Epidemiological and pathophysiological aspects of abdominal pain predominant functional gastrointestinal disorders in children and adolescents: A Sri Lankan perspective

Niranga Manjuri Devanarayana

EPIDEMIOLOGICAL AND PATHOPHYSIOLOGICAL ASPECTS OF ABDOMINAL PAIN PREDOMINANT FUNCTIONAL GASTROINTESTINAL DISORDERS IN CHILDREN AND ADOLESCENTS:

A SRI LANKAN PERSPECTIVE

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CONTENTS

OUTLINE OF THE THESIS

Recurrent abdominal pain is a common worldwide symptom seen in children and adolescents. It has a significant impact on quality of life of the affected children and their family members and a severe burden on the already stretched healthcare systems around the world. Many organic diseases can present as abdominal pain, but the majority of affected children have abdominal pain predominant functional gastrointestinal disorders (AP-FGIDs) such as irritable bowel syndrome, functional dyspepsia and functional abdominal pain.

This thesis has attempted to explore some epidemiological and pathophysiological aspects of AP-FGIDs in Sri Lankan children and adolescents.

Part I - *Introduction to abdominal pain predominant functional gastrointestinal disorders*

Chapter I of this thesis gives a detailed account of the global prevalence and international perspective of pediatric functional gastrointestinal disorders. **Chapter 2** discusses the underlying pathophysiological mechanisms of AP-FGIDs and proposes an up-to-date evidence-based management plan.

Part II - *Epidemiology and risk factors of abdominal pain predominant functional gastrointestinal disorders*

This part of the thesis consists of 5 chapters. **Chapter 3** shows the results of an island-wide epidemiological survey conducted in Sri Lankan children ages 10 to 16 years to assess the prevalence and clinical profile of AP-FGIDs, and its association with emotional stress. In **chapter 4**, the epidemiology and symptom characteristics of different subtypes of irritable bowel syndrome is discussed in detail, which is the commonest type of AP-FGID seen in Sri Lankan children. **Chapter 5** is a systematic review and meta-analysis of the epidemiology of irritable bowel syndrome in Asian children and adolescents. Exposure to child abuse is widely considered as a predisposing factor to abdominal pain. Results of a study conducted in 13 to 18 year old Sri Lankan students, to assess the association between AP-FGIDs and exposure to physical, emotional and sexual abuse, is given in the **chapter 6**. **Chapter 7** describes the

impact of AP-FGIDs on the physical, social, emotional and school related quality of life in teenagers and the factors determining their healthcare consultation.

Part III - Abdominal pain predominant functional gastrointestinal disorders and gastric motility

Up to now, there is no exact pathophysiological mechanism to describe the abdominal pain present in children with AP-FGIDs. Abnormalities of gastrointestinal motility has been suggested as one of the possible underlying pathophysiological mechanisms. This part of the thesis shows the abnormalities of gastric motility in all 4 main types of AP-FGIDs in Sri Lankan children, namely functional abdominal pain (**chapter 8**), irritable bowel syndrome (**chapter 9**), functional dyspepsia (**chapter 10**) and abdominal migraine (**chapter 11**).

Part IV - Summary, conclusions and future perspectives

This section gives a summary of the important findings of this thesis, main conclusions drawn and some future perspectives on functional gastrointestinal disorders in children.

PART I

INTRODUCTION TO ABDOMINAL PAIN-PREDOMINANT FUNCTIONAL GASTROINTESTINAL DISORDERS

Chapter 1

Global prevalence and international perspective of pediatric gastrointestinal disorders

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SUMMARY

Prevalence of Functional Gastrointestinal disorders (FGIDs) has dramatically increased over the past decade and now represents a large global healthcare burden. With growing population trends and increasing predisposing factors such as obesity and psychological stress, it can be predictable that the incidence of FGIDs will increase further and become a significant healthcare problem. Although FGIDs are not life threatening, research shows that children suffering from FGIDs tend to have a lower QoL than their healthy peers and frequently miss school as a result of the disorder. In addition many FGIDs such as constipation and IBS has high healthcare expenditure and are becoming a major challenge on already-overstretched healthcare budgets, both in developing and in developed countries, competing perhaps with other prioritized diseases. These factors suggest that FGIDs need to be one of the main research focal points of the twenty-first century.

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) consist of a group of chronic gastrointestinal problems characterized by recurrent symptoms that cannot be explained by structural and biochemical abnormalities. Chronic and disabling nature of symptoms and their remarkably high prevalence across the globe has identified them as a concern for pediatric public health. Initial epidemiological data and hospital-based studies from the Western world provided a notion that these disorders were possibly a result of a 'Western life-style'. However, compelling data have emerged from Asian and Latin American countries indicating that FGIDs have a global dimension in prevalence. They have come to challenge the already overstretched health budgets of both developed and developing countries and compete with other prioritized communicable and non-communicable diseases such as HIV, tuberculosis, malnutrition, obesity and malignancies. Moreover, biology and pathophysiology of FGIDs are shown to be increasingly associated with psychological stress, early adverse life events, infections and urbanization, all of which are common across the globe. In addition, certain categories of FGIDs are commonly seen among children living in deprived and disrupted societies such as those affected by war. These disorders are known to have deleterious ramifications on childhood functioning and health-related quality of life (QoL). This chapter reviews the current epidemiological trends and international perspectives of FGIDs in children.

CLASSIFICATION AND DEFINITIONS

Historical facts

Recurrent abdominal pain

In 1909, a British Pediatrician, GF Still, wrote: "I know of no symptom which can be more obscure in its causation than colicky abdominal pain in childhood".[1] A century later, childhood abdominal pain remains a curious enigma. Recently, significant progress has been made to shed some light upon this subject.

The term 'recurrent abdominal pain' came into use in the 1950s, following John Apley's use of the term.[2] The majority of children with recurrent abdominal pain had no recognizable organic cause for their symptoms and were thought to have abdominal pain of functional origin. However, Apley's diagnostic entity soon proved to be too general, as it transpired that up to 68% of children with recurrent abdominal pain could be classified as having irritable bowel syndrome (IBS) using established adult diagnostic criteria.[3] In addition, constipation had come to be widely acknowledged as a common organic cause for abdominal pain. Previously, constipation has been recognized as an organic disorder that could cause harm through an

accumulation of feces in the body. Traditionally, medical staff regularly prescribed laxatives to "decontaminate" the bowel, a practice that continued even up to the 1950s.[4]

Classification of functional gastrointestinal disorders (FGIDs)

The first internationally accepted classification system of adult FGIDs was known as the Rome I classification. This has since been iterated and updated,[5] and it is currently the most widely accepted classification system for FGIDs.

The Rome II classification of FGIDs, introduced in 1999, was a historical landmark in pediatric gastroenterology.[6] For the first time, FGIDs in children were formally recognized, establishing a foundation for future research and enabling researchers to link the historic 'recurrent abdominal pain' classification to modern FGIDs.

Rome III criteria

The currently accepted diagnostic criteria for FGIDs are known as the Rome III criteria. They were introduced in 2006 and, as discussed, developed out of the two previous criteria (Rome I and Rome II). The classification includes two separate systems, one for infants and toddlers and the other for children and adolescents.[7,8] **Table 1.1** gives the details of classification of FGIDs in children and adolescents. The Rome III Committee has reduced the required duration of symptoms of most FGIDs from 3 months to 2. Furthermore, a threshold of symptom frequency of at least once a week has also been introduced. *

In defecation disorders, functional fecal retention was excluded from current classification criteria as a separate diagnostic entity. However, several significant clinical characteristics of constipation have been included, such as non-retentive fecal incontinence with a frequency of occurrence of at least once a month. These modifications have made the Rome III criteria more inclusive and more useful in the diagnosis of FGIDs in children and more likely to positively diagnose the whole spectrum of FGIDs than previous Rome II criteria.[9,10] However, much still needs to be done to refine them and, more importantly, to convince pediatricians to use them in day-to-day clinical practice.

* The Rome III revised duration and symptom thresholds do not apply to abdominal migraine and cyclical vomiting syndrome.

Table 1.1 Classification of childhood functional gastrointestinal disorders (FGIDs) in Rome III criteria

1. **Vomiting and aerophagia**
   - 1a. Adolescent rumination syndrome
   - 1b. Cyclic vomiting syndrome
   - 1c. Aerophagia
2. **Abdominal pain-related FGIDs**
   - 2a. Functional dyspepsia
   - 2b. Irritable bowel syndrome
   - 2c. Abdominal migraine
   - 2d. Childhood functional abdominal pain
3. **Constipation and incontinence**
   - 3a. Functional constipation
   - 3b. Nonretentive fecal incontinence

Box 1.1 - Limitations of the Rome II classification system

Several studies have shown a significant percentage of children with non-organic recurrent abdominal pain to have FGIDs. Walker *et al.*[11] showed that 73% of children with 'full terminology of recurrent abdominal pain' can be classified into FGIDs such as IBS and functional abdominal pain by using the Rome II criteria. A school-based study from Asia has shown that 73% of children with recurrent abdominal pain have FGIDs.[12] However, Rome II criteria had limitations. A prospective study in school children demonstrated that at least 8% of children with chronic abdominal pain for a 3-month duration could not be assigned to a particular functional gastrointestinal disorder group using Rome II criteria.[13] Another study found only a fair agreement between physicians and parents using Rome II criteria.[14] Furthermore, two additional studies on defecation disorders illustrated that Rome II criteria for defecation disorders were too restrictive and would exclude a significant proportion of children when applied to clinical settings.[15,16] These findings paved the way to modify the Rome II criteria.

EPIDEMIOLOGY OF FUNCTIONAL GASTROINTESTINAL DISORDERS (FGIDS)

Vomiting and aerophagia

Aerophagia

Aerophagia is a functional gastrointestinal disorder characterized by repetitive swallowing of air that leads to abdominal distension, excessive belching and/or flatus. Clinically, children with aerophagia present with non-distended abdomen in the morning and gradual distension of the abdomen throughout the day. Excessive belching is noted during the day. In addition, frequency of passing flatus increases, especially during the night. On physical examination, the abdomen shows gross distension and the percussion note is tympanic all over the abdomen. Although it seems benign, in severe cases aerophagia leads to serious complications such as pneumoperitonium, volvulus and intestinal perforation.[17,18,19]

Until recently, there were no studies assessing the epidemiology of aerophagia. Initially, aerophagia was believed to be more prevalent in children with chronic neurological conditions such as Rett's syndrome and autism.[20,21] However, subsequent studies have found aerophagia in a significant percentage of otherwise healthy children. In a prospective study among 243 black American schoolchildren, attending a community primary care clinic, Uc and co-workers[22] reported aerophagia in 2.4%. Only a few studies have assessed the community prevalence of aerophagia. Two recent school-based studies in 10- to 16-year-olds have reported this condition in 6.3% and 7.5%, respectively.[23,24] In these studies there was no significant gender difference in prevalence.[23,24] Higher prevalence of aerophagia was observed in older children but there was no clear correlation with age. The identified risk factors were lower socio-economic status, large family size, having a working mother, living in an urban area and exposure to stressful life events. Furthermore, children with aerophagia had difficulty in sleeping and missed school because of their symptoms.

Cyclic vomiting syndrome

Cyclic vomiting syndrome (CVS) is a clinical entity associated with recurrent episodes of severe nausea and vomiting that may last for hours to days with well-demarcated symptom-free intervals. The disorder is typically associated with negative laboratory, endoscopic and radiological test results. There is a stereotypical pattern of symptoms in most of the individuals with regard to time of day, duration and onset of symptoms. Vomiting begins late night or early morning with intense nausea, often triggered by psychological distress. Associated symptoms include pallor, listlessness, retching, abdominal pain, headache and photophobia.[7,25]

Data on the epidemiology of CVS in children is limited. A population-based survey from Aberdeen, Scotland, involving children aged 5-15 years, has shown the prevalence of cyclical vomiting to be 1.9% in the United Kingdom.[26] Reported prevalence of CVS is 2.3% in Australia,[27] 0.5% in Sri Lanka[10] and 1.9% in Turkey.[28] Although overall sex ratio for the whole population was 1:1, cyclic vomiting was commoner among boys in the younger age group of less than 7 years. The sex ratio reversed in children older than 7 years. Travel, stress, tiredness and lack of sleep were the recognized precipitating factors. In a prospective surveillance study in Ireland, the incidence of CVS was found to be 3.5/100,000 children per annum. In this study, the median age of diagnosis was 7.42 years and the median age of onset was 4 years. The majority of children missed school because of their symptoms, indicating the disabling nature of the disease.[29] Current research is inconclusive, as there seems to be considerable heterogeneity and variability of the prevalence rates in different studies conducted in different geographical locations.

Rumination syndrome

Rumination syndrome is defined as effortless, repetitive, painless regurgitation of partially digested food into the mouth soon after the meal, which is subsequently re-chewed and re-swallowed, or in the alternative, expelled.[7] Rumination syndrome is thought to be common in children who are neurologically handicapped with developmental abnormalities and learning difficulties.[30,31] In clinical settings, rumination syndrome is frequently misdiagnosed as gastro-esophageal reflux, gastoparesis and recurrent vomiting. These misconceptions and misdiagnoses and poor awareness among clinicians have led to underdiagnosis of this important and sometimes disabling disease in children. However, recent data show its increasing prevalence among otherwise healthy people with normal cognitive function.[32-34]

Data for this disorder have been derived from case series from tertiary care referral centers and therefore include a bias towards severe cases. A recent small-scale epidemiological survey in Sri Lanka noted a prevalence of 4% among 12- to 16-year-old children in a semi-urban school.[10]

Abdominal pain predominant functional gastrointestinal disorders

Functional dyspepsia

Functional dyspepsia is a disorder characterized by the presence of persistent or recurrent pain or discomfort that does not subside with defecation and which is localized to the central region of the abdomen above the umbilicus.[7] Epidemiology of functional dyspepsia has not been adequately studied across the world. A school-based study in Italy of children aged 6-19 years using Rome II criteria have noted ulcer-like dyspepsia in 3.4% of children and dysmotility-like

dyspepsia in 3.7%.[35] A prospective survey from the same country and that included children of a much more diverse age range showed a prevalence of 0.3%.[36] A study from Asia has evaluated prevalence of AP-FGIDs in children and shown a prevalence of functional dyspepsia of 2.5%.[23] The prevalence was higher among girls than boys. A detailed symptom analysis showed that the majority of children have pain several times a week and the pain is short-lasting (less than 1 hour). Furthermore, children with functional dyspepsia also suffer from a range of intestinal-related symptoms such as bloating, loss of appetite, nausea, burping and flatulence, as well as extra-intestinal symptoms such as headaches, limb pains, sleeping difficulties and light-headedness.[23]

Irritable bowel syndrome (IBS)

IBS denotes the presence of abdominal pain that is relieved by defecation and/or associated with change in bowel frequency and/or consistency of the stool with the onset of pain. Even though, epidemiology of IBS has been studied in details in adults, research assessing this important disease condition in children is sparse and limited. Early studies from the Western world led to the belief that IBS is a disease of affluent societies. Emerging data from Asia, both in children and adults, have suggested otherwise. Studies on prevalence of IBS in Europe and the USA are old and many having conducted nearly a decade ago. According to these studies prevalence of IBS among school children in the United Kingdom and the United States are 1.29% and 10.05%, respectively.[3,37] In addition, a higher prevalence (20%) was observed in children in Russia (Western Siberia) according to the Rome II criteria.[38] In contrast to this, a prospective study from Italy using the same criteria reported a much lower prevalence (0.21%).[36] Wide variation in the age of the recruited in different studies may have contributed to these differences in reported prevalence of IBS. Two of the studies found that IBS is much more common among girls and prevalence increases as they grow older.[3,37] To date, no study has used the sub-classification criteria of IBS.

In the last decade, however, the epidemiology of IBS has been well studied. Most of these studies have been fairly large and have included over 400 children, and used Rome II or Rome III criteria to establish the diagnosis. The prevalence of IBS in Asian countries varies between 2.8%, in Sri Lankan children aged 10-16 years,[10] to 25.7%, in Korean girls.[39] Furthermore, studies from other developed nations in Asia such as Japan have also shown high prevalence of IBS (14.6 -19%).[40] Prevalence in China varies between 13.25% - 20.72%,[41-43] and a study from Sri Lanka has shown a prevalence of 6.2%.[44] **Figure 1.1 and Table 1.2** show the distribution and prevalence of epidemiological studies of IBS around the world.

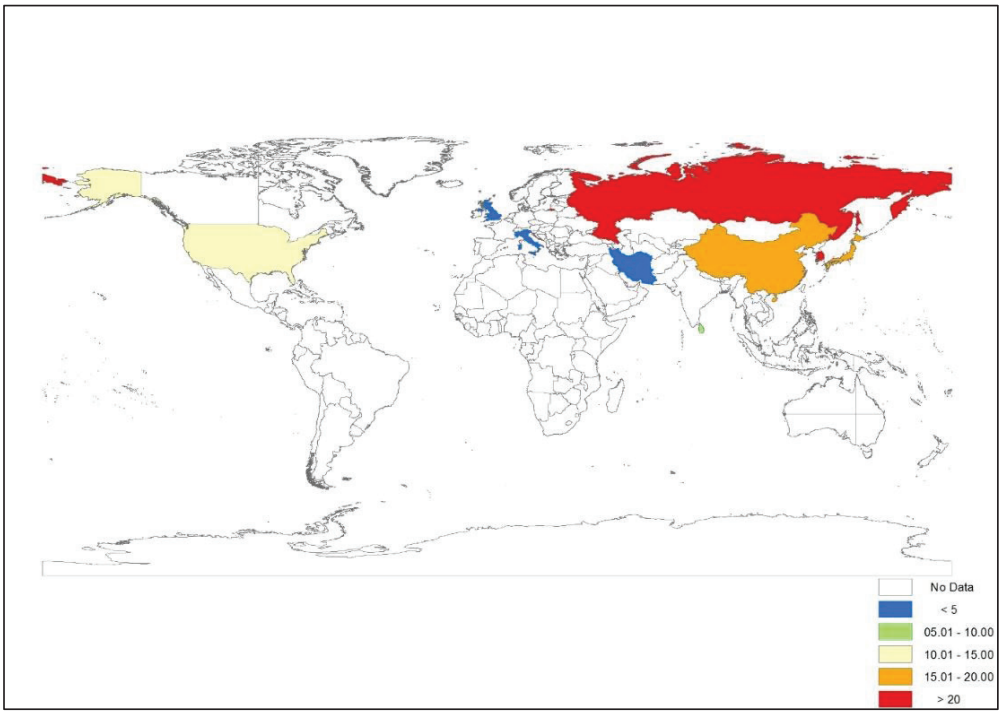

Figure 1.1 - Global distribution of irritable bowel syndrome in children

Table 1.2 - Prevalence of IBS in the world

Country	Year of publication	Age group (years)	Prevalence (%)
Sri Lanka	2012	10-16	6.2
Sri Lanka	2011	10-16	4.9
Sri Lanka	2010	12-16	7.0
Japan	2011	15	14.6
China	2011	12-18	19.9
China	2010	10-18	20.72
China	2005	6-18	13.25
Iran	2009	14-19	4.1
Korea	2007	15-17(girls only)	25.7
Italy	2004	0-12	0.21
Russia	2001	14-17	20.0
USA	1996	12-16	10.0
UK	1996	11-17	1.29
Italy	2004	0-12	0.7

