those showing postprandial symptoms. This has led to a considerable

interest in these receptors as possible therapeutic targets for IBS. The 5-HT₄ receptor agonists are predicted to enhance gastrointestinal propulsion and will be helpful in constipation predominant IBS. The antagonists at the 5-HT₃ receptor slows gastrointestinal transit and reduce visceral sensation; this should be useful in diarrhea predominant IBS.

If pharmacological treatment is considered, in a chronic condition such as IBS, the drug should be withdrawn periodically to determine whether it is still required. Intermittent treatment at times of stress can be effective.

Antibiotics: The role of antibiotics as a treatment remains controversial. While it is true that infectious gastroenteritis are known to trigger IBS symptoms and often clinicians choose to use antibiotics as a trial to see if it would help ruling out a treatable cause, especially in developing countries. However, it should be noted that IBS is less commonly reported from developing countries and it is possible that there may be reluctance amongst the clinicians to diagnose IBS. In an adult study (aged ≥ 18 years), encouraging results in symptoms were noted in IBS patients treated with Rifaximin for at least 2 weeks [34]. In a study of 43 children with IBS symptoms, whose Visual Analogue Scale (VAS) score to evaluate symptoms (abdominal pain, constipation, diarrhea, bloating, flatulence) showed improvement after 1 month treatment with 600 mg of Rifaximin [35]. The rationale behind this treatment is to eradicate small intestinal bacterial overgrowth [34,35]. An alternative and safer approach is to use probiotics rather than antibiotics.

Dietary interventions: These form an important strategy in managing children with IBS. Wherever available a pediatric dietician should be involved when such interventions are considered.

A recent Cochrane review [36] considered seven trials: two trials compared fiber supplements with placebo; two trials studied a lactose-free diet in comparison to placebo, and three trials compared supplements of lactic acid producing bacteria with placebo. The authors concluded that there is a lack of high quality evidence on the effectiveness of dietary interventions.

In a study, 59 children (4 to 18 years) were randomized to receive either a probiotic or a placebo for 6 weeks [5], probiotic was superior to placebo both in primary (subjective assessment of relief of symptoms) and secondary endpoints (abdominal pain/discomfort, abdominal bloating/gassiness and family assessment of life disruption). *Lactobacillus reuteri* has also been effective in relieving functional abdominal pain

compared with placebo [37]. Other RCTs have also shown encouraging results with probiotics [38].

In an observational study involving 46 children (1 to 18 years) with IBS treated with partially hydrolyzed guar gum (Optifibre Nestlé) for a period of 6 to 8 weeks [31], 82% patients showed improvement in their alternating constipation and diarrhea and (58% showed improvement in their diarrhea only symptoms. In the same study group, 68% also showed significant improvement in their abdominal pain. Similar beneficial findings were replicated in a recent RCT from Italy involving 60 children (8-16 y) with IBS and RAP being treated with PHGG with statistically significant results showing tendency toward normalization of bowel movements in IBS subgroups [39].

Parents generally accept dietary treatment more willingly than drugs. In our practice we try long chain fatty acid supplementation (Calogen Nutricia) to slow intestinal transit for IBSD, PHGG for IBSA and PEG-based laxative for IBSC. If this is unsuccessful we try probiotic supplement (*Li reuteri*) [37] or dairy free diet. If symptoms persist, drugs (Merbentyl, Peppermint oil) are tried [24]. In selected cases we have used gut-focused hypnotherapy with encouraging results.

THE INDIAN SCENARIO

An infective trigger may often be the starting point of IBS symptoms. With the ever increasing challenge to achieve and the associated stress, IBS is more often likely to be seen in Indian children than ever before. It is also important that more emphasis is given towards making a clinical diagnosis of IBS due to the limited availability of resources and the economic viability of conducting often unnecessary laboratory and radiological investigations.

The management of IBS remains a challenge worldwide with no clear consensus available, this will make it even more challenging in the context of a developing country like India where psychological or dietary interventions may only be available in tertiary centres. The management will be largely dependent on the physician and it is of paramount importance that a trusting relationship is developed with the patient/family to ensure success of any intended therapy.

The first step should always be an explanation and reassurance unless the symptoms are very severe at the initial presentation. Where there is a clear history of an infective trigger and diarrhea-predominant IBS symptoms, it may be appropriate to consider the presence of small intestinal bacterial overgrowth. While an abnormal bowel flora may occur in IBS, in the absence of more data the use broad spectrum antibiotics is

expensive, increases antibiotic resistance and puts the child at risk of antibiotic associated diarrhea.

Some amount of psychological counseling can be provided by the clinician and the knowledge that there is nothing seriously wrong in the child often works wonders. Other stressful triggers in school and home may be easily addressed if the parents feel confident about the diagnosis and make adjustments to the child's lifestyle. Pharmacological and to a certain extent dietary adjustments can be tried even in the absence of a specialist dietician; however, where such services are available the management should include a multi-disciplinary team including dieticians and clinical psychologists.

In the absence of evidence-based data, any conclusions on the dietary and lifestyle management of IBS in the Indian Subcontinent must be speculative. However, the traditional Indian food often contains vegetable oil, ghee, etc. and this may have a beneficial effect in children with IBS as these food items consists of a significant proportion of long-chain fatty acid.

Treatment of IBS and IBSA based on partially hydrolyzed guar gum, which is naturally occurring and other soluble fibers may be effective [31].

Hypnotherapy could be mirrored by meditation, yoga and chanting [40]. Yoga exercises were found to be effective in significantly reducing abdominal pain in children with IBS and this persisted after 3 months of completion of therapy [40].

CONCLUSIONS

IBS often presents a clinical challenge because of the nature of the symptoms and its interpretation amongst parents and physicians. A detailed focused history will clarify lot of uncertainties about the symptoms and investigations should be kept to the minimum and aimed at ruling out other serious pathologies. Successful management of IBS in children revolves around time spent at explaining and reassuring the child and the parents. Where a treatment is contemplated it is important that the expected benefits and possible side-effects are explained to the family before commencing on the therapy. Whenever available and feasible the aim should be to involve a multi-disciplinary team in managing children with IBS.

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