Several researchers have studied subtypes of IBS in children using Rome criteria described for adults.[10, 40,46] Classification of IBS according to the bowel habits of the individual is extensively used in adult studies and clinical trials. The following subtypes have been identified in this classification: diarrhea-predominant IBS, constipation-predominant IBS, mixed IBS (alternating diarrhea and constipation) and unsubtyped IBS (not falling into any of the aforementioned categories depending on predominant bowel habits). Using this sub-classification, in two studies Zhou *et al.*,[42,43] have shown that unsubtypable IBS predominates among Chinese children. Other countries such as Korea, Iran and Sri Lanka have shown wide variations in distribution of subtypes of IBS.[39,44,47] **(Table 1.3)**

Table 1.3 – Distribution of IBS subtypes around the world

Author	**Rajindrajith and Devanarayana**	**Devanarayana *et al.***	**Zhou *et al.***	**Zhou *et al.***	**Sohrabi *et al.***	**Son *et al.***
Country	Sri Lanka	Sri Lanka	China	China	Iran	Korea
Sample size	1717	417	3671	2013	1436	1517
Publication year	2012	2011	2011	2010	2009	2007
Diagnostic criteria for IBS	Rome III (child)	Rome III (child)	Rome III (adults)	Rome III (adults)	Rome II (adults)	Rome II (adults)
IBS-C (%)	27.1	26.7	20.14	20.14	52.5	34.6
IBS-D (%)	28.0	26.7	17.76	18.47	11.8	26.9
IBS-M/IBS-A (%)	27.1	33.3	10.27	10.31	18.6	38.5
IBS-U (%)	17.8	13.3	51.1	51.08	-	-

Functional abdominal pain

Functional abdominal pain according to the Rome III criteria is a different clinical entity compared to the recurrent abdominal pain described by Apley.[2] The definition includes persistent or recurrent pain episodes, at least once a week for 2 months, without the presence of organic diseases[7]. Epidemiology of this disorder is not well studied in children. A study carried out in Sri Lanka has shown a prevalence of 4.4%.[23] Another study in Sri Lanka has also

shown that functional abdominal pain has the highest prevalence rates among all of the FGIDs in children.[48]

Abdominal migraine

Abdominal migraine is a well-known cause for abdominal pain in children. In the current Rome III criteria, it is recognized as paroxysmal episodes of intense periumbilical pain lasting for more than 1 hour with associated symptoms such as nausea, anorexia, vomiting, headache, photophobia and pallor. Affected children are otherwise well between attacks and the period between episodes may last for weeks to months.[7] Abdominal migraine has been recognized as a common cause of recurrent abdominal pain in children in several hospital-based studies using Rome II or Rome III criteria.[10,11,49] In a study using International Classification of Headache Disorders, 4.4% children evaluated for abdominal pain had abdominal migraine.[50] An epidemiological survey conducted in the United Kingdom, using International Headache Society criteria, noted 4.1% of children as having abdominal migraine.[51] In this study, the prevalence of abdominal migraine was higher among girls and attacks were associated with exposure to stressful events, travel, tiredness and consumption of certain food items. In a Sri Lankan school-based survey involving children aged 10-16 years, It was found that only 1% of children suffered from abdominal migraine according to the accepted criteria.[10] It was also noted that this disorder is associated with family- and school-related psychological stress. Other painful conditions such as headache and limb pains, photophobia, light-headedness and sleeping difficulties were commonly associated with abdominal migraine. In addition other functional abdominal symptoms such as bloating, loss of appetite, flatulence, burping, nausea and vomiting were also commonly seen in children with this disorder.[23]

Functional defecation disorders

Functional constipation

Functional constipation is a cosmopolitan problem with prevalence rates varying by geographical location and environmental consideration. Rates are high enough to be considered a public health issue. Epidemiology of functional constipation has been well studied in both the Western world and Asia using well-established criteria. Studies from Western countries during the first decade of the new millennium have shown a prevalence ranging from 0.7% in Italy to 16% in the United States.[22,36] A significant number of studies have been conducted in both developed and developing nations across Asia.[47,52-57] In these studies, particularly among developed countries in the Asian region, prevalence of functional constipation is more or less close to the prevalence in the Western world.[52,54-56] Similarly, studies from South America, particularly in Brazil, have shown higher prevalence rates of functional constipation (20%-

28%), similar to the developed nations in Asia.[58,59] In addition, studies from Sri Lanka have revealed that functional constipation as an emergent issue, with a prevalence rates ranging between 4.2% and 15.4%.[10,53,57] Data from Asian countries constantly challenge the common paradigm that constipation is a disease of the Western countries. Rapidly changing dietary habits, lifestyles and stressful events in the developing Asian economies such as Korea, China and Sri Lanka may have contributed to closing the gap in prevalence of constipation between different nations and regions of the world.

Table 1.4 - Prevalence of constipation in the world

Country	Year of publication	Age group (years)	Prevalence (%)
Hong Kong/China	2005	3-5	29.6
Hong Kong/China	2008	3-5	28.8
Korea	2010	5-13	6.7
Iran	2010	14-19	2.5
Taiwan	2011	7-12	32.2
Taiwan	2012	6-15	12.2
Sri Lanka	2012	10-16	15.4
The Netherlands	2010	2	12
USA	2009	5-8	10
Turkey	2007	7-12	7.2
Turkey	2003	2003	12.4
Sweden	2006	2.5	6.5
Italy	2005	0-0.5	17.6
Italy	2004	0-12	0.7
Italy	2005	0-12	2.6
Brazil	1999	8-10	20
Brazil	2002	1-10	26.8
Greece	1999	2-14	15
Greece	1999	2-14	6
Finland	2004	10-11	1.5

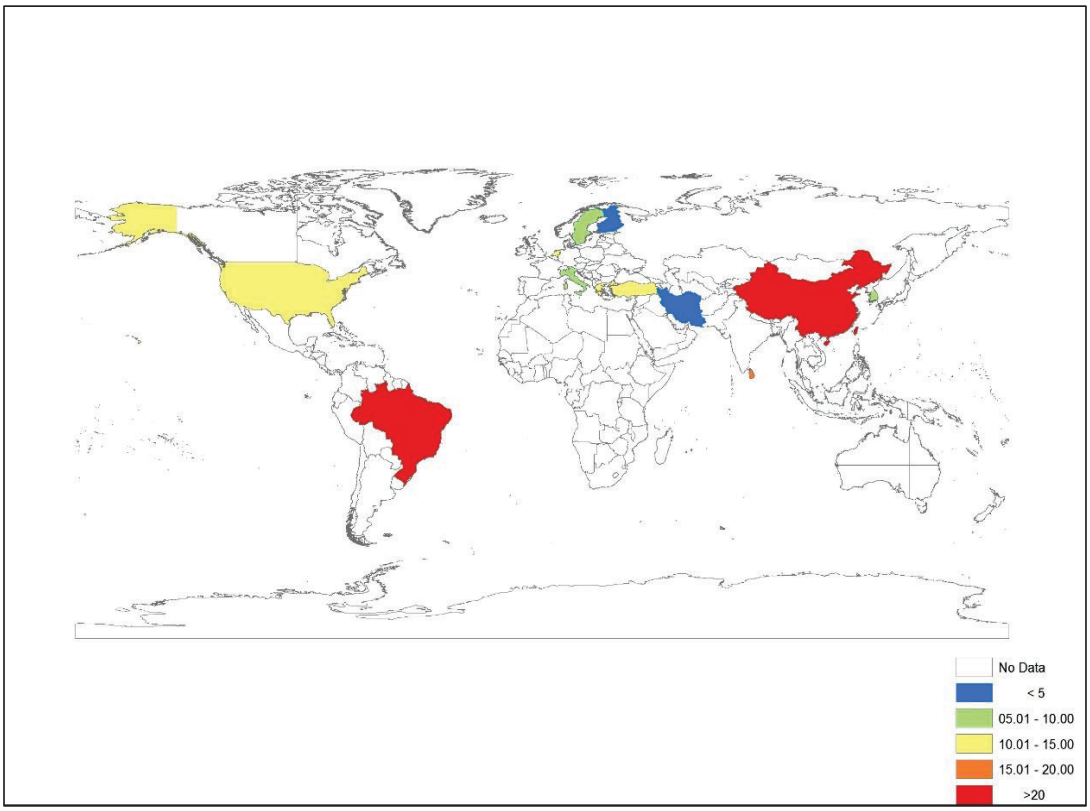

Figure 1.2 - Global distribution of constipation in children

Functional non-retentive fecal incontinence

Fecal incontinence is defined as passing stools in inappropriate places irrespective of the amount. It is a common problem in the pediatric age range and has significant social repercussions on affected children. Prevalence of functional fecal incontinence ranges from 0.8% to 4.1% in Western countries.[60,61] Recent studies from Asia noted much higher prevalence ranging from 2% in Sri Lanka to 7.8% in Korea.[43,52,62] Epidemiological studies on fecal incontinence have not attempted to differentiate between various types of functional fecal incontinence up until recently although these subtypes have different pathophysiological mechanisms. A school-based survey conducted in Sri Lanka has shown that the majority of children suffering from functional fecal incontinence are having constipation-associated fecal incontinence. Only 0.4% of them had functional non-retentive fecal incontinence. This study has also highlighted that the bowel habits of these children are quite different from children with constipation-associated fecal incontinence. [62]

GLOBAL PERSPECTIVE OF FUNCTIONAL GASTROINTESTINAL DISORDERS

For decades, gastrointestinal infections in the developing world and inflammatory bowel disease in the West were considered to be the main causes of gastrointestinal-related morbidity and mortality. However, with the availability of oral rehydration therapy, vaccination against gastrointestinal infections and therapeutic advances such as immunosuppressants and monoclonal antibodies, the disease burden of gastrointestinal infections has been reduced and the natural history of inflammatory bowel disease has been modified. Against this backdrop, FGIDs in children are emerging as one of the most prevalent types of disorders and they are receiving greater attention in the twenty-first century.

Type and geographical distribution

In summary, the geographical burden of FGIDs is shifting from the West to the East, where the prevalence of most subtypes is increasing. The fast-growing population will probably identify Asia as the epicenter of FGIDs in the future. Follow-up data with regard to the course of life and long-term prognosis of childhood FGIDs are limited. The available data suggest that a significant percentage (25%-30%) of children with functional constipation and fecal incontinence grow up to be adults with persistent symptoms.[63,64] In addition, in a small retrospective study by Kahn *et al.*,[65] childhood constipation appeared to be a predictor of IBS in adulthood.

Age distribution

Relationship between age and FGIDs has been evaluated to reveal a wide variation and heterogeneity in symptoms for all subtypes. The main reason for this is that different studies have recruited children in different age groups, varying from birth to 19 years. Therefore, a precise age distribution in epidemiology cannot be described with certainty. However, several trends have been highlighted. For example, a study among school children in Sri Lanka has illustrated a negative correlation between prevalence of AP-FGIDs.[23,66] A more descriptive analysis of IBS patients by the same group of researchers has found linear reduction of probability in developing IBS with age. On the other hand, three other epidemiological studies from the United States and China have noted a trend of increasing prevalence of IBS with age.[3,40,41]

Similarly, the majority of previous studies have shown a reduction of prevalence of defecation disorders with age. Two epidemiological studies from Sri Lanka have demonstrated that both constipation and fecal incontinence show the highest prevalence at the age of 10 years and a decline with advancing age.[57,62] A study from the Netherlands also noted a similar reduction in

prevalence of fecal incontinence with age.[61] It is likely that maturation provides better control over bodily functions, including bowel habits.

In contrast to this, the few available studies on aerophagia and rumination syndrome have not shown a significant relationship between their prevalence and age.[24,29] The mean age of developing cyclical vomiting is between 4.6 and 6.9 years.[67] These contrasting findings need further epidemiological evaluation.

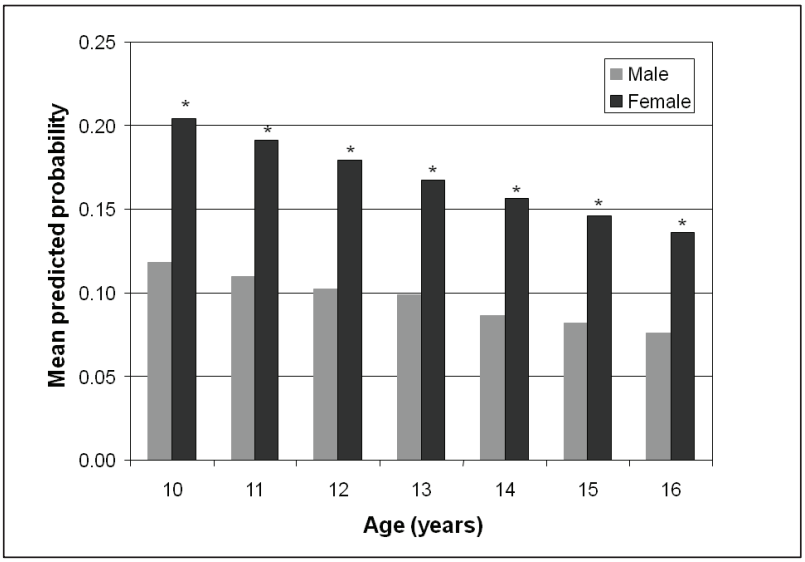

Figure 1.3 - Age related prevalence of abdominal pain predominant FGIDs in children
(Adopted from Devanarayana *et al.* Abdominal pain-predominant functional gastrointestinal diseases in children and adolescents: prevalence, symptomatology, and association with emotional stress. J Pediatr Gastroenterol Nutr 2011;53:659-65.)

Gender distribution

Sex difference studies among adults have clearly shown that several FGIDs, such as IBS and constipation, are found with higher frequency among females.[68] In contrast, gender differences of most FGIDs are not clearly visible in children. Some previous studies have shown a clear female preponderance in development of AP-FGIDs in children. These studies have shown a higher prevalence of functional dyspepsia and IBS in girls than in boys,[3,23,44] which is comparable with previous adult studies conducted in IBS and functional dyspepsia around the world.[68] Newly developed Asian economies, the Middle East and developing nations such as Sri Lanka also show a similar female preponderance in prevalence of IBS.[3,40,41,43,44] A convincing biological reason for this phenomenon has never been articulated. Effects of female sex

hormones on gastrointestinal tract and brain-gut interactions have been suggested as a possible reason.[69] However, since most of the children included in previous studies are of young age and have not achieved menarche to acquire a fully mature hormonal profile of a female, the gender difference seen in the AP-FGIDs cannot be fully attributed to the effects of female sex hormones. It is also possible that factors other than gender specific hormonal difference, such as true biological differences between males and females, may play an important role in the natural history of the AP-FGIDs that predisposing girls to develop them. Sex-related biological differences in the integration, processing and modulation of pain may also be key mechanisms responsible for the greater female prevalence of many chronic pain disorders such as FGIDs. Psychosocial factors, including how boys and girls are socialized to express emotions differently, are also likely to play an important part in sex differences in prevalence. These considerations lie outside the scope of the present chapter.

Sex-specific prevalence of constipation is more complex and is currently unclear. A few large studies have shown a predilection of girls to develop constipation but the ratios are not statistically significant.[52,54] Several other studies have noted almost equal prevalence between girls and boys.[70,71] A study from Sri Lanka noted higher prevalence of constipation in boys.[57] This is in contrast to the data from adult studies, which show a clear, statistically significant female preponderance.[72] Progesterone is known to increase transit time of the large and small bowel in women and childbirth-associated physiological disruption of pelvic floor muscles may have contributed to the higher prevalence of functional constipation in the older population.[73,74] Lack of these physiological phenomena in children would have contributed to lack of gender difference in prevalence of constipation in children and adolescents. Several studies from both developed and developing countries have convincingly demonstrated that functional fecal incontinence is clearly more common among boys.[61,75,76]

The only available epidemiological study on aerophagia does not show a difference of prevalence between girls and boys.[24] Some recent studies on CVS have found no gender difference in prevalence[29,77] while others have found that CVS has a higher prevalence rate among girls.[28,78] Finally, hospital-based data have illustrated a higher prevalence of rumination syndrome among females.[79,80]

Sociodemographic factors

Sociocultural influences on the development and persistence of a wide variety of FGIDs are not evidently seen in the pediatric literature. Although studies on most of the FGIDs do not show a significant influence by sociocultural factors, defecation disorders such as functional

constipation and functional fecal incontinence are clearly more common among children from low socio-economic strata.[44,61,62] Poor toilet facilities and large number of family members sharing the same toilet may lead to fecal withholding, which predispose children to develop both constipation and functional fecal incontinence. In addition, delayed seeking of medical care for constipation may also contribute to the development of defecation disorders in children from disadvantaged socioeconomic backgrounds. Furthermore, children living in socially disrupted environments, such as areas affected by war, have higher chances of developing functional defecation disorders.[81,82]

Growth

Pediatric obesity and overweight are rising global health problems. Apart from associations with many chronic diseases, including hypertension, hypercholesterolemia and non-alcoholic steatohepatitis, obesity in children seems to predispose them to develop AP-FGIDs, although the mechanisms are not clear.[83,84] Several other investigators have noted that functional defecation disorders, both constipation and fecal incontinence, are significantly more common in children with obesity.[85] Obese children are known to have poor gastric accommodation.[86] In addition, 10% of morbidly obese children have delayed colonic transit time.[87] These mechanisms may at least partly explain the increase in FGIDs seen in obese children.

Psychological factors and child abuse

Psychological factors are well recognized and principal contributory factors to the development of FGIDs in children. Psychological stress is known to alter receptor functions of the central corticotrophin-releasing factor signaling system, inducing acute and chronic stress-induced visceral hyperalgesia. This is thought to be a major pathophysiological mechanism for the development of FGIDs.[88] Stressful life events have become a common problem in the day-to-day lives of children. A series of epidemiological investigations from Sri Lanka has shown that several FGIDs are associated with school- and home-related stress.[23,24,54] In addition, other studies from Asian populations have also shown that frequency of IBS is increased in children exposed to stress.[39,40]

Child maltreatment is a major social welfare problem. Every year about 4%-16% of children are physically abused and one in ten is neglected or psychologically abused. Exposure to multiple types and repeated episodes of maltreatment increases the risk of severe psychological harm.[89] The association between being abused during childhood and the development of FGIDs as an adult is well known.[90] Emerging data show such associations also exists in children.[91] A preliminary study, from Sri Lanka, has indicated that child abuse is associated with AP-FGIDs.[92]

Infections

Gastrointestinal infections are a common health problem in children. It is estimated that each year 1 billion children in the world under the age of 5 years suffer from gastroenteritis.[93] Although the majority recovers without consequences, a small percentage progress to develop FGIDs such as IBS - known as post-infectious IBS (PI-IBS). PI-IBS is much more common after infection with *Campylobacter* species.[94] Two studies have clearly demonstrated an association between bacterial gastroenteritis and IBS in children. Saps *et al.* [95] have reported a significant incidence of post-infectious (bacterial) AP-FGIDs. Preliminary investigations suggest that 36% of children exposed to bacterial enteritis subsequently developed FGIDs, with 31% diagnosed with PI-IBS. Pediatric data from Walkerton Health Study,[96] demonstrated a higher incidence of IBS after exposure to a bacterial gastroenteritis outbreak with *Escherichia coli* and *Campylobacter* species.

These studies have demonstrated that children are at risk of developing IBS after gastrointestinal infections. Gastrointestinal infections are a common occurrence in the developing world. It has been noted that a poorly nourished child living in socially impoverished and cramped conditions without access to proper sewerage disposal and running water will have eight or more gastrointestinal infections a year when compared to a child living with better sanitary facilities.[97] These contentions imply that children living in the developing world have a higher predilection to develop PI-IBS than children in the developed world and that this will become a significant burden for these low-income countries with comparatively small health budgets.

Diet and food allergies

Dietary habits have been studied as possible mechanisms for FGIDs in children. According to a recent retrospective study, 19% of children with cow's milk protein allergy during infancy have developed AP-FGIDs later on in life. IBS was reported to be the most common FGID within this group of allergy sufferers.[98] Similarly, constipation has also been associated with cow's milk protein allergy in children. Furthermore, several studies have reported improvement of symptoms of constipation with an elimination diet.[99-101] However, most of these retrospective studies are limited by a lack of appropriate independent allergy corroboration or diagnosis and significant recall bias. These limitations have reduced the applicability of the results in general terms and careful clinical appraisal and laboratory confirmation are needed before recommending a bovine milk-elimination diet for FGIDs in children.

Fibre is an important component in the human diet. It is recommended that a child should take a reasonable amount of fibre-containing foods in his or her diet (age+ 5 g per day). Fibre is known to improve stool frequency, stool volume and colonic transit time.[100] Several studies have shown low-fibre diet as a risk factor for developing constipation in children. Two studies from Asia noted low mean intake of dietary fibre in young children with functional constipation, especially in terms of fruits and vegetables.[102] In addition, another study has also shown an association between constipation and consumption of fast food, which is known to be low in fibre.[103] Therefore, a diet low in fibre is a risk factor for developing functional constipation in children.

Quality of life

Even though FGIDs are not life threatening, they are known to lead to a lower quality of life (QoL) for the children who have them. Significantly lower QoL scores have been reported in all four domains (i.e. physical, emotional, social and school functioning domains) in affected children.[104] Youssef *et al.*[105] studied QoL in a group of children with functional abdominal pain and compared the results against those of children suffering from inflammatory bowel disease, children suffering from gastro-esophageal reflux and healthy children. Children with functional abdominal pain had lower physical and emotional scores than healthy children. Furthermore, QoL scores of children with functional abdominal pain were comparable with children suffering from inflammatory bowel disease and gastro-esophageal reflux. These two studies clearly indicate clearly the low QOL in children with abdominal pain-predominant FGIDs. Moreover, the scores are similar to severe organic disorders such as inflammatory bowel disease, indicating a significant component of suffering in these children.

Several studies have shown poor QoL in children with functional constipation. According to one study from the United States, the mean quality of life score of children with functional constipation was lower than that of children with organic disorders such as reflux oesophagitis.[106] Another study, performed in Australia, also noted similar findings in children with slow transit constipation.[107] In addition, both studies have clearly shown that QoL ratings on parent reports were significantly lower than that of child reports. .

Co-morbid factors

A large number of co-morbid factors are known to be associated with FGIDs in children. Some studies from Sri Lanka found extra-intestinal symptoms such as headache, limb pain, photophobia and sleeping difficulties more frequently in children with AP-FGIDs than in controls.[23] Similarly, Dong, *et al.*[41] noted an association between functional headache and

irritable bowel syndrome in Chinese children. Children with aerophagia were also noted to have an array of extra-intestinal symptoms.[24] These symptoms can significantly contribute to the suffering and poor QoL of children who are already having pain and discomfort. In this light, extra-intestinal symptoms need to be addressed in the management of children with FGIDs.

Healthcare seeking

Although FGIDs are a considerable problem in the community, healthcare-seeking patterns for this group of disorders in children are not well understood. Evaluating ambulatory healthcare data, one study reported that chronic constipation is a common cause for an ambulatory healthcare visit for children in the United States.[108] Two other studies have assessed the healthcare use of children with constipation in a single-birth cohort at different time points. The first study noted that children suffering from constipation have the highest number of medical appointments in comparison with all other gastrointestinal complaints.[109] The second study illustrated that children with constipation seek medical care more often than children with other illnesses such as bronchial asthma and migraine.[110] In contrast, another study from Sri Lanka has shown that despite high prevalence rates, healthcare-seeking for chronic constipation remains very low (3.8%).[111] Younger age, family history of constipation and associated vomiting were significant predictive factors for visits to a doctor. Healthcare-seeking for other FGIDs in children have not been studied in depth in different parts of the world with different healthcare systems; therefore, further research into this important area would aid in the planning and allocation of healthcare resources for FGIDs in a global level.

SUMMARY

Prevalence of FGIDs has dramatically increased over the past decade and now represents a large global healthcare burden. With growing population trends and increasing predisposing factors such as obesity and psychological stress, it can be predictable that the incidence of FGIDs will increase further and become a significant healthcare problem. Although FGIDs are not life threatening, research shows that children suffering from FGIDs tend to have a lower QoL than their healthy peers and frequently miss school as a result of the disorders. In addition, many FGIDs such as constipation and IBS has high healthcare expenditure and are becoming a major challenge on already-overstretched healthcare budgets, both in developing and in developed countries, competing perhaps with other prioritized diseases. These factors suggest that functional gastrointestinal diseases need to be one of the main research focal points of the twenty-first century.

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Chapter 2

Childhood functional abdominal pain: mechanisms and management

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ABSTRACT

Chronic abdominal pain is one of the most common clinical syndromes encountered in day to day clinical pediatric practice. Although common, its definition is confusing, predisposing factors are poorly understood and the pathophysiological mechanisms are not clear. The prevailing viewpoint in the pathogenesis involves the inter-relationship between changes in hypersensitivity and altered motility, to which several risk factors have been linked. Making a diagnosis of functional abdominal pain can be a challenge, as it is unclear which further diagnostic tests are necessary to exclude an organic cause. Moreover, large, well-performed, high-quality clinical trials for effective agents are lacking, which undermines evidence-based treatment. This Review summarizes current knowledge regarding the epidemiology, pathophysiology, risk factors and diagnostic work-up of functional abdominal pain. Finally, management options for children with functional abdominal pain are discussed including medications, dietary interventions, probiotics and psychological and complementary therapies, to improve understanding and to maximize the quality of care for children with this condition.

INTRODUCTION

At the beginning of the 1900s Still, a British pediatrician, wrote "I know of no symptom which can be more obscure in its causation than colicky abdominal pain in childhood".[1] Today, more than a century later, both clinicians and researchers are still struggling to understand this enigmatic clinical issue. This lack of understanding often leads to extensive investigations, non-effective therapeutic modalities, poor patient satisfaction, reduced health-related quality of life, staggering health-care costs and an insurmountable amount of suffering in the patients' themselves.[2] However, the landscape has changed, especially during the past two decades. Definitions are being refined from the previously labelled and vague 'chronic or recurrent abdominal pain' to the more-specific symptom-based Rome III criteria. Pathophysiological mechanisms are being explored and knowledge is expanding. New noninvasive investigational techniques are emerging to elaborate underlying abnormalities. Although the traditional pharmacological treatment modalities are failing, some novel pharmacological agents and non-pharmacological therapeutic components are showing promising results. In this Review, we concentrate on the scientifically valid and clinically relevant entity of pain-predominant functional gastrointestinal disorders (FGIDs) rather than simply recurrent abdominal pain.

DEFINITIONS

In 1958, John Apley, a British pediatrician who pioneered research in children with abdominal pain, named the condition as "recurrent abdominal pain syndrome of childhood" and defined it as "at least three episodes of abdominal pain, severe enough to affect their activities over a period longer than 3 months".[3] Since then, for nearly four decades, this definition has been the standard definition used to diagnose chronic abdominal pain in both research and clinical practice. In 1996, Hyams *et al.*[4] observed that 51% of children with recurrent abdominal pain could be classified as having IBS utilizing the criteria designed for adults. In 1999, the Rome II criteria for children were published and were appropriate to be used as diagnostic tools and to advance empirical research.[5] Using these criteria, it was noted that 73–89% of children with recurrent abdominal pain (RAP) could be classified as having a pain-predominant FGID.[6,7] Since then, the term RAP has been replaced by abdominal-pain-predominant FGIDs (AP-FGIDs); namely, functional dyspepsia, IBS, functional abdominal pain (FAP) and abdominal migraine. Although the Rome II criteria laid a firm foundation to study pain-predominant FGIDs, they were found to have several limitations. The Rome II criteria demanded persistence of symptoms for over 3 months before the diagnosis.[5] In addition, Saps and Di Lorenzo[8] noted that the diagnostic agreement between pediatric gastroenterologists and gastroenterology fellows when adhering to the Rome II criteria was low. Another study assessing the Rome II criteria reported only limited agreement between physician diagnosis and parent-reported symptoms.[7] These

limitations led to the development of the new Rome III criteria, introduced in 2006.[9] The Rome III criteria have been shown to be more inclusive than the Rome II criteria, and the majority of children with RAP can be classified as having one or more of the FGIDs.[10,11] Unfortunately, the renewed Rome III criteria failed to improve the diagnostic agreement between pediatric gastroenterologists and gastroenterology fellows compared with the Rome II criteria.[12] Another limitation of the current Rome III criteria is the substantial overlap among FGIDs in children with nausea.[13] The Rome III classification and the definitions for AP-FGIDs are given in **Box 2.1**.

A range of studies have noted that the majority of children with RAP have no organic pathology that can account for their symptoms.[6,14] As epidemiology, pathophysiology and treatment options might be different in these distinct disease entities, it could be helpful for both clinicians and researchers to use up-to-date and accepted criteria to diagnose different types of AP-FGIDs to optimize and tailor individual treatment.

EPIDEMIOLOGY

The first epidemiological study on RAP was conducted in the UK by Apley and Naish in 1958. This landmark study found that 10.8% of British school children had RAP.[3] Studies published in the 2000s conducted in Western and Asian countries have reported more or less similar prevalence rates of RAP (between 10% and 12%).[15–19]

Using the Rome III criteria, a school-based study among 1,850 Sri Lankan school children showed that FGIDs related to abdominal pain were highly prevalent. According to this study, FAP, IBS, functional dyspepsia and abdominal migraine were found in 9.7%, 4.9%, 0.6% and 1.9% of children, respectively.[20] Similar to this finding, a study from Colombia reported a prevalence of pain-predominant FGIDs in 27.9% of children (FAP 2.4%, IBS 5.1%, functional dyspepsia 2.4%, abdominal migraine 1.6%).[21] An observational prospective multicenter study showed that among pediatric patients with IBS, constipation-predominant IBS was the prevalent subtype (45%), with a prevalence of 62% in girls (P <0.005); diarrhea-predominant IBS was reported in 26% of children, with a prevalence in boys of 69% (P <0.005); and alternating-type IBS was described in 29% of children, without a difference between the sexes.[22] By contrast, other studies have reported a female preponderance for IBS, with diarrhea-predominant IBS and mixed-type IBS as the most common forms.[23] The prevalence of functional dyspepsia is reported to vary from 0.3–2.5%,[24,25] and that of abdominal migraine from 1.0–4.1% in children.[21,25,26]

Box 2.1 - ROME III criteria for AP-FGIDs

Functional dyspepsia*

- Persistent or recurrent pain or discomfort centered in the upper abdomen (above the umbilicus)
- Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e. not IBS)
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the individual's symptoms

IBS*

- Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time: improved with defecation; onset associated with a change in frequency of stool; onset associated with a change in form (appearance) of stool
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the individual's symptoms

Abdominal migraine‡

- Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 h or more
- Intervening periods of usual health lasting weeks to months
- The pain interferes with normal activities
- The pain is associated with 2 or more of the following: anorexia; nausea; vomiting; headache; photophobia; pallor
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the individual's symptoms

Functional abdominal pain*

- Episodic or continuous abdominal pain
- Insufficient criteria for other FGIDs
- No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms

Functional abdominal pain syndrome*

- Must include childhood functional abdominal pain at least 25% of the time and 1 or more of the following: some loss of daily functioning; additional somatic symptoms such as headache, limb pain, or difficulty sleeping

*Criteria fulfilled at least once per week for at least 2 months before diagnosis. ‡Criteria fulfilled 2 or more times in the preceding 12 months.

Abbreviation: AP-FGID, abdominal-pain-related functional gastrointestinal disorder.

RISK FACTORS AND PATHOPHYSIOLOGY

The prevailing viewpoint is that the pathogenesis of functional pain syndromes involves the inter-relationship between changes in visceral sensation, so-called visceral hyperalgesia or hypersensitivity, and altered gastrointestinal motility.[27] The symptoms of hypersensitivity are pain and discomfort, whereas the symptoms of altered motility can be diarrhea, constipation, nausea, bloating and distension. Several factors have been linked to this hypersensitivity and altered motility and discussed herein (**Figure 2.1**).

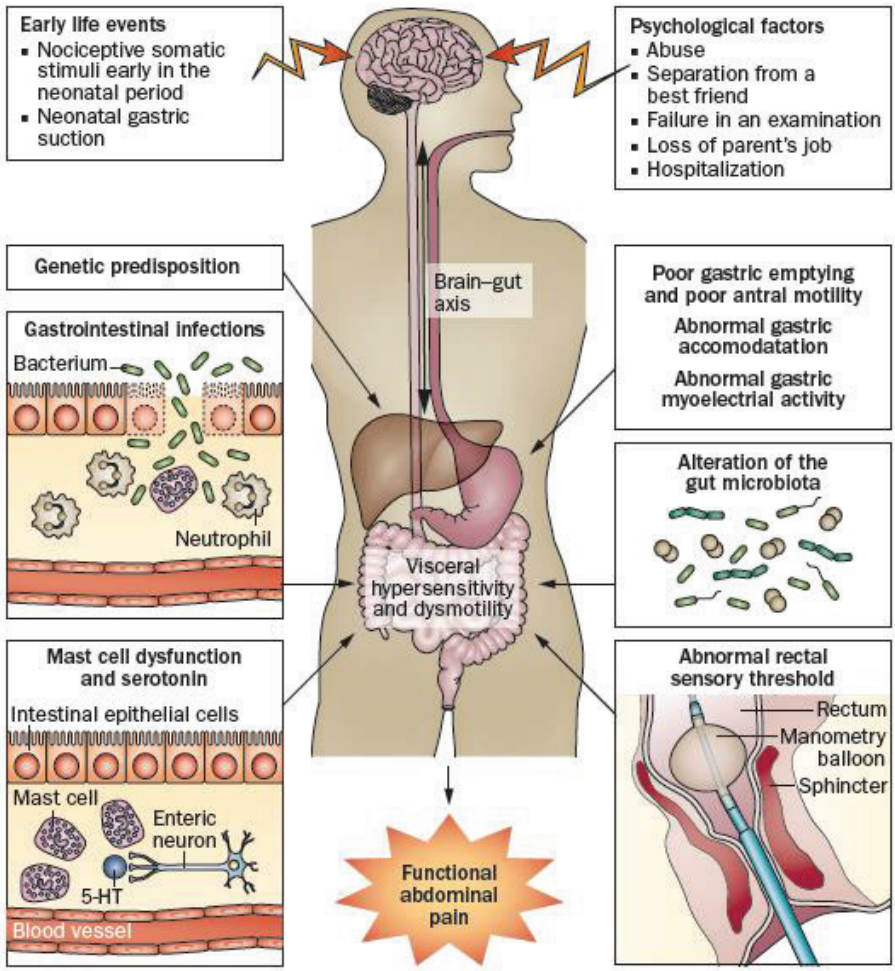

Figure 2.1 - Pathogenesis of childhood abdominal pain. Several risk factors are associated with changes in visceral hypersensitivity and motility and contribute to the development of functional abdominal pain. Abbreviation: 5-HT, 5-hydroxytryptamine: FGID, functional gastrointestinal disorder.

Visceral hypersensitivity

Several investigators have studied visceral sensitivity in children with FAP and IBS.[28–31] These studies clearly demonstrate that children with FAP or IBS as a group have a lower sensory threshold for gastric or rectal balloon distension than healthy controls. However, the clinical utility value of this invasive test is debatable as not all patients have abnormal test results.[30] Imaging studies of adults with IBS have shown that rectal hypersensitivity is associated with greater activation of the rostral anterior cingulate cortex than in healthy individuals.[32,33] To date, it is unknown whether children with IBS have similar reduced sensory thresholds (centrally mediated) that lead to visceral hypersensitivity.

Gastrointestinal motility abnormalities

A series of studies have shown an association between abnormalities in physiological function in the stomach and the gastric antrum and AP-FGIDs and RAP. Using a non-invasive ultrasonographical method, delayed liquid gastric emptying and impaired antral motility was found in children with RAP, FAP, IBS or functional dyspepsia.[34–36] The gastric emptying rate had a statistically significant negative correlation with symptom severity in children with FAP and functional dyspepsia.[35,36] Furthermore, among children with IBS, patients who had been exposed to stressful events had markedly lower gastric emptying rates than patients who had no history of exposure to stress.[34] Similarly, several other studies have described that children with functional dyspepsia have abnormal gastric emptying to both solids and liquids.[37,38] In addition, using the octanoic acid breath test, Hoffman and Tack[39] demonstrated abnormalities in solid emptying in children with functional dyspepsia.

One important physiological function of the proximal stomach is meal accommodation. Abnormalities in meal accommodation are suggested as a possible pathophysiological mechanism for functional dyspepsia in adults.[40,41] Two small studies have demonstrated abnormal gastric accommodation to a solid meal in children with functional dyspepsia.[38,42]

Muscular activity of the stomach is preceded by gastric electrical activity; therefore, it is possible that children with RAP and FGIDs have abnormal gastric myoelectrical activity. Several studies have demonstrated abnormal electrical rhythms (such as tachygastria and bradygastria) in children with functional dyspepsia.[43,44] However, the relationship between abnormal gastric motility and clinical symptoms in children with FGIDs is not completely elucidated: not all children with symptoms have disturbed motility and vice versa.

Early life events

Early life events, such as hypersensitivity to cow's milk protein, pyloric stenosis, umbilical hernia repair and Henoch–Schönlein purpura, are known to be associated with the development of visceral hyperalgesia and abdominal pain in children.[45–47] The putative mechanisms include sensitization of spinal neurons, impaired stress response, and/or altered descending limb inhibitory control.[29] In a rat model, Miranda *et al.*[48] found that exposure to nociceptive somatic stimuli in the early neonatal period resulted in chronic somatic and visceral hyperalgesia. In addition, the same group of researchers found that neonatal gastric suction also led to visceral hyperalgesia through corticotrophin-releasing factor.[49] These observations suggest a possibility of the existence of a critical vulnerable period in early development of the nervous system that can be associated with prolonged structural and/or functional alterations that affect pain perception. Stress is a known trigger for symptoms of FAP and IBS.[50] Therefore, adverse events in early life might give rise to long-lasting or permanent alterations in central nervous system responses to stress and bowel sensitivity, thereby inducing an increased susceptibility to the development of FGIDs.[49]

Psychological factors

Psychological stress has long been recognized as a risk factor for the development of FGIDs in children. Several patient studies have shown an association between RAP and exposure to stressful events.[51–55] In children this stress can be, for example, separation from the best friend at school, failure in an examination, loss of a parent's job and hospitalization.[19,25,56] In addition, exposure to abuse is also an important risk factor for abdominal pain in children.[57] Studies among adults have shown an association between abuse as a child and development of IBS in later life.[58] Also, in children, an association was found between all three types of child abuse (physical, emotional and sexual) and AP-FGIDs.[15,27] Furthermore, anxiety and depression were reported to be substantially more frequent among children with FGIDs than in healthy children.[59–63]

How these psychological factors lead to the development of FGIDs is still debated. Depression and anxiety can be the result of ineffective mechanisms of coping with stress, as limited coping strategies are demonstrated in children with chronic abdominal pain.[64] This finding might also account for the association with traumatic life events. In addition, stressors have been shown to be associated with enhanced visceral perception.[65] Several functional MRI studies have shown that abuse and related stresses lead to activation of the anterior mid cingulate and posterior cingulate cortices.[66] Furthermore, a simultaneous deactivation of the anterior cingulate cortex supragenual region, an area associated with the down regulation of pain signals, was noted in

adults with FGIDs.[67] Animal studies have shown that exposure to stress predisposes them to develop stress-induced visceral hypersensitivity,[68] altered defecation,[69] intestinal mucosal dysfunction,[70] alterations in the hypothalamo–pituitary–adrenal (HPA) axis[71] and disruption of the intestinal microbiota.[72] Similarly, studies conducted in adults with IBS have revealed stress-induced alterations in gastrointestinal motility, visceral sensitivity, autonomic dysfunction and HPA axis dysfunction.[51] Therefore, it is possible that, through the same mechanisms, abuse and stress lead to the alteration of both the HPA and brain–gut neural axes, predisposing individuals to develop FGIDs.

Inflammation of the intestinal mucosa

Faure and colleagues[73] have analyzed the inflammatory cells in the colonic and gastric mucosa of children with functional dyspepsia or IBS. Of 12 patients with IBS, 11 had minimal inflammation of the intestinal mucosa, whereas 9 of 17 patients with functional dyspepsia had variable degrees of inflammation; however, the place of inflammation was not specified, which is a drawback of this important study. Another study noted that 71% of children evaluated for suspected functional dyspepsia had duodenal eosinophilia (>10 eosinophils per high-power field of view).[74] However, the real clinical utility of such findings is still not clear.

Mast cell dysfunction and 5-hydroxytryptamine

5-hydroxytryptamine (5-HT, serotonin) is considered to be an important regulatory chemical compound in the brain–gut axis.[75] 5-HT is released by the enterochromaffin cells of the intestinal mucosa and its action is regulated by the 5-HT selective reuptake transporter (also known as sodium-dependent serotonin transporter, SERT) and organic cation transporter-1 (OCT-1).[76] Studies have shown variable results of 5-HT signaling in colonic mucosa in adults with IBS.[77] One study conducted in children with either IBS or functional dyspepsia was unable to demonstrate increased numbers of enterochromaffin cells in the gastric mucosa of children with functional dyspepsia or the colonic mucosa of children with IBS.[73] However, the 5-HT content in the colonic mucosa was increased in the IBS group and normal in the gastric mucosa of individuals with functional dyspepsia. No difference of TPH1 (tryptophan 5-hydoxylase 1, the rate-limiting enzyme in the synthesis of 5-HT) mRNA expression was observed in the gastrointestinal biopsy samples of both those with IBS or functional dyspepsia compared with controls. Children with IBS had lower expression of SERT mRNA in the rectal mucosa than healthy controls. These findings indicate that children with IBS have an increased availability of 5-HT in their rectal mucosa.[73] Possibly, 5-HT interacts with peripheral nerves in the submucosa and contributes to the development of abdominal pain through heightening visceral sensitivity and stimulating pain pathways in children with FGIDs.

Human gut microbiota

Alteration of the gut microbiota has long been considered as a potential mechanism for the development of pain-predominant FGIDs. In an elegant study, Saulnier *et al.*[78] noted that children with IBS had a greater proportion of the phylum Proteobacteria, and genera such as *Dorea* (a member of Firmicutes) and *Haemophilus* (a member of Proteobacteria); in addition, it was also noted that species such as *H. parainfluenzae* and *Ruminococcus* were more abundant and Bacteroides were markedly less abundant in children with IBS than healthy individuals as controls.[78] Another study comparing the fecal microbiota of healthy children and pediatric patients with diarrhea-predominant IBS noted that levels of *Veillonella*, *Prevotella*, *Lactobacillus* and *Parasporbacterium* were increased in patients with IBS, whereas a reduction in levels of *Bifidobacterium* and *Verrucomicrobium* was reported.[79] Although further studies are needed to clarify and clearly identify the exact changes in the gut microbiota of children with FGIDs, these research efforts provide some insight to the possibility of alteration of the microbiota leading to symptom generation. These microbes might alter visceral perception, gut motility, intestinal gas production and gut permeability with their metabolites leading to pain-predominant FGIDs.[80,81]

Genetic and environmental factors

Genetic and environmental factors have long been considered as risk factors for the development of pain-predominant FGIDs. In a genome-wide association study in adults, a locus on chromosome 7p22.1 has consistently been shown to be associated with a genetic risk of developing IBS, although it still did not reach genome-wide significance in the meta-analysis of combined index and replication findings.[82] The most convincing genetic association is with the *TNFSF15* polymorphism, which has been observed in three independent cohorts in Sweden, the USA and England.[83,84] The *TNFSF15* polymorphism has been associated with constipation-predominant IBS, diarrhea-predominant IBS and postinfectious IBS phenotypes. TL1A, the protein encoded by *TNFSF15*, modulates inflammatory responses, which supports the role of immune activation in IBS.[83,84] A twin study, performed by Levy *et al.*,[85] showed a 17% concordance for IBS in monozygotic twin patients, with only 8% concordance in dizygotic twins, supporting a genetic contribution to IBS. This study, however, also showed that a parental history of IBS was a stronger predictor of developing IBS than having a twin with IBS, suggesting that social learning is much more important than genetic factors. Furthermore, Buonavolonta *et al.*[86] noted that parents of children with FGIDs have a higher prevalence of similar diseases than parents of children without FGIDs. Another study found that children of parents with IBS tend to use health care substantially more for gastrointestinal problems than children of parents who do not have IBS.[85]

In addition, parental response to a child's pain behaviors seems to be a key factor in the development and recurrence of FAP, and interventions that target changes in parental responses can decrease complaints of pain and other illness behaviors in children.[87] In addition, high somatization scores in mothers and fathers are associated with high somatization scores in children with RAP.[88] Parents' over-reactive behavior during pain episodes probably influences not only the frequency and intensity of the abdominal pain but also the cognition of pain and extraintestinal somatic symptoms, which are an integral part of FAP. These findings suggest the possibility of genetic predisposition and social and environmental susceptibility to developing pain-predominant FGIDs.

Postinfectious causes

Studies in adults have established the possibility of developing IBS after an episode of acute gastroenteritis.[89] The possible mechanisms are genetic predisposition, psychological status during infection, acute inflammation leading to alteration of 5-HT metabolism, sensitivity of enteric neurons, ongoing immune cell activation in the gastrointestinal tract and an altered gut microbiota.[90] In one study, children developed IBS after exposure to an outbreak of *Escherichia coli* gastroenteritis. Female sex, increased duration of symptoms, use of antibiotics and weight loss were statistically significant risk factors for developing IBS in this group of children.[91] On the other hand, it has been shown that rotavirus gastroenteritis does not seem to be a risk factor for FGIDs in children.[92]

CLINICAL EVALUATION

A comprehensive history-taking and physical examination of children with AP-FGIDs are essential to rule out most organic causes. Alarm symptoms that might be related to organic causes of AP-FGIDs are summarized in **Box 2.2**.[93] Several studies evaluating the medical history of children with chronic abdominal pain have provided some evidence that frequency, severity, location and timing (postprandial or waking during night) of abdominal pain do not help distinguish between organic abdominal pain and FAP.[93,94]

Abdominal pain diaries can be helpful in clarifying details of the abdominal pain and possible triggering factors, such as specific foods or stressors. An assessment of the stool pattern can differentiate between different subtypes of AP-FGIDs. Furthermore, dietary history and the history of previous treatment strategies for AP-FGIDs should be investigated. Owing to the high degree of association of AP-FGID with a range of psychological problems, particular attention

must be paid to this part of the history. Children suspicious for any psychological disorder should be referred to a mental health professional.

The physical examination should consist of a basic abdominal examination to identify any obvious abnormalities rather than to confirm a diagnosis of an AP-FIGDs. A lack of physical findings might be reassuring to both physician and patient.

Box 2.2 - Warning symptoms in childhood AP-FGIDs

Historical findings

- Persistent right upper or right lower quadrant pain
- Persistent vomiting
- Gastrointestinal blood loss
- Chronic severe diarrhea
- Involuntary weight loss
- Unexplained fever
- Family history of IBD, coeliac disease or familial Mediterranean fever

Examination findings

- Deceleration of linear growth
- Uveitis
- Oral lesions
- Skin rashes
- Icterus
- Anaemia
- Hepatomegaly
- Splenomegaly
- Arthritis
- Costovertebral angle tenderness
- Tenderness over the spine
- Perianal abnormalities

Abbreviation: AP-FGID, abdominal-pain-related functional gastrointestinal disorder.

LABORATORY INVESTIGATIONS

Although no evidence is available to evaluate the predictive value of laboratory tests, in general, urinalysis, blood analysis and stool analysis are often ordered by clinicians to distinguish between organic and FAP.[95] Notably, performing multiple tests might provide nonspecific results that are unrelated to the presenting symptom or have no clinical relevance, which might cause confusion and lead to further invasive testing and procedures.[96] A limited and reasonable screening protocol could include a complete blood cell count, levels of C-reactive protein and screening for coeliac disease. If a child has diarrhea alongside abdominal pain, one might

consider stool analysis for infection with *Giardia lamblia*. Several studies have investigated the prevalence of lactose intolerance in children with abdominal pain, but elimination of lactose often does not result in resolution of abdominal pain.[97,98] Also, *Helicobacter pylori* infection can be found in children with RAP.[99] This finding does not, however, necessarily indicate a causal relationship between the two, as children with *H. pylori* infection are not more likely to have abdominal pain than children without *H. pylori* infection.[100] In the past few years, elevated concentrations of fecal calprotectin has been shown to be a valuable biomarker in diagnosing IBD in children.[101] A study in 126 children with an FGID showed fecal calprotectin concentrations within the normal limit; therefore, this approach seems to be a useful and noninvasive test for distinguishing between FAP and IBD in these children.[102] A proposed diagnostic flowchart is shown in **Figure 2.2**.

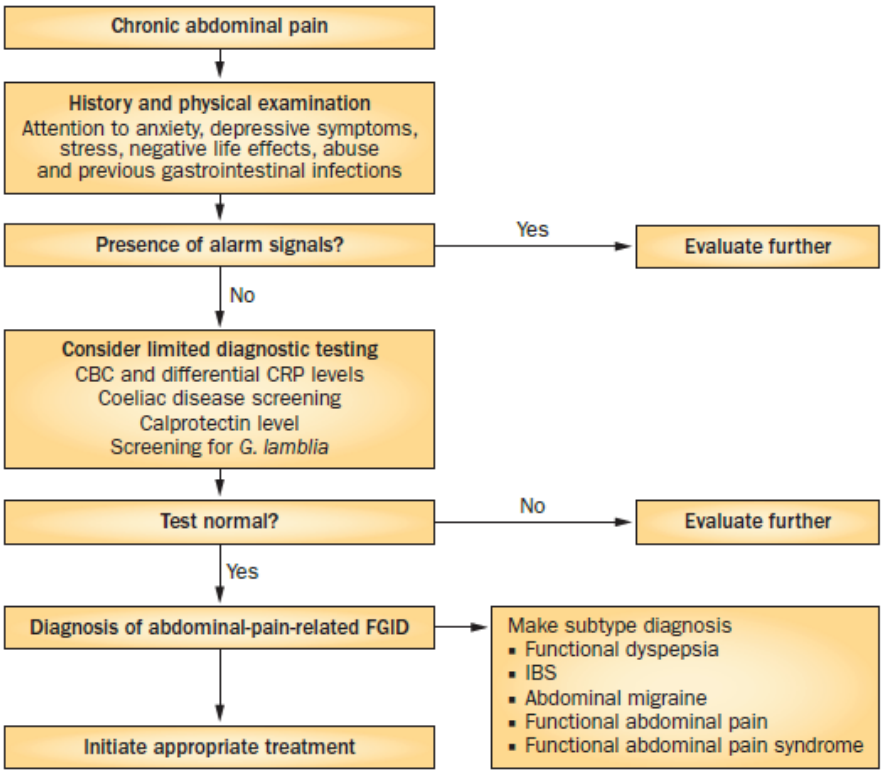

Figure 2.2 - Diagnostic algorithm for childhood functional abdominal pain. Abbreviations: CBC, complete blood count; CRP, C-reactive protein; FGID, functional gastrointestinal disorder.

Radiological and endoscopic investigations

A retrospective study in 644 children with RAP showed that abdominal abnormalities were detected by ultrasonographical examination in just 2% of patients. When atypical symptoms were present, such as jaundice, vomiting, back or flank pain, urinary symptoms or abnormal findings on physical examination, abnormalities observed by ultrasonography increased to 11%.[103] Ultrasonography should therefore only be used in children with RAP and atypical clinical features. A prospective study of 290 children with chronic abdominal pain demonstrated a diagnostic value of esophagogastroduodenoscopy in 38% of the children. At least two alarm symptoms were predictive of diagnostic yield, but without alarm symptoms the diagnostic yield was still 34%, including reflux esophagitis (n = 16), eosinophilic esophagitis or gastroenteritis (n = 6), erosive esophagitis (n = 1), coeliac disease (n = 1) and *H. pylori* infection (n = 1).[104] However, medical therapy started after identification of the disorders was effective in only 67% of children during the year after diagnosis, questioning the relationship between the abnormalities found during endoscopy and the clinical symptoms. When presenting with functional dyspepsia, abnormalities have been shown in only 6.3% of children.[105] The use of esophagogastroduodenoscopy in the presence of alarm symptoms might be considered in the diagnostic work-up of chronic abdominal pain in children.

MANAGEMENT STRATEGIES

Treatment of children with an AP-FGIDs starts with explaining the diagnosis to the parent(s) and child. The Rome III criteria encourage physicians to make a positive diagnosis of an AP-FGID rather than using exhaustive investigations to exclude an underlying organic cause. A multidisciplinary approach to management of childhood AP-FGIDs might be needed in case of social and psychological comorbidities. The primary goal of therapy might not always be complete eradication of pain, but resumption of a normal lifestyle with regular school attendance, normal sleep pattern and participation in extracurricular activities. An active listening approach of the physician and an encouraging attitude towards treatment helps improve the patient's responses to therapeutic attempts.[106] Furthermore, parents should be informed that a solicitous response (specifically showing concern or anxiety) by parents might negatively influence the treatment outcomes in children.[107] In instances of persisting symptoms and serious disruption of a child's well-being, pharmacological therapy or non-pharmacological treatment can be considered. If possible, treatment should be individualized, taking into account risk factors, comorbidities and personal preferences of each patient and their parents. A therapeutic flowchart for AP-FGIDs is shown in **Figure 2.3**.

Pharmacological treatment

Evidence for pharmacological treatment in children with AP-FGIDs is very low, only a few placebo-controlled randomized controlled trials (RCTs) are available, as detailed in a systematic review.[108] Pharmacotherapeutic agents used to treat AP-FGIDs encompass antispasmodic agents, antidepressants, antireflux agents, antihistamine agents and laxatives.[108] The role of placebo in functional disease in general is substantial and will therefore be discussed separately before addressing the efficacy of the different drugs used in children with AP-FGIDs.

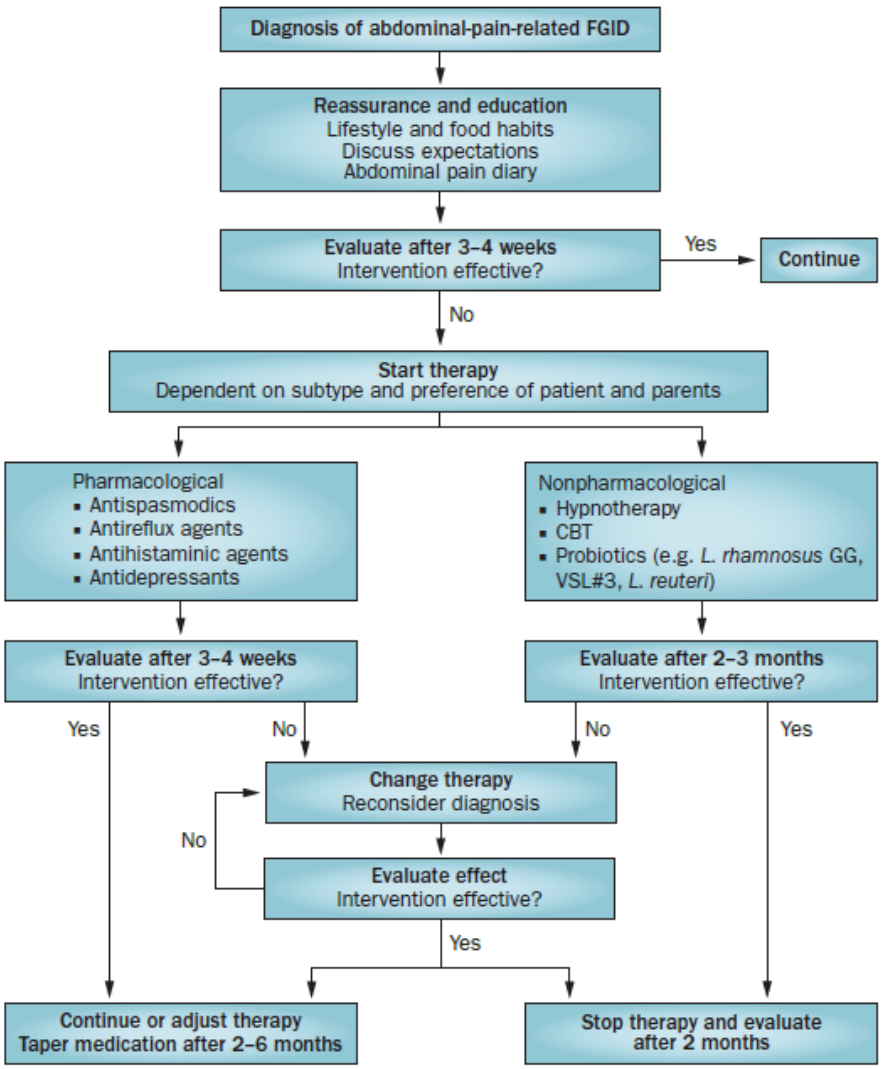

Figure 2.3 - Therapeutic algorithm for childhood functional abdominal pain. Abbreviations: CBT, cognitive behavioral therapy; FGID, functional gastrointestinal disorder.

The role of placebo

Owing to a strong placebo response, several studies[109,110] have failed to demonstrate a statistically significant benefit of an intervention, although an absolute improvement was seen in the trial by Saps *et al.*[110] that evaluated the effect of amitriptyline compared to placebo. These researchers hypothesized that the placebo effect was due to a high level of expectancy of the children and the parents, and the frequent contact between the doctors and the patients.[110] Furthermore, it is known that an active listening approach and encouraging attitude towards treatment help improve patient responses to both therapeutic attempts and placebo.[111,112] On the other hand, a strong placebo response might point towards variation in the natural course of disease or fluctuations in symptoms.[113] A physician should keep in mind that all these components can result in a 50% chance of improvement, no matter which medication is prescribed.[109,110]

Antispasmodics

Antispasmodic agents are thought to be helpful in the treatment of AP-FGIDs through their effects on decreasing smooth muscle spasms in the gastrointestinal tract, resulting in a reduction of abdominal pain.[114] These agents are effective in adults with IBS.[115] Two pediatric trials have evaluated the effect of antispasmodic agents compared with placebo.[116,117] Kline *et al.*[116] compared peppermint oil to placebo in 50 children with IBS—the menthol component of peppermint oil is known to block Ca^{2+} channels,[118,119] which might lead to reduction of colonic spasms.[120] After 2 weeks, 76% of children receiving peppermint oil reported improvement in severity of symptoms versus 19% of children receiving placebo (P <0.001). Unfortunately, no follow-up data were available. Another trial investigated the efficacy of mebeverine in 115 children with FAP.[117] Mebeverine is considered an antispasmodic owing to its anticholinergic effects on smooth muscles.[121] After 4 weeks of treatment and 12 weeks of follow-up, no statistically significant effect on abdominal pain was shown compared to placebo. Both studies were affected by a high drop-out rate, 16% and 24% for the peppermint oil and mebeverine trial, respectively. Notably, peppermint oil and mebeverine were well tolerated.

Antidepressants

Antidepressants, such as tricyclic antidepressants and selective 5-HT-reuptake inhibitors, are used as a therapy for AP-FGIDs.[122] Amitriptyline (a tricyclic antidepressant) works primarily by inducing pain tolerance through peripheral or central antinociceptive properties and anticholinergic effects when administered in low doses.[123] Beneficial effects have been shown in the treatment of adults with IBS[124] and functional dyspepsia.[125] However, these effects were not confirmed in pediatric AP-FGIDs, when comparing amitriptyline to placebo.[110,126] Saps *et al.*[110]

included 90 children with AP-FGIDs; 59% of children receiving amitriptyline compared to 53% receiving placebo reported feeling better after 4 weeks treatment, a difference that was not statistically significant. Bahar *et al.*[126] investigated the efficacy of amitriptyline for 8 weeks in 33 adolescents with IBS. An inconsistent improvement of pain and no statistically significant improvement in any IBS-related symptoms were found. However, children receiving amitriptyline reported significantly greater improvements in overall quality of life scores at week 6, 10 and 13 ($P = 0.019$, $P = 0.004$ and $P = 0.013$, respectively).[126] Adverse events were only reported in the study by Saps and colleagues;[110] two children in the amitriptyline group dropped out due to fatigue, rash and headaches. An association between dose-response of tricyclic antidepressants with prolongation of corrected QT interval has been demonstrated;[127] therefore, a screening echocardiogram should always be performed before initiating amitriptyline therapy.[128] In addition, preliminary results of a small study suggest that low doses of amitriptyline can be considered as a safe drug in children with AP-FGIDs.[129]

Two trials describe the effectiveness of selective 5-HT-reuptake inhibitors in the pediatric AP-FGID population, both investigating citalopram. In a small open-label trial, Campo *et al.*[130] included 25 children (aged 7–18 years) with RAP who were treated for 12 weeks. Abdominal pain, anxiety, depression, other somatic symptoms and functional impairment all improved markedly compared with baseline. However, these promising results were not confirmed by a second placebo-controlled randomized trial in 115 children (aged 6–18 years) with FAP receiving citalopram for 4 weeks.[131] No statistically significant difference was observed in treatment response rate between citalopram and placebo at week 4 (40.6% versus 30.3%, $P = 0.169$) and at 12 weeks follow-up (52.5% versus 41.0%. $P = 0.148$). The study was, however, conducted in a tertiary-care setting and the results might not be generalized to other pediatric-care settings. The quality of the study was limited due to a drop-out rate >20% and important differences in baseline characteristics of the study participants.

Antireflux agents

One placebo-controlled RCT evaluated the efficacy of a H2 receptor antagonist, famotidine. See *et al.*[132] included 25 children with RAP and dyspeptic symptoms who received famotidine twice daily for 3 weeks. In cases of persisting symptoms, after crossing over, treatment continued for another 3 weeks. A notable benefit of famotidine compared with placebo was found when assessing global symptom improvement (67% versus 15%, $P = 0.015$). However, no substantial decrease in abdominal pain was demonstrated. Famotidine inhibits gastric acid secretion[133] and is therefore promising in patients with dyspeptic symptoms. No controlled studies on the use of

PPIs in children with FAP are available. Among adults with nonulcer dyspepsia, PPIs were markedly more effective than placebo in the reduction of dyspeptic symptoms.[134]

Antihistaminic agents

Cyproheptadine is an antihistaminic agent with possible Ca^{2+} channel blocking and anti-5-HT effects.[135–137] Because of its anti-5-HT effect, cyproheptadine was hypothesized to be effective in pediatric AP-FGIDs. In a double-blind placebo-controlled trial, a beneficial effect of cyproheptadine was demonstrated in 29 children with FAP.[138] After 2 weeks of treatment a significant improvement in abdominal pain frequency ($P = 0.002$), pain intensity ($P = 0.001$) and global improvement ($P = 0.005$) was demonstrated. Nevertheless, results should be interpreted cautiously because of the small sample size and limited follow-up of only 2 weeks. Furthermore, a small retrospective trial evaluated the effect of cyprohepatidine in children with abdominal migraine. After treatment, 83% of the children reported an excellent or fair response and 17% reported no response.[139] Duration of treatment varied between 10 months and 3 years. Large clinical trials with longer follow-up periods are needed to confirm these results.

Laxatives

No RCTs evaluating the effect of laxatives in the treatment of children with AP-FGIDs are available. In the past decade, new laxatives such as lubiprostone and linaclotide have been shown to be effective in treating adults with constipation-predominant IBS, without serious adverse effects.[140] Still, these drugs have not yet been evaluated in children with the same condition.

Nonpharmacological treatment

Dietary interventions

Food might trigger symptoms in AP-FGIDs;[141] however, recognition of specific food components triggering symptoms is difficult. Malabsorption and intolerance to carbohydrates are commonly indicated as an underlying cause. Fermentation of malabsorbed carbohydrates by the colonic microbiota could result in symptoms of carbohydrate intolerance, including abdominal pain, bloating, borborygmi, flatulence and diarrhea.[142] Therefore, carbohydrates such as lactose have been the major target of dietary modification for functional gut symptoms.[143] Restriction of lactose, however, did not result in symptom improvement in children with RAP.[144,145] In addition, in a study published in 2012, neither lactose intolerance nor fructose intolerance could be established as a cause of RAP in 220 children.[98] Attention has been drawn to diets low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP). Avoiding poorly absorbed short-chain carbohydrates could result in improvement of gastrointestinal

symptoms,[143] and has already shown promising results in adults with IBS.[146] A randomized, double-blind, crossover trial in 33 children with IBS showed a decrease in frequency of abdominal pain after 48 h of a low FODMAP diet compared with a high FODMAP diet.[147] Low FODMAP diets seem to be effective, but more (long-term) studies are needed to further assess their efficacy and safety. In addition, intake of numerous regular food products had to be eliminated or markedly reduced, very strictly, which can make maintenance of this diet problematic for children and their parents.

Dietary fibres are carbohydrates that are not hydrolyzed or absorbed in the upper part of the gastrointestinal tract.[148] Fibre is thought to improve bowel function by softening stools and enhancing colonic transit, though there is the unwanted adverse effect of increasing gas production.[115,148] Historically, increasing dietary fibre intake has been a standard recommendation for patients with IBS, but the efficacy of this approach is controversial. Four pediatric trials evaluating fibre supplementation did not show a favorable effect in children with chronic abdominal pain.[149–152] Horvath *et al.*[153] performed a meta-analysis of three RCTs including data from 182 children using psyllium fibre or glucomannan. After pooling, there was no significant difference in experiencing 'no pain' and/or 'satisfactory improvement' between the fibre group (52.4%) and placebo group (43.5%); (relative risk [RR] 1.17, 95% CI 0.75–1.81).[153] Only partially hydrolyzed guar gum resulted in a significant improvement in frequency of IBS symptoms compared with placebo (43% versus 5%, $P = 0.025$), but no effect on pain intensity was seen. No serious adverse events were reported in any of the trials.

Probiotics

The gut microbiota can directly influence intestinal homeostasis by affecting bowel motility and modulation of intestinal pain, immune responses and nutrient processing, whereas alterations of these bacteria can distort the homeostasis.[80] As differences have been found in the gut microbiota of children and adults with IBS compared with healthy controls, it seems prudent to try to improve AP-FGID-related symptoms with probiotics.[78,154]

A meta-analysis of five pediatric RCTs[155] reported a significantly higher treatment success of *Lactobacillus rhamnosus* GG, *Lactobacillus reuteri* DSM 17938 and VSL#3 compared with placebo (pooled RR 1.50; 95% CI 1.22–1.84).[155] Subgroup analysis showed results being mainly applicable for IBS (pooled RR 1.62; 95% CI 1.27–2.06). Future research needs to determine which species, specific strains and combinations of strains of probiotics are most efficacious in AP-FGIDs, or whether probiotic treatment should be adapted to the disturbances in the gut microbiota of the individual patient.

Cognitive behavioural therapy

Acceptance of the biopsychosocial model of FGIDs has provided the basis for the use of psychosocial interventions, including family therapy, cognitive behavioral techniques (CBT), relaxation, hypnotherapy, guided imagery and biofeedback. CBT aims to change attitudes, cognitions and behavior from children and parents that might have a role in generating or maintaining symptoms.[124] Eight RCTs have been conducted in children with RAP. Four trials evaluated the efficacy of family-orientated CBT (CBT-family) compared with standard care, all of which showed beneficial effects in favor of CBT-family.[156–159] Levy *et al.*[160] included 200 children and adolescents in their trial and the results are therefore of particular interest owing to the large size of the cohort. A greater decrease in gastrointestinal symptom severity (estimated mean difference [MD], –0.36; 95% CI, –0.63 to –0.01) and greater improvements in pain coping responses (estimated MD 0.61; 95% CI 0.26–1.02) were still reported 12 months after CBT-family.[160] However, two studies that corrected for patient–therapist time, by comparing it with physiotherapy or with supportive sessions with the pediatric gastroenterologist did not find compelling evidence for CBT, suggesting that the time spent with child and parents is one of the most important components of therapy.[161,162] This notion was also suggested by the results of Humphreys *et al.*, who divided 64 patients (4–18 years) into four groups comparing CBT, dietary fibre supplementation, biofeedback and parental support in different combinations.[163] Results were only statistically significant when data from individual CBT, biofeedback and parental support were combined and compared with fibre. In conclusion, CBT has shown efficacy, especially when patients' families are involved, although its working mechanism seems highly influenced by patient–therapist time.

Hypnotherapy

Gut-directed hypnotherapy is a trance-based therapy in which a therapist gives the client suggestions aimed at changing intestinal hypersensitivity, ego-strengthening and stress reduction.[164] The mechanisms by which gut-directed hypnotherapy acts in improving abdominal symptoms in FAP and IBS are still not well understood, but beneficial effects are reported in adult and pediatric trials with long-lasting effects.[165–167] Some evidence exists that gut-directed hypnotherapy affects IBS through a combination of effects on gastrointestinal motility, visceral sensitivity, psychological factors, and/or effects within the central nervous system.[168,169] After performing a systematic review (including three RCTs),[170] Rutten *et al.* concluded that the therapeutic effects of hypnotherapy seem superior to standard medical care in children with FAP or IBS. Hypnotherapy was given in individual or group sessions with qualified therapists or by self-exercises on CD. Effects persist up to 5 years after treatment. These results

were supported by a trial comparing hypnotherapy to a waiting list control group in 38 children with FAP and IBS. 55% of children showed a decrease of 80% in abdominal pain after hypnotherapy, compared with 5.6% of waiting list controls (RR 9.90; 95% CI 1.14–69.28; *P* = 0.002).[171] To date, no studies have compared CBT with hypnotherapy in children or adults with FGIDs.

Complementary and alternative medicine

The NIH defines complementary and alternative medicine (CAM) as a group of diverse medical and health-care systems, practices and products that are not presently considered to be part of conventional medicine.[172] CAM comprises many different treatment modalities, including acupuncture, yoga, homeopathy, mind–body therapy and musculoskeletal manipulations. Although >40% of children with IBS and FAP use some form of CAM,[173] data on efficacy and safety of almost all forms of CAM in these children and adolescents is lacking. Two RCTs compared yoga to a waiting list in adolescents and young adults with IBS.[174,175] Beneficial effects in adolescents were seen in functional disability, gastrointestinal symptoms[175] and physical functioning[174], but no statistically significant improvement of abdominal pain was observed. No other pediatric trials regarding CAM have been formally published.

PROGNOSIS AND LONG-TERM FOLLOW-UP

Several longitudinal epidemiological studies have been performed and link pediatric FAP to abdominal pain later in life.[176] A comprehensive systematic review evaluating the prognosis of chronic abdominal pain in 1,331 children demonstrated persisting symptoms in 29.1% of the children after 5 years (median, range 1–29 years) follow-up even when they had received treatment for the pain.[177] In 2014, Horst *et al.*[178] studied 392 children with AP-FGIDs, of whom 41% still met the criteria for AP-FGIDs after 9 years follow-up. Furthermore, there is evidence from prospective studies that adults with IBS began experiencing recurrent FAP as a child.[179] In particular, females are more likely to meet IBS criteria in adulthood.[180] However, another study demonstrated that persistent abdominal pain in childhood did not predict abdominal pain in adulthood.[181] Instead of persisting abdominal pain symptoms in adulthood, some study authors have concluded that these children are at an increased risk of adult psychiatric disorders, such as anxiety and depressive disorders.[130,181] This finding was also shown for children with dyspepsia; both children with and without abnormal histological findings were at increased risk of chronic dyspeptic symptoms, anxiety disorder and reduced quality of life in adolescence and young adulthood.[182]

Several factors influence the prognosis of childhood AP-FGIDs. Children with a history of chronic abdominal pain had a four times higher risk of persistent abdominal pain than children who presented for the first time with chronic abdominal pain.[177] The longer the duration of follow-up, the worse was the prognosis, with symptoms persisting in 25.4% of patients at 1–5 years follow-up increasing to 37.4% of patients at ≥10 years follow-up.[177] In addition, the presence of nongastrointestinal symptoms, such as back pain, headaches, dizziness, weakness and low energy, at the initial pediatric evaluation was associated with an increased likelihood of FGIDs in adolescence and young adulthood.[178,183] Furthermore, a positive family history of anxiety,[130] RAP or IBS[184] and depressive symptoms[178] are important determinants of persistent abdominal pain in adulthood.

CONCLUSIONS

AP-FGIDs in childhood are a common problem worldwide. Enhancements of the terminology and the introduction of the Rome criteria have encouraged health-care providers to make a positive diagnosis and have advanced empirical research in childhood AP-FGIDs. Increased knowledge of the pathophysiology has led to a biopsychosocial model, in which genetic, physiological and psychological factors interplay. Potential targets for pharmacological and non-pharmacological therapy are arising from this model. To date, high-quality efficacy studies of treatment in pediatric AP-FGIDs are scarce. Available evidence indicates beneficial effects of hypnotherapy and CBT-family. Evidence for a low FODMAP diet and probiotics is promising, as well as for drug treatment such as peppermint oil, cyproheptadine or famotidine, but well-designed trials with long-term follow-up are needed to confirm these preliminary results. The use of homogeneous outcome measures, sufficient sample size and a control arm are necessary. Future research should focus on identifying factors predicting response to optimize and tailor individual treatment.

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PART II

EPIDEMIOLOGY AND RISK FACTORS OF ABDOMINAL PAIN PREDOMINANT FUNCTIONAL GASTROINTESTINAL DISORDERS

Chapter 3

Abdominal pain-predominant functional gastrointestinal disorders in children and adolescents: prevalence, symptomatology and association with emotional stress

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ABSTRACT

Background and objectives: Functional gastrointestinal disorders (FGIDs) are common among children, but little is known regarding their prevalence in developing countries. We assessed the prevalence of abdominal pain predominant FGIDs in addition to the predisposing factors and symptomatology, in Sri Lankan children.

Patients and Methods: A cross-sectional survey was conducted among a randomly selected group of 10- to 16-year-olds in 8 randomly selected schools in 4 provinces in Sri Lanka. A validated, self-administered questionnaire was completed by children independently in an examination stetting. FGIDS were diagnosed using Rome III criteria.

Results: A total of 2180 questionnaires were distributed and 2163 (99.2%) were included in the analysis (1189 [55%] boys, mean age 13.4 years, standard deviation 1.8 years). Of them, 270 (12.5%) had at least one abdominal pain-predominant FGIDs. Irritable bowel syndrome (IBS) was seen in 107 (4.9%), functional dyspepsia in 54 (2.5%), functional abdominal pain in 96 (4.4%) and abdominal migraine (AM) in 21 (1.0%) (2 had AM and functional dyspepsia, 6 had AM and IBS). Extraintestinal symptoms were more common among affected children (p<0.05). Abdominal pain-predominant FGIDs were higher in girls and those exposed to stressful events (p<0.05). Prevalence negatively correlated with age (r= -0.05, p=0.02).

Conclusion: Abdominal pain-predominant FGIDs affects 12.5% of children aged 10 to 16 years and constitutes a significant health problem in Sri Lanka. IBS is the most common FGID type present. Abdominal pain-predominant FGIDs were higher in girls and those exposed to emotional stress. Prevalence of FGIDs decreased with age. Extraintestinal symptoms are more frequent in affected children.

INTRODUCTION

Chronic or recurrent abdominal pain (RAP) is a global health problem affecting 10% to 12% of children and adolescents.[1-3] The majority of them have abdominal pain-predominant functional gastrointestinal diseases (AP-FGIDs) and < 25% have organic causes for their symptoms.[4,5] The main abdominal pain predominant FGIDs, defined in the Rome III criteria, are functional dyspepsia (FD), irritable bowel syndrome (IBS), abdominal migraine (AM) and functional abdominal pain (FAP).[6] Because the pathophysiology, clinical profile and management strategies vary with the subtype,[7,8] it is important to classify chronic/recurrent abdominal pain into different etiologic categories.

Epidemiological studies are needed to identify the true burden of these disorders in the community because a significant percentage of patients with FGIDs do not seek health care.[9,10] So far, the majority of studies on these disorders are hospital based.[4,11,12] There are only a few epidemiological studies have been published in the world, and data published so far have reported AP-FGIDs in 13.8% of Asian children[13] and 0.5% of Western children.[14].

Pain characteristics, associated symptoms and bowel habits play a significant role in Rome III diagnostic criteria for AP-FGIDs.[6] It is also suggested that other somatic symptoms such as headache, limb pain, and sleeping difficulty are more common in children[15] and adults with IBS,[16] but so far very few studies have assessed intestinal-related and extraintestinal symptoms associated with AP-FGIDs.

The exact etiology of FGIDs is not fully understood. The symptoms cannot be explained by the traditional biomedical models. The new biopsychosocial model suggests that these disorders originate from simultaneous interactions among biological, social and psychological factors.[17] Biological factors including familial predisposition,[5] sociocultural factors including lower socioeconomic status[18] and psychological factors including emotional stress[19] are known to be associated with FGIDs. The interplay between these risk factors needed to be studied in depth to understand the possible pathological processes involving FGIDs, especially in children.

The present study was conducted with the objectives of identifying the prevalence of different types of abdominal AP-FGIDs in Sri Lanka, clinical profile of the affected children, and social and psychological factors associated with these disorders.

PATIENTS AND METHODS

An island-wide, cross-sectional survey was conducted in 4 randomly selected provinces (out of 9 provinces) in Sri Lanka. From every selected province, 2 schools each (1urban and 1 rural) were randomly selected. From every school, 12 classes each were randomly selected from academic years 6 to 12 (2 from each academic year). All the children present in the selected classes on the day of the survey were included in the study. School administration and parents were informed and consent to administer the questionnaire was obtained before conducting the study.

Data were collected using a pretested questionnaire that consisted of two parts. Part I included questions on sociodemographic and family factors and exposure to stressful life events. Part 2 is the Questionnaire on Pediatric Gastrointestinal Symptoms – Rome III version (self-reported form for children and adolescents, 10 years of age and older),[20] translated into the native language and validated for Sri Lankan children. The questionnaire was administered in an examination setting to ensure confidentiality and privacy. Adequate time was given to each child to complete the questionnaire and research assistants were available during this period to clarify any question.

Children with abdominal pain were categorized into AP-FGIDs (FD, IBS, AM, and FAP) using Rome III criteria for childhood FGIDs.[6] In this survey, we did not perform a physical examination on affected children.

Data were analyzed using χ^2 and Fisher exact tests using EpiInfo (EpiInfo 6, version 6.04 (1996) Centres of Disease Control and Prevention, Atlanta, Georgia, USA and World Health Organization, Geneva, Switzerland). $P<0.05$ was taken as significant. Ethical approval for the present study was granted by the ethics committee of the Sri Lanka College of Pediatricians.

RESULTS

A total of 2180 questionnaires were distributed and all of them were returned. Of them, 2163 (99.2%) were included in the analysis (1189 [55%] boys, mean age 13.4 years, SD 1.8 years). Seventeen incompletely filled-out questionnaires were excluded from the analysis.

Prevalence of AP-FGIDs

According to Rome III criteria, 270 had at least 1 AP-FGIDs. (**Table 3.1**). Two children with AM also had FD and 6 with AM also had IBS. Of 96 children with FAP, 42 (43.8%) fulfilled criteria for functional abdominal pain syndrome (FAPS). IBS and FD were significantly common among girls

and so was the total AP-FGIDs. **Figure 3.1** illustrates age-related predicted probability of having an AP-FGID. There was a negative correlation between prevalence of AP-FGIDs and age (correlation coefficient -0.05, 95% confidence interval (CI) -0.008 to -0.095, *P*=0.02).

Table 3.1 – Prevalence of abdominal pain-predominant FGIDs according to sex

FGID type	Male	Female	Total
	n (%)	*n* (%)	*n* (%)
FD	18 (1.5%)†	36 (3.7%)*,†	54 (2.5%)‡
IBS	43 (3.6%)‡	64 (6.6%)*,§	107 (4.9%)¶
AM	8 (0.7%)	13 (1.3%)	21 (1.0%)
FAP	44 (3.7%)	52 (5.3%)	96 (4.4%)
Abdominal pain-predominant FGID -Total	110 (9.3%)	160 (16.4)*	270 (12.5%)

AM=abdominal migraine; FAP=functional abdominal pain; FD=functional dyspepsia; FGID= functional gastrointestinal disorder; IBS=irritable bowel syndrome

* Girls versus boy, $P<0.01$ (unpaired *t* test)

† One also had AM, ‡ Two also had AM, § Four also had AM, ¶ Six also had AM

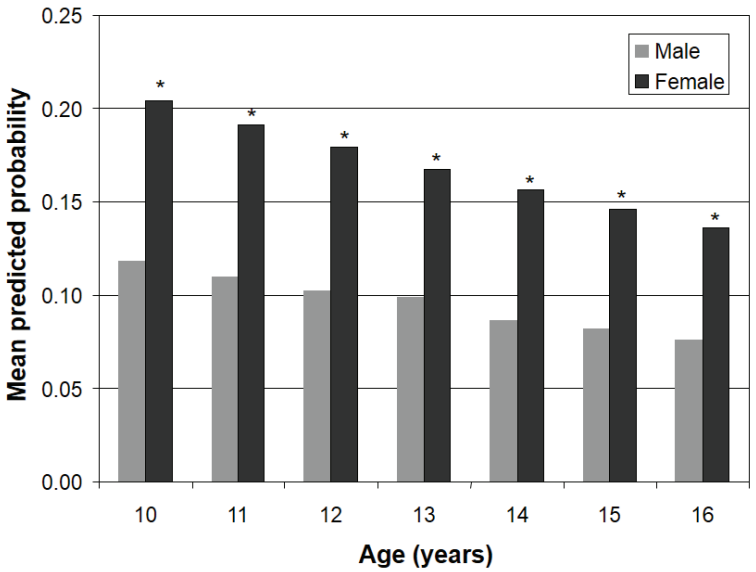

Figure 3.1– Mean predicted probability of developing abdominal pain predominant FGIDs according the age and sex (*$p<0.05$)

Association between sociodemographic characteristics and AP-FGIDs

A total of 1893 children without abdominal AP-FGIDs were identified as controls. **Table 3.2** demonstrates the association between the socioeconomic characteristics and AP-FGIDs. Socioeconomic characteristics were not significantly different between patients with AP-FGIDs and controls (P>0.05).

Pain characteristics in children with AP-FGIDs

Table 3.3 demonstrates the distribution of pain characteristics of children with AP-FGIDs. The only characteristic that significantly differed between subtypes was the presence of severe abdominal pain, which was more common among children with AM (P<0.05).

Of 270 children with AP-FGIDs, 87 (32.2%) had disturbances in school attendance because of pain (FD 22 [40.7%], IBS 36 [33.6%], AM 7 [33.3%], and FAP 22 [22.9%]).

Intestinal and extraintestinal symptoms in affected children

Intestinal-related symptoms such as bloating, loss of appetite, nausea, vomiting, flatulence and burping and extraintestinal symptoms such as headache, limb pain, sleeping difficulty and photophobia were commoner among children with FGIDs compared to controls (P<0.05) (**Table 3.4**).

Association between stress and AP-FGIDs

Table 3.5 shows the association between stressful life events and AP-FGIDs. After multiple logistic regression analysis, separation from best friend (adjusted odds ratio [OR] 1.5, 95% CI 1.1- 2.1, P=0.017] , failure in an examination [adjusted OR 1.7, 95% CI 1.0-2.6, P= 0.033], loss of parent's job [adjusted OR 2.0, 95% CI 1.0-3.8, P= 0.039] and hospitalization of the child himself or herself for another illness [adjusted OR 1.6, 95% CI 1.0-2.4, P= 0.031] were independently associated with AP-FGIDs.

Table 3.2 – Demographic and family characteristics of children with abdominal pain-predominant FGIDs compared to controls

Variable		Abdominal pain-predominant FGIDs (*n*=270) *n* (%)	Controls (*n*=1893) *n* (%)
Family size	Only child	27 (10.0)	146 (7.7)
	2-3 children	230 (85.2)	1660 (87.7)
	≥ 4 children	13 (4.8)	87 (4.6)
Birth order*	Eldest	109 (44.9)	767 (43.9)
	2nd child	89 (36.6)	568 (32.5)
	3rd child	28 (11.5)	297 (17.0)
	4th child or more	17 (7.0)	115 (6.6)
Maternal employment	Leading profession (e.g., doctor, engineer)	7 (2.6)	43 (2.3)
	Lesser profession (e.g., nurse, teacher)	8 (3.0)	119 (6.3)
	Skilled non manual (e.g., clerk)	3 (1.1)	70 (3.7)
	Skilled manual (e.g., mason, carpenter)	12 (4.4)	55 (2.9)
	Unskilled/unemployed	240 (88.9)	1605 (84.8)
	Mother not living	—	1 (0.0)
Father's social class	Leading profession	43 (15.9)	270 (14.3)
	Lesser profession	10 (3.7)	109 (5.8)
	Skilled non manual	49 (18.1)	343 (18.1)
	Skilled manual	113 (41.9)	795 (42.0)
	Unskilled/unemployed	50 (18.5)	355 (18.8)
	Father not living	5 (1.9)	21 (1.1)
Location of school	Urban	192 (71.1)	1390 (73.4)
	Rural	78 (28.9)	503 (26.6)

FGIDs = functional gastrointestinal disorders, *Families with more than one child

P>0.05 for all comparisons between patients and controls (unpaired t test)

Table 3.3 – Abdominal pain characteristics according to the FGIDs

		FD† *n* (%)	IBS‡ *n* (%)	AM *n* (%)	FAP *n* (%)	Total *n* (%)
Frequency of pain	Once per month	0	0	3 (14.3)	0	3 (1.1)
	Once per week	21 (38.9)	44 (41.1)	8 (38.1)	52 (54.2)	124 (45.9)
	Several times per week	29 (53.7)	58 (54.2)	10 (47.6)	41 (42.7)	132 (48.9)
	Everyday	4 (7.4)	5 (4.7)	0	3 (3.1)	11 (4.1)
Duration of pain	2 months	16 (29.6)	31 (29.0)	0	38 (59.4)	85 (31.5)
	3 months	14 (25.9)	13 (12.1)	4 (19.0)	25 (26.0)	54 (20.0)
	4-11 months	10 (18.6)	47 (43.9)	13 (61.9)	20 (20.8)	86 (31.9)
	≥ 12 months	14 (25.9)	16 (15.0)	4 (19.0)	13 (13.6)	45 (16.7)
Duration of pain episodes	Less than 1 hour	37 (68.5)	59 (55.1)	0	68 (70.8)	164 (60.7)
	1-2 hours	8 (14.8)	31 (29.0)	10 (47.6)	12 (12.5)	56 (20.7)
	3- 4 hours	4 (7.4)	8 (7.5)	2 (9.5)	6 (6.3)	20 (7.4)
	Most of the day	5 (9.3)	9 (8.4)	9 (42.9)	10 (10.4)	30 (11.1)
Severity of pain	Mild	11 (20.4)	20 (18.7)	0	26 (27.1)	57 (21.1)
	Moderate	31 (57.4)	67 (62.6)	0	50 (52.1)	148 (54.8)
	Severe	12 (22.2)	20 (18.7)	21 (100)*	20 (20.1)	65 (24.1)
Location of pain	Upper abdomen	54 (100)	26 (24.3)	8 (27.6)	0	86 (31.9)
	Periumbilical/lower abdomen	0	50 (46.7)	13 (61.9)	70 (72.9)	127 (47.0)
	Both upper and lower abdomen	0	31 (29.0)	0	26 (27.1)	57 (21.1)

AM = abdominal migraine; FAP = functional abdominal pain; FD = functional dyspepsia; FGIDs = functional gastrointestinal disorders; IBS = irritable bowel syndrome

* $P<0.001$, compared with other 3 types of FGIDs (unpaired *t* test)

† Two children had FD and AM.

‡ Six children had IBS and AM.

Table 3.4 – Intestinal-related and extraintestinal symptoms in children with abdominal pain-predominant FGIDs

	FD *n* (%)	IBS *n* (%)	AM *n* (%)	FAP *n* (%)	FGID-total *n* (%)	Controls *n* (%)
Intestinal-related symptoms						
Bloating	19 (35.2)***	48 (44.9)***	9 (42.9)***	43 (44.8)***	115 (42.6)***	462 (24.4)
Loss of appetite	10 (18.5)***	31 (29.0)***	13 (61.9)***	21 (21.9)***	69 (25.6)***	101 (5.3)
Nausea	10 (18.5)***	31 (29.0)***	12 (57.1)***	25 (26.0***)	72 (26.7)***	70 (3.7)
Vomiting	2 (3.7)***	17 (15.9)***	4 (19.0)***	2 (2.1)	24 (8.9)***	24 (1.3)
Flatulence	23 (42.6)***	67 (6.0)***	11 (52.4)***	51 (53.1)***	148 (54.8)***	369 (19.5)
Burping	40 (74.1)*	72 (67.3)**	16 (76.2)*	65 (67.7)	187(69.3)***	414 (21.9)
Extra-intestinal symptoms						
Headache	11 (20.4)***	47 (43.9)***	16 (76.2)***	31 (32.3)***	99 (36.7)***	92 (4.7)
Sleeping difficulty	17 (31.5)***	65 (60.7)***	11 (52.4)***	37 (38.5)***	127 (47.0)***	125 (6.6)
Limb pain	15 (27.8)***	53 (49.5)***	15 (71.4)***	34 (35.4)***	110 (40.7)***	108 (5.7)
Photophobia	4 (7.4)***	29 (27.1)***	12 (57.1)***	15 (15.6)***	55 (20.4)***	38 (2.0)
Light-headed	10 (18.5)	46 (43.0)	13 (61.9)	29 (30.2)	94 (34.8)	75 (4.0)

AM = abdominal migraine; FAP = functional abdominal pain; FD = functional dyspepsia; FGIDs = functional gastrointestinal disorders; IBS = irritable bowel syndrome

*$p<0.05$, **$p<0.001$, ***$p<0.0001$, compared with controls (unpaired *t* test)

Table 3.5 - Distribution of responders according to exposure to stressful life events

Stressful event	FGIDs *n* (%)	Controls *n* (%)	OR (95% CI)	*P*
Change in school	10 (3.7)	80 (4.2)	0.81 (0.4-1.7)	0.81
Suspension from school	3 (1.1)	7 (0.4)	3.03 (0.62-13.03)	0.12
Frequent punishment in school	14 (5.2)	76 (4.0)	1.31 (0.7-2.42)	0.46
Separation from best friend	62 (23.0)	62 (3.3)	1.63 (1.18-2.25)	0.002
Sitting for government examination	124 (45.9)	711 (37.6)	1.41 (1.08-1.84)	0.01
Failure in an examination	30 (11.1)	110 (5.8)	2.03 (1.29-3.16)	0.014
Being bullied at school	14 (5.2)	75 (4.0)	1.33 (0.71-2.45)	0.43
Severe illness in a close family member	49 (18.1)	272 (14.4)	1.32 (0.93-1.87)	0.12
Death of a close family member	33 (12.2)	146 (7.7)	1.67 (1.09-2.53)	0.016
Loss of a parent's job	14 (5.2)	45 (2.4)	2.25 (1.16-4.29)	0.014
Divorce or separation of parents	2 (0.7)	17 (0.9)	0.82 (0.13-3.73)	0.93
Birth of a sibling	25 (9.3)	129 (6.8)	1.40 (0.87-2.23)	0.18
Frequent domestic fights	15 (5.6)	55 (2.9)	1.97 (1.05-6.64)	0.034
Frequent punishment by the parents	18 (6.7)	72 (3.8)	1.81 (1.02-3.16)	0.041
Father's alcoholism	17 (6.3)	85 (4.5)	1.43 (0.8-2.51)	0.25
Hospitalization of the child for other illness	44 (16.3)	180 (9.5)	1.85 (1.27-2.69)	0.0009
Exposure to at least 1 stressful event	198 (73.3)	1190 (62.8)	1.63 (1.21-2.19)	0.0009

CI = confidence interval; FGIDs = Functional gastrointestinal disorders; OR = odds ratio.

DISCUSSION

Community-based studies to assess the burden of AP-FGIDs in children are rare. In the present epidemiological survey we demonstrated that 12.5% of native Sri Lankan children had at least one AP-FGIDs. IBS was the most prevalent FGIDs, followed by FAP and FD. There was a negative correlation between the prevalence of AP-FGIDs and age. Intestinal-related and extraintestinal symptoms were more common in children with all 4 types of abdominal pain-predominant FGIDs compared to controls. There was a significant association between exposure to stressful life events and presence of an AP-FGIDs.

Prevalence of FGIDs depends on several factors. Of them, the definition used in the diagnosis is one of the main determinants. A previous school-based study in children ages 10 to 16 years, using Rome III criteria, has shown IBS as the most common FGIDs followed by FD and FAP.[13] In contrast, another study using Rome II criteria has shown FD as the most common AP-FGIDs.[14] Inclusion of children of different age groups and differences in diagnostic criteria and methods of data collection could have contributed to this difference. One percent of the children in our study had AM, lower than the previous study that found AM in 3% of schoolchildren.[13] Another study from the United Kingdom, using different criteria, has shown AM in 4.1%.[21] These differences of prevalence may result from small sample size and disparity of definitions. The prevalence of FAP in our sample is comparable to that previously reported in Sri Lanka.[13] FAPS is a newly described entity in Rome III process and indicates significant loss of daily function or having somatic symptoms.[6] Forty-three percent of children with FAP had FAPS. Helgeland *et al.*[4] have shown that nearly 60% of children with FAP had FAPS. Children referred to a secondary-care hospital would be more likely to have somatic symptoms and disruption of daily activities than a community sample and this probably explains the difference between the 2 studies.

In our sample, at all ages, girls had a significantly higher probability of having an AP-FGID. We found that FD and IBS were significantly more common among girls. Similar to our results, a previous study conducted in children with abdominal pain has shown higher prevalence in girls.[22] One hospital-based study on children with dyspepsia[23] and 3 studies in children with IBS, failed to show a significant sex difference.[13,15,24] Our findings are compatible with findings of adult studies from Western countries, which have shown that girls have a higher tendency to develop IBS.[10] Heitkemper and Jarrett[25] have previously suggested the difference in hormonal profiles in girls and boys as a contributory factor for higher prevalence of IBS in women; however, in our sample, this sex difference was significant even in young girls (10-11years) in whom the majority have not attained menarche and do not have the full hormonal profile of women. Therefore, we believe that the sex difference in the prevalence of IBS predates the

effects of reproductive hormones. This observed sex difference may results from differences in pain perception between boys and girls. Visceral hypersensitivity plays an important role in the pathogenesis of AP-FGIDs in children.[26,27] A study comparing children with FAP and IBS has found a higher rectal hypersensitivity in girls than in boys.[28] Adult studies have also shown similar results.[29] Therefore, it is possible that the heightened visceral sensitivity in girls predisposes them to be more likely to manifest IBS. We failed to demonstrate a significant sex difference in AM. This is similar to the findings of Abu-Arafeh and Russell.[21]

The prevalence of AP-FGIDs declined with age in both boys and girls. The reason for this phenomenon is unclear. We previously reported a similar age-related decline in the prevalence of functional defecation disorders such as constipation[30] and fecal incontinence.[18]

There are conflicting data on the association between socioeconomic factors and AP-FGIDs. Previous studies in adults have shown that an affluent childhood living conditions is associated with IBS.[31,32] Similarly, adult studies in Asia (China, Singapore) have shown that the prevalence of IBS is higher among people who have achieved higher educational status.[33,34] In contrast, Drossman *et al.*[35] noted that functional bowel diseases are more common in households with low incomes. Based on these data, in the present study we hypothesized that socioeconomic factors play a significant role in the development of FGIDs in children. In contrast to our hypothesis, we did not find a significant association between FGIDs and social class. Similar to our results, other studies in children with IBS[15] and recurrent abdominal pain [2,36] have failed to demonstrate such an association. Therefore, it is possible that social factors may play an inconsequential role in the causation of AP-FGIDs in children. Psychological factors such as emotional stress and biological factors such as heightened visceral sensitivity[37] and abnormal motility[38] probably play a more significant part in the pathogenesis of these disorders.

In our study, most intestinal-related symptoms (bloating, loss of appetite, nausea, vomiting, flatus and burping) were more common in FD, IBS, FAP and AM compared with controls. Previous studies have shown that bloating is a significant problem in children[24] and adults[39] with IBS. Furthermore, bloating correlated with patient-perceived severity of IBS.[40] However, association of these features with other AP-FGIDs such as FD, AM and FAP has not been described in children in the past. Delayed gastric emptying and abnormal antral motility have been reported in children with all four types of AP-FGIDs.[41] Gastrointestinal motility dysfunctions may have contributed to abnormal gas dynamics and, therefore, to increased flatulence and burping noted in our patients. Further studies involving children with AP-FGIDs would help to explore this possibility. In the present study, loss of appetite and nausea were less

prevalent in children with FD than in other 3 types of FGIDs. Comparable to our results, a previous study using Rome II criteria has demonstrated early satiety in <10% of children with functional dyspepsia;[42] however, in the same study, nausea is seen in approximately 70% of children with FD, significantly higher than in our sample. The previous study was conducted in a tertiary-care gastroenterology unit, whereas our study was a school survey. Differences in patient selection and variation in genetic and environmental factors must have influenced the different results observed in two studies between two communities may have caused this difference.

Pain characteristics of FD, IBS, FAP and AM in our sample behaved as per definition. All of the children with FD had pain in the upper abdomen, 7% had daily symptoms, and only 22% had severe pain. In contrast to this, a hospital-based study by Hyams *et al.*[23] reported daily symptoms in the majority (69%). Furthermore, in our sample, only 4.7% of children with IBS had daily symptoms and most of them had pain duration of <1 hour. Compared with these findings, a hospital-based study in United States in children ages 5 to 17 years noted that 60% of them have daily symptoms, with 34% having pain duration of > 1 hour.[43] It is possible that children in our community- based sample have less severe pain and lower pain duration compared with both of these hospital-based studies. Severity of the pain is one of the significant determinants of health care seeking. Therefore, children with a higher frequency of pain would seek health care more frequently and are more likely to be included in hospital-based studies. The majority of children with AM in our study had pain in the lower abdomen or around the umbilicus. Abu-Arafeh and Russell[21] noted that 78% of children with AM in their sample had periumbilical pain.

In our study, extraintestinal symptoms such as headache, difficulty in sleep, limb pains, limb pain, photophobia and feeling lightheaded were noted to occur more frequently in children with all 4 types of AP-FGIDs. Similar to our findings, Dong *et al.*[15] have reported headaches and difficulty in sleeping more commonly in children with IBS. Another community-based study has found that adults with dyspepsia have significantly higher somatic symptom scores than controls.[9] Extraintestinal somatic symptoms are an integrated part of FGIDs and contribute significantly to the severity of disease and quality of life.[40] Therefore, it is important to seek these symptoms in the clinical evaluation of children because they may contribute to significant distress and poor quality of life.

Psychological stress plays a key role in initiating and precipitating FGIDs in susceptible individuals. Human and animal studies have shown that both psychological and physical

stresses can alter gastric motility and visceral sensitivity.[44] In our study, school-related stressful life events such as separation from best friend and failure at an examination, family related events such as loss of parent's job and other stressors such as hospitalization of the child himself or herself for another illness were significantly associated with AP-FGIDs. According to previous studies, RAP and defecations disorders such as constipation and fecal incontinence are more common among those exposed to stressful life events.[18,19,30] Failure at an examination is a significant stress in the competitive school environment in Sri Lanka. Loss of job by a parent would undoubtedly put children under stress because of financial restrains. Alteration of the function of the brain-gut axis under these circumstances may have predisposed children to develop AP-FGIDs. Furthermore, positive family history of functional gastrointestinal disorders and psychiatric disorders are recognized risk factors for developing FGIDs.[45,46] Information regarding such disorders in first-degree relatives would have been useful to determine the familial tendency. Unfortunately, during validation of the questionnaire and a previous study,[13] we understood that the majority of children are unaware of diseases and symptoms that are present in their family members, especially parents. Therefore, we did not assess family history of FGIDs and psychiatric disorders in the present study.

The present study has several strengths. We have included more than 2000 children from 4 randomly selected provinces (out of 9) of the country to obtain a representative sample. Furthermore, we used standard Rome III criteria to diagnose FGIDs in children. In this questionnaire-based school survey, however, we did not perform a physical examination to exclude organic causes for abdominal pain. In a previous study we have identified organic diseases in 10.9% of children with RAP. The organic diseases observed in the previous study include urinary tract infection, gastresophageal reflux, urinary calculi, antral gastritis and intestinal amoebiasis.[5] Parasitic infestations such as giardiasis and amoebiasis have been considered to be possible mimickers of FGIDs; however, in that study, prevalence of these diseases was 1.8%.[5] Similarly, several previous studies conducted in Sri Lanka have demonstrated a low prevalence of parasitic infections.[47,48] Therefore, it is unlikely that parasitic infestations have directly contributed to abdominal symptoms in these children.

In conclusion, AP-FGIDs are common among Sri Lankan children ages 10 to 16 years. IBS is the most common abdominal pain-predominant FGID diagnosed, followed by FAP and FD. AP-FGIDs are significantly higher in girls compared with boys. There is a negative correlation between the age and prevalence of AP-FGIDs. Intestinal-related and extraintestinal symptoms are more frequent in affected children, compared with controls. Exposure to stressful life events is significantly associated with AP-FGIDs.

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Chapter 4

Subtypes and symptomatology of irritable bowel syndrome in children and adolescents: a school-based survey using Rome III criteria

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Rajindrajith S, Devanarayana NM.

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ABSTRACT

Background/Aims: This study was conducted with objectives of assessing subtypes of irritable bowel syndrome (IBS) in children aged 10-16 years, their symptomatology and gender differences.

Methods: For this survey, 107 children who fulfil Rome III criteria for IBS and 1,610 healthy controls were recruited from 8 randomly selected schools, in 4 provinces in Sri Lanka. Data was collected using a previously validated, self-administered questionnaire.

Results: Constipation predominant, diarrhea predominant and mixed type IBS were almost equally distributed (27-28%), while untypabed IBS had a lower prevalence (17.8%). IBS was more common in girls (59.8% vs. 40.2% in boys, P=0.001). Bloating, flatulence, burping, headache and limb pain were significantly higher in affected children (P<0.05).

Conclusions: This study highlights the distribution of IBS subtypes among Sri Lankan children and adolescents and its female preponderance. This study also shows a higher prevalence of other intestinal-related and extraintestinal somatic symptoms among affected children.

INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder (FGIDs), characterized by abdominal pain and altered bowel habits. Available epidemiological studies have reported IBS in 7%-14% of school children. [1-3] Office-based studies using Rome criteria have found IBS in 21%- 45% of children with recurrent abdominal pain.[4-7] These studies have highlighted the high burden of the disease, both in the community and referral centers. Furthermore, IBS has a significant impact on quality of life of affected children.[8]

Previous adult studies have demonstrated a higher prevalence of IBS in females.[9] Furthermore, females seek health care for IBS more often than males.[10] Gender difference in symptomatology and associated features has been overlooked in pediatric studies.

Altered bowel habits (altered bowel frequency and consistency) are among the cardinal features of IBS. Rome III criteria for adults has classified IBS in to constipation predominant IBS (IBS-C), diarrhea predominant IBS (IBS-D), mixed IBS (IBS-M), and unsubtyped IBS (IBS-U), depending on the stool consistency.[11] However, such a classification has not been specified for IBS in children.[12] Despite this, a recent study in children has sub-typed IBS to IBS-C, IBS-D, IBS-M, and IBS-U using adult criteria.[3] According to previous studies, the commonest IBS subtype seen in both children and adults is IBS-M.[3,13]

Classification of IBS into relevant subgroup is important since clinical features and managements vary between different subtypes. Many recently developed drugs in adults were developed based on IBS subtype.[14-17] For example; alosetron was developed to treat IBS-D,[14] while linaclotide[15,16] and lubiprostone[17] were used to treat IBS-C. Therefore, it is fundamental to identify subtypes of IBS in children since most future treatment strategies will target on specific IBS subtype.

The current research was conducted with the objectives of characterizing subtypes of IBS in children and identifying gender differences in the symptomatology. To our knowledge, this is the first pediatric study to analyze bowel habits and symptom characteristics in different IBS subtypes.

MATERIALS AND METHODS

This is an island-wide survey, conducted in 8 randomly selected schools, in 4 randomly selected provinces (out of 9 provinces) in Sri Lanka. In each school, 2 classes each were selected from

academic years (grades) 6-11 (12 classes from each school). All students in selected classes, present during the day of the survey, were included.

Information regarding abdominal pain characteristics, bowel habits and associated symptoms were collected using a self-administered questionnaire. The questionnaire was developed based on Rome III diagnostic questionnaire for pediatric functional gastrointestinal disorders[18] and has previously been pretested for Sri Lankan children and used in an epidemiological survey.[3] The questionnaire was in native language and easy to understand. School administration and parents were informed before the study and consents were obtained. The questionnaire was distributed in an examination setting to ensure confidentiality and privacy. Children were given unlimited time to fill the questionnaire and verifications were provided by research assistants.

IBS was diagnosed using Rome III criteria for pediatric FGID[12] and subtyping was done using criteria described by Longstreth *et al.*[11] (**Table 4.1**).

Table 4.1 – Diagnostic criteria for irritable bowel syndrome (IBS) and subtypes

Rome III criteria for pediatric IBS[12]

Abdominal discomfort or pain that occurs at least once per week for more than 2 months associated with at least 2 of the following three features for at least 25% of the time;

1) Abdominal pain improved with defecation
2) Onset associated with change in stool frequency
3) Onset associated with a change in consistency of stools

Subtypes of IBS[11]

1) Constipation predominant IBS - hard or lumpy stools $\geq$ 25% and loose (mushy) or watery stools < 25% of bowel movements
2) Diarrhea predominant IBS - loose (mushy) stools or watery stools $\geq$ 25% and hard or lumpy stools < 25% of bowel movements
3) Mixed IBS – hard or lumpy $\geq$ 25% and loose (mushy) or watery stools $\geq$ 25% of bowel movements
4) Unsubtyped IBS – insufficient abnormality of stool consistency to meet criteria for IBS-C, IBS-D or IBS-M.

IBS, irritable bowel syndrome; IBS-C, constipation predominant IBS; IBS-D, diarrhea predominant IBS; IBS-M, mixed IBS.

Exclusion criteria were

1) functional gastrointestinal disorders other than IBS
2) chronic disorders needing long term medication other than IBS
3) disabled children
4) children with learning difficulties
5) children who had received drugs that modify bowel habits during previous month

Ethical Review Committee of the Sri Lanka College of Pediatricians approved this study protocol.

Statistical methods

Data were analyzed using EpiInfo (EpiInfo 6, version 6.04 (1996) Centres of Disease Control and Prevention, Atlanta, Georgia, USA and World Health Organization, Geneva, Switzerland). A $P<$ 0.05 was taken as significant. Multiple logistic regression analysis was performed on variables which showed significant associations with IBS during univariate analysis.

RESULTS

During the survey, 2,180 questionnaires were distributed and all of them were returned. A total of 1,717 children (boys 950 [55.3%] mean age 13.4 $\pm$ 1.7 [SD] years) were included in the final analysis. Seventeen incompletely filled questionnaires and 446 children with FGIDs other than IBS were excluded from the analysis.

Hundred and seven children had IBS (mean age 12.9 $\pm$ 1.8 [SD] years). They were compared with 1,610 children without FGIDs (mean age 13.5 $\pm$ 1.7 [SD] years).

Irritable bowel syndrome and sex distribution

Table 4.2 shows the distribution of IBS subtypes according to sex. When mean predicted probabilities of IBS were plotted against the age (**Figure 4.1**), IBS was significantly higher among girls in all age groups ($P<$ 0.01). There was a significant negative correlation between probability of developing IBS and age, in both genders (**Figure 4.1**).

Following multiple logistic regression analysis, female sex (adjusted OR, 1.9; 95% CI, 1.3-2.8; P=0.002) and age (OR 0.83; 95% CI, 0.74-0.93; P=0.002) remained to be significantly associated with IBS.

Abdominal pain characteristics of irritable bowel syndrome

Table 4.3 shows abdominal pain characteristics in children with IBS. Severe pain was less common in children with IBS-D compared to other 3 subtypes.

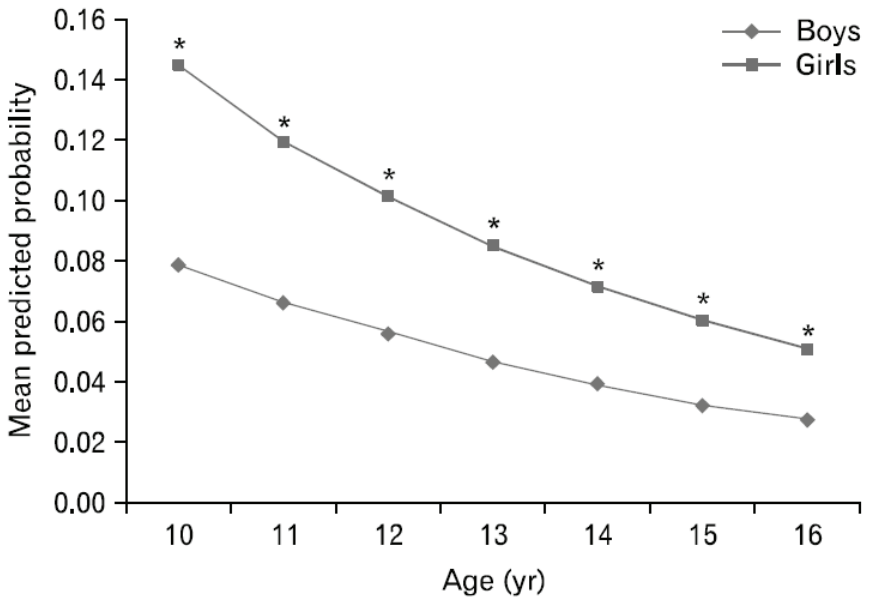

Figure 4.1 – Mean predicted probabilities of IBS according to age and sex

**Girls vs. boys, p*<0.01 (unpaired t test)

Table 4.2 – Subtypes of irritable bowel syndrome according to sex

IBS subtype	Male	Female	Total
IBS-C (*n* [%])	8 (27.6)	21 (72.4)*	29 (27.1)
IBS-D (*n* [%])	13 (43.3)	17 (56.7)	30 (28.0)
IBS-M (*n* [%])	13 (44.8)	16 (55.2)	29 (27.1)
IBS-U (*n* [%])	9 (47.4)	10 (52.6)	19 (17.8)
IBS –Total (*n* [%])	43 (40.2)	64 (59.8)*	107 (100)

*Female vs. male, *p*<0.01 (unpaired *t* test)

IBS, irritable bowel syndrome; IBS-C, constipation predominant IBS; IBS-D, diarrhea predominant IBS; IBS-M, mixed IBS; IBS-U, unsubtyped IBS.

Table 4.3 – Abdominal pain characteristics in children with irritable bowel syndrome

	IBS-C	IBS-D	IBS-M	IBS-U	IBS-Total
Frequency of pain (*n* [%])					
Once per week	12 (41.4)	15 (50)	10 (34.5)	7 (36.8)	44 (41.1)
Several times per week	14 (48.3)	15 (50)	17 (58.6)	12 (63.2)	58 (54.2)
Everyday	3 (10.3)	0	2 (6.9)	0	5 (4.7)
Duration of a pain episodes (*n* [%])					
Less than 1 hour	13 (44.8)	19 (63.3)	15 (51.7)	12 (63.2)	59 (55.1)
1-2 hours	8 (27.6)	9 (30)	9 (31)	5 (26.3)	31 (29)
3- 4 hours	4 (13.8)	0	2 (6.9)	2 (10.5)	8 (7.5)
Most of the day	4 (13.8)	2 (6.7)	3 (10.3)	0	9 (8.4)
Severity of pain (*n* [%])					
Mild	9 (31.0)	4 (13.3)	2 (6.9)	5 (26.3)	20 (18.7)
Moderate	13 (44.8)	25 (83.3)	18 (62.1)	11 (58)	67 (62.6)
Severe	7 (24.1)	1 (3.3)*	9 (31)	3 (15.7)	20 (18.7)
Location of pain (*n* [%])					
Upper abdomen	8 (27.6)	6 (20)	8 (27.6)	4 (21.1)	26 (24.3)
Lower abdomen	11 (37.9)	16 (53.3)	11 (37.9)	12 (63.2)	50 (46.7)
Both	10 (34.5)	8 (26.7)	10 (34.5)	3 (15.7)	31 (29)

*P=0.023, compared to other three types (unpaired t test)

IBS, irritable bowel syndrome; IBS-C, constipation predominant IBS; IBS-D, diarrhea predominant IBS; IBS-M, mixed IBS; IBS-U, unsubtyped IBS.

Table 4.4 – Bowel habits according to subtypes of irritable bowel syndrome

	IBS-C	IBS-D	IBS-M	IBS-U	IBS-total
Frequency of defecation (*n* [%])					
< 3 per week	10 (34.5)	0	10 (34.5)	2 (10.5)	22 (20.6)
3-6 per week	5 (17.2)	1 (3.3)	2 (6.9)	3 (15.8)	11 (10.3)
Once daily	10 (34.5)	12 (40.0)	13 (44.8)	11 (57.9)	46 (42.9)
2-3 per day	4 (13.8)	9 (30.0)	2 (6.9)	3 (15.8)	18 (16.8)
> 3 per day	0	8 (26.7)	2 (6.9)	0	10 (9.3)
Stool consistency (*n* [%])					
Hard	6 (20.7)	0	4 (13.8)	0	10 (9.3)
Normal	21 (72.4)	22 (73.3)	15 (51.7)	17 (89.5)	75 (70.1)
Very soft/mushy	0	6 (20.0)	6 (20.7)	0	12 (11.2)
Changing	2 (6.9)	2 (6.7)	4 (13.8)	2 (10.5)	10 (9.3)
Large diameter stools (*n* [%])	6 (20.7)	4 (13.3)	9 (31.0)	2 (10.5)	21 (19.6)
Withholding posture (*n* [%])	9 (31.0)	8 (26.7)	9 (31.0)	3 (15.8)	29 (27.1)
Pain during defecation (*n* [%])	11 (37.9)	10 (33.3)	10 (34.5)	3 (15.8)	34 (31.8)

Straining (*n* [%])	23 (79.3)	22 (73.3)	20 (69.0)	13 (68.4)	78 (72.9)
Urgency (*n* [%])	24 (82.8)	20 (66.7)	18 (62.1)	13 (68.4)	75 (70.1)
Feeling of incomplete evacuation (*n* [%])	20 (69.0)	22 (73.3)	21 (72.4)	11 (57.9)	74 (69.2)
Fecal incontinence (*n* [%])	4 (13.8)	1 (3.3)	2 (6.9)	0	7 (6.5)
Mucoid stools (*n* [%])	10 (34.5)	17 (56.7)	13 (44.8)	7 (36.8)	47 (43.9)

IBS, irritable bowel syndrome; IBS-C, constipation predominant IBS; IBS-D, diarrhea predominant IBS; IBS-M, mixed IBS; IBS-U, unsubtyped IBS.

Table 4.5 – Intestinal-related and extraintestinal symptoms associated with irritable bowel syndrome

	IBS-C	IBS-D	IBS-M	IBS-U	IBS-total	Controls
Intestinal symptoms (*n* [%])						
Bloating	20 (68.9)***	15 (50.0)***	21 (72.4)***	6 (31.6)***	62 (57.9)***	86 (5.3)
Loss of appetite	7 (24.1)***	7 (23.3)***	11 (37.9)***	6 (31.6)***	31 (29.0)***	75 (4.7)
Nausea	8 (27.6)***	10 (33.3)***	8 (27.6)***	4 (21.1)***	30 (28.0)***	49 (3.0)
Vomiting	6 (20.7)***	3 (10.0)***	7 (24.1)***	1 (5.3)	17 (15.9)***	13 (0.8)
Excessive flatus	19 (65.5)***	21 (70)***	16 (55.2)***	11 (57.9)***	67 (62.6)***	254 (15.8)
Burping	10 (34.5)*	13 (43.3)**	10 (34.5)*	7 (36.8)	40 (37.3)***	284 (17.6)
Extra-intestinal symptoms (*n* [%])						
Headache	17 (58.2)***	13 (43.3)***	11 (37.9)***	6 (31.6)***	47 (43.9)***	104 (6.4)
Sleeping difficulty	15 (51.7)***	9 (30.0)***	16 (55.2)***	4 (21.1)***	44 (41.1)***	57 (3.5)
Limb pain	11 (37.9)***	16 (53.3)***	17 (58.6)***	9 (47.4)***	53 (49.5)***	132 (8.2)
Photophobia	8 (27.6)***	7 (23.3) ***	9 (31.0)***	5 (26.3)***	29 (27.1)***	30 (1.9)

*P <0.05, **P <0.001, ***P <0.0001, compared to controls (unpaired t test)

IBS, irritable bowel syndrome; IBS-C, constipation predominant IBS; IBS-D, diarrhea predominant IBS; IBS-M, mixed IBS; IBS-U, unsubtyped IBS.

Bowel habits in children with irritable bowel syndrome

Regular bowel habits of children with IBS are shown in **Table 4.4**. The bowel habits reported in this table are that present during the last two months prior to collecting the data.

Intestinal-related and extra-intestinal symptoms associated with irritable bowel syndrome

Intestinal-related symptoms and extra-intestinal symptoms were present in significantly higher proportions in children with all types of IBS (**Table 4.5**).

Intestinal-related symptoms (bloating, loss of appetite, nausea, vomiting, flatulence and burping), and extraintestinal symptoms (headache, sleeping difficulties, limb pain and photophobia) were compared between boys and girls with IBS. Only symptom that showed a significant gender difference was burping (boys 24 [56%] vs. girls 16 [25%], P=0.002).

Impact on Education

Out of 107 children with IBS, 50 (46.7%) had missed school at least one day during previous 2 months compared to that of 86 (5.3%) among controls (P<0.0001, unpaired t test).

DISCUSSION

To the best of our knowledge, this is the first pediatric study that has described bowel habits and symptoms according to different subtypes of IBS. In this study, IBS-C, IBS-D and IBS-M were equally distributed, while IBS-U had a lower prevalence. IBS was commoner among females and it negatively correlated with age. Other intestinal-related and extraintestinal symptoms were significantly higher in children with IBS.

IBS is a common abdominal pain predominant FGID among children[1-3] and adults.[19,20] A previous pediatric study using Rome III criteria and has reported IBS in 7% of Sri Lankan children.[3] Distribution of IBS subtypes in the present study was similar to that reported previously.[3] Identification of IBS subtypes is becoming important in clinical practice and research, since pharmacological management of IBS becoming more specific and most new therapies are developed targeting specific IBS subtypes. Therefore, it is important to use this classification in the future, when evaluating affected children.

In this study, IBS was more common among girls. This is similar to previous adult studies which have also shown female preponderance.[20] Differences in activities of male and female gonadal hormone have been suggested as a possible cause for this difference.[21] However previous

pediatric studies failed to show a gender difference in IBS.[1-3] Small sample size[3] and younger age of children,[2] may have contributed to this. We also noted that IBS-C was more prevalent among girls which is similar to an adult study.[9] Contrary to these findings, another adult study using Rome III criteria have found no gender difference in prevalence of subtypes.[22].

We found a linear reduction in probability of developing IBS as children became older, in both girls and boys. Such correlation has been previously demonstrated in children with defecation disorders such as constipation.[23]

Analysis of symptoms has shown that the majority of affected children had abdominal pain several times a week which lasted for less than one hour. Severe pain was most prevalent among children with IBS-M (31%) and it was significantly lower in IBS-D (3.3%). Previous adult studies have also shown the highest pain severity in IBS-M when using Rome III criteria[22] and alternating IBS, which is similar to IBS-M type, when using Rome II criteria.[24].

In our study, regular bowel habits of affected children were compatible with IBS subtype. More than one-third of children with IBS-C had bowel motions less than 3 per week and more than 50% with IBS-D had opened bowel several times per day. Furthermore, no one in the IBS-C group had very soft or mushy stools and none of the children with IBS-D had hard stools. These observations show their general trend of bowel habits towards constipation or diarrhea are in keeping with the clinical diagnosis. Furthermore, we also found that the supportive symptoms of IBS, such as straining, urgency, feeling of incomplete evacuation and mucoid stools were common in children with all subtypes of IBS. Two previous studies have shown that straining and urgency are common clinical features in children with IBS.[1,2] However, prevalence of these 2 symptoms, in previous studies, was lower compared to our findings. Contrast to this, adult studies have shown that over 80% of patients with all subtypes have straining, urgency and sense of incomplete evacuation.[24] These are troublesome symptoms causing significant distress and should not be overlooked in the clinical evaluation.

Intestinal-related symptoms such as bloating, loss of appetite, nausea, vomiting, flatulence and burping were significantly higher in all IBS subtypes compared to controls. Our results are compatible with previous studies which have shown that bloating is an important problem among both children and adults with IBS.[1,25] Another study, conducted among adults attending a specialized gastroenterology clinic, has shown that bloating is a predictor of severity of IBS.[26] Similar to our study, one previous study in patients with IBS-C has shown more bloating in affected individuals.[27] In the current study, other features of abnormal gastrointestinal gas

handling, such as burping and flatulence, were also common among children with IBS. These clinical features have not been studies in details in children with IBS previously. Serra *et al.*[28] have demonstrated impaired transit and tolerance of gas in adults with IBS. It is possible that children with IBS have abnormal expulsion of intestinal gas due to altered gastrointestinal motility. Analysis of gender differences showed burping more commonly in boys. Similarly, a previous study in Mexico has reported higher prevalence of burping in males.[29] Contrary to our finding, previous adult studies have reported bloating more commonly in females with IBS.[29,30]

Extraintestinal symptoms, such as somatic pain and discomfort, are important predictors of disease severity in IBS.[26] According to adult data, two-thirds of patients with IBS suffer from extraintestinal symptoms.[31] In the current study, headache, sleeping difficulty, limb pain, and photophobia were significantly commoner among children with all four subtypes of IBS. Similar to our results, Dong *et al.* also found headache and sleeping difficulty in a higher percentage of affected children.[2] An adult study using Somatic Symptom Checklist has also shown that symptoms such as headache, insomnia and eye pain are common among a community sample of IBS. According to that study, there is a significant association between somatization and IBS.[32] High prevalence of somatic symptoms in our children with IBS is suggestive of a similar association in pediatric population. Somatization is believed to be more common among females,[33,34] however we failed to demonstrate any significant symptom predilection to a particular gender. Somatization of our study sample of 10-16-year-olds probably different from mature adults and this may have resulted in this lack of difference.

This study also demonstrated the impact of IBS on schooling of affected children. Significantly higher percentage of children with IBS has missed school during previous two months compared to that of healthy controls Therefore, it is possible that abdominal pain, altered bowel habits and extraintestinal symptoms may have disturbed daily functions of affected children in our sample, preventing them from attending school.

In conclusion, this study shows the distribution of IBS subtypes in 10-16 year olds, their symptom characteristics, and bowel habits. IBS-C, IBS-D and IBS-M have almost equal distribution while IBS-U has a relatively lower prevalence. Girls are more commonly affected than boys. Intestinal-related symptoms and extraintestinal symptoms are significantly more common in those with IBS, indicating higher occurrence of somatization among affected children.

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Chapter 5

Irritable bowel syndrome in children and adolescents in Asia: a systematic review and meta-analysis of the epidemiology

This chapter of the thesis was published as

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ABSTRACT

Objectives: Several cross-sectional surveys have been conducted to study the prevalence of irritable bowel syndrome (IBS) in children. The aim of this study was to conduct a systematic review and a meta-analysis of published literature to provide better understanding of the prevalence of IBS among Asian children.

Method: A computer assisted search of MEDLINE, EMBASE, psycINFO and regional data bases of Asia was carried out. Selected articles were reviewed in depth and data were extracted. Pooled prevalence, gender differences as well as 95% confidence intervals were calculated. Heterogeneity of the studies was assessed using *I2* test.

Results: Sixteen cross sectional studies which reported prevalence of IBS (in children and adolescents) and qualified to be included, were taken into the final analysis containing 38,076 subjects. Selected studies are from China, Korea, Japan, Iran, Sri Lanka, and Saudi Arabia. Studies showed a marked heterogeneity with *I2* of 98.59 ($p<0.0001$). Prevalence of IBS ranges from 2.8% to 25.7%, with a pooled prevalence of 12.41% (95% CI 9.87-14.95%). Prevalence risk ratio of female: male is 1.39. Prevalence of subtypes is diverse and varies between studies.

Conclusions: The published data indicate that IBS is a significant problem among Asian children and adolescents. Female gender predisposes children and adolescents to develop IBS.

INTRODUCTION

Irritable bowel syndrome (IBS) in children is characterized by chronic abdominal pain and changing bowel habits including frequency of defecation and stool consistency in the absence of organic disease.[1] It is a common problem in pediatric practice and according to office-based practice, between 21-45% children with chronic abdominal pain have IBS.[2-4]

This malady could lead to reduction in quality of life and poor quality of school work.[5,6] In addition, it is well known fact that a sizeable proportion of children suffering from pain predominant functional gastrointestinal diseases (FGIDs), including IBS, grow up to be adults with similar problem.[7] With the very limited number of therapeutic options available, pediatricians and pediatric gastroenterologists face a daunting task to manage these children.

Initial epidemiological studies from Western countries have shown that 15% of school children in the USA, 14-24% in Russia, and 2% in the UK are suffering from IBS, perhaps promulgating the notion that IBS is a disease of the Western World.[8-10] However, in the recent past, a new wave of epidemiological research has emerged in Asia and increased the depth and width of knowledge on IBS in this region. Despite these efforts, there remain difficulties to differentiate the true regional and global nature of IBS, its epidemiological facts and predisposing factors, details which are crucial for practicing clinicians.

Asia is the home for over 50% of the world's childhood population. In addition, most of Asian countries are going through a rapid change in socio-economic status and their cultural foundations are constantly being challenged by globalization. In that light, we believe that studying epidemiological patterns of IBS in Asian children in a systematic way will provide a greater perspective for understanding the burden of IBS, its epidemiological distribution, and patterns of subtypes. Therefore the aim of this study was to conduct a systematic review and meta-analysis of published literature to estimate the prevalence of IBS among Asian children.

METHOD

Literature search strategy

A detailed literature search was carried out (from 1948 to October 2014) using MEDLINE, PsycINFO, EMBASE, Global Index Medicus, Index Medicus for South East Asia, East Mediterranean Index Medicus and West Pacific Index Medicus to identify epidemiological studies that reported on the prevalence of IBS in children/adolescents aged 18 years or less in Asia. Search strategy used the following terms; irritable bowel syndrome [MeSH Terms] *OR* irritable bowel syndrome[Text Word] *OR* Irritable Bowel disease*[Text Word] *OR* irritable

colon[Text Word] *OR* irritable colon syndrome [Text Word] *OR* mucous colitis[Text Word]) *OR* spastic colon*[Text Word] *OR* spastic colitis[Text Word] *OR* Functional Gastrointestinal Disorder[Text Word] *OR* Functional Gastrointestinal Disorders[Text Word] combined with epidemiology[Text Word]) *OR* epidemiologic study[Text Word] *OR* epidemiologic studies[Text Word]) *OR* frequenc*[Text Word] *OR* occur*[Text Word].

Literature review

Abstracts of all the articles meeting the above search criteria were reviewed by 2 independent investigators (SR, NMD) and full texts of studies were retrieved when they were eligible for inclusion according to the following criteria. 1) Cross sectional surveys from Asia. 2) School or community samples. 3) Included children from 0-18 years. 4) Defined diagnostic criteria. 5) Published in English language as full papers. All possibly relevant full text articles were again independently reviewed by the same authors and consensus was reached on each of the articles. Diagnosis of IBS was made by Rome II (adult/ children), or Rome III (adult/children) criteria.[1,11-13] Quality assessment of all included studies was conducted using the method described by Al-Jader LN, *et al.*[14]

Data extraction

Data extraction was also done independently by SR and NMD. We used Microsoft Excel spreadsheet (Mircrosoft, Redmond, WA) to enter data in a systematic manner. The data that were included were year of the publication, country of origin, method of data collection, nature of the sample, sample size, definition used to diagnose IBS, sub-typing (when available), age range and sex of the subjects, and prevalence of IBS.

Statistical analysis and mapping

The prevalence of IBS and the sample size of each of the selected studies were used to calculate the standard error of the prevalence. The individual study results were pooled using a random effect model as there was a high level of heterogeneity between the studies. Heterogeneity was measured using the *I2* statistic. The prevalence of IBS among males and females was compared by calculating the prevalence risk ratio. Meta-analysis was performed in Stata version 12 (College Station, Texas, USA) using 'metaan' package. Mapping was done using ArcGIS 10.2 (ESEI, Readlands, CA).

RESULTS

Literature search

The literature search identified 1212 citations. There were 18 studies that fulfilled the eligibility criteria. Two studies were excluded due to duplication of data. Therefore 16 studies were included in the final analysis (**Figure 5.1**).[6,15-29] The total number of subjects in these studies was 38076. Details of these studies are provided in **Table 5.1**.

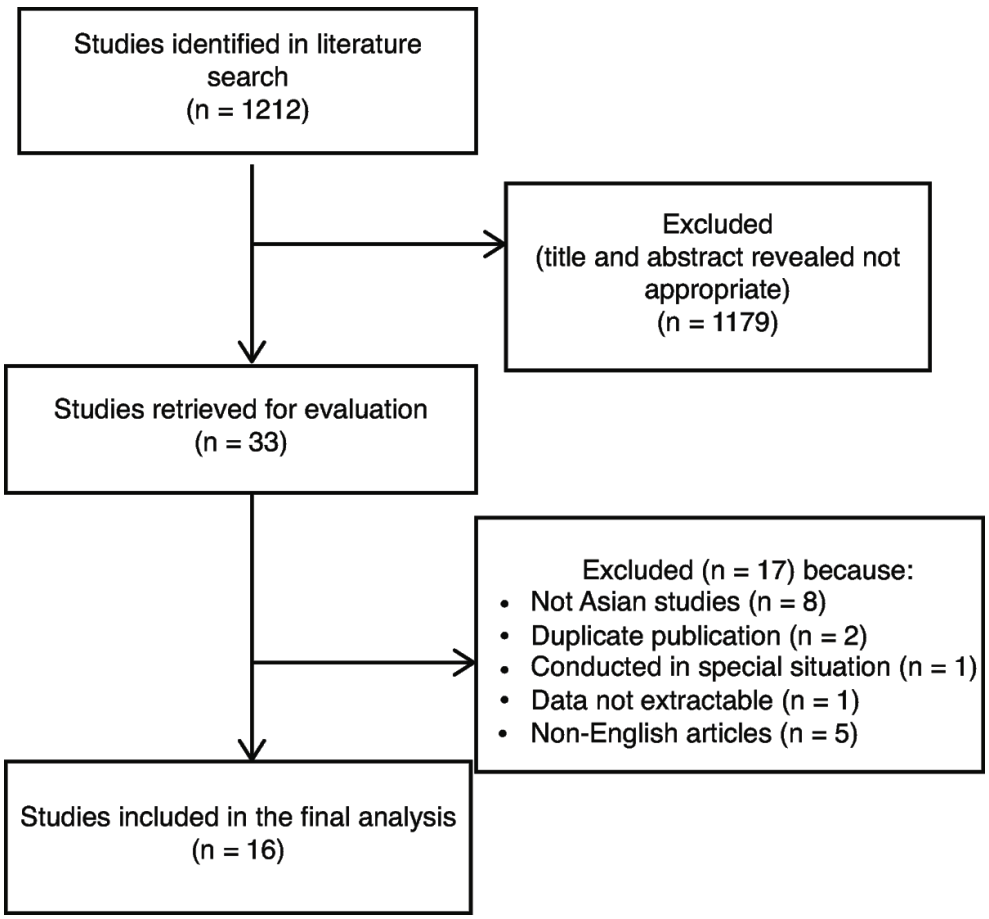

Figure 5.1: Flow chart summarizing the study methodology

All studies are cross sectional surveys. They were conducted in Japan (*n*=2),[6,20] Korea (*n*=3),[19,21,28] China (*n*=6),[16,17,22,23,26,29] Iran (*n*=1),[27] Saudi Arabia (n=1)[24] and Sri Lanka (*n*=3).[1,18,25] One paper from Japan[20] reported data from two separate studies and we could clearly identify prevalence of IBS in children and adolescents in both studies. Therefore, in the analysis they were considered as two separate studies. The study conducted by Devanarayana *et al.*[25] had given prevalence of IBS according to both Rome II and Rome III criteria for children. We

selected the prevalence rate obtained using Rome III criteria for the statistical analysis. The two studies from Korea[19,28] included only females in their samples. Study from Saudi Arabia included only males.[24]

Prevalence of IBS in Asian children

The pooled prevalence of IBS in all 16 studies with a total of 38076 subjects was 12.4% (95% CI 9.9-15.0) with a statistically significant heterogeneity between studies (I^2 98.6%, P<0.0001). The lowest prevalence (2.8%) was reported from Sri Lanka and the highest (25.7%) from South Korea which included only females.[25,28] **Figure 5.2** shows the forest plot of data from selected studies. **Figure 5.3** illustrates the mapping data of prevalence of all Asian studies.

Prevalence of IBS according to age groups

Only five studies have studied the age related prevalence.[6,16,19,26,29] The age groups reported were diverse and therefore could not fit into an analytical model. However, one study has shown a reduction of mean predicted probability of developing IBS with increasing age.[18]

Prevalence of IBS according to sex

Eleven studies have provided prevalence of IBS according to sex.[6,16-18,20-22,25-27,29] Out of these studies, 5 had found a significantly higher prevalence of IBS in girls **(Table 5.1)**.[6,18,21,27,29] The pooled prevalence for females was 13.9% (95% CI 10.0%-17.7%) and for males 9.4% (95% CI 6.6%-12.3%). Prevalence risk ratio of female to male was, 1.39 indicating that females have a higher tendency to develop IBS **(Figure 5.4)**. When analyzed the 11 studies that have both male and female prevalence separately (excluding single sex studies) the prevalence risk ratio was 1.30.

Prevalence of sub-types of IBS

Table 5.2 shows the prevalence of the different IBS sub-types. Studies from China[22,26] have indicated untyped IBS (IBS-U) as the commonest sub-type, while studies from Sri Lanka and one study from Korea have shown approximately an even distribution of all four sub-types.[18,25,28] The study from Iran has found higher prevalence of constipation predominant IBS (IBS-C) in their population.[27]

Table 5.1 - Characteristics of the studies included in the analysis

Study and reference	Year	Location of Survey	Population	Age Range (years)	Sample Size	Method of Data collection	Case Ascertainment	Case definition	Total prevalence %	Age specific Prevalence %	Male Prevalence %	Female Prevalence %
1. Devanarayana *et al.*[15]	2014	Sri Lanka	School based	13-18	1850	Cross sectional survey	Subject questionnaire	Rome III (Child)	4.9	No	-	-
2.Zhu *et al.*[16]	2014	China	School based	8-13	7472	Cross sectional Survey	Subject questionnaire	Rome II	10.81	8 years: 13.4 9 years: 12.7 10 years:11.2 11years:10,2 12 years:10.2 13 years: 9.4	10.3	11.3
3.Xing *et al.*[17]	2014	China	School based	11-18	1714	Cross sectional Survey	Subject questionnaire	Rome III (Child)	5.6	No	5.0	6.2
4. Sagawa *et al.*[6]	2013	Japan	School based	10-17	3976	Cross sectional survey	Subject questionnaire	Rome III (Child)	5.9	10-11 years: 3.7 12-14 years: 6.3 15-17 years: 12.8	4.6	6.9*
5. Rajindrajith and Devanarayana [18]	2012	Sri Lanka	School based	10-16	2163	Cross sectional survey	Subject questionnaire	Rome III (Child)	4.9	No	1.9	3.0*

6. Song *et al.*[19]	2012	Korea	School based	12-17	820	Cross sectional survey	Subject questionnaire	Rome II (Adult)	12.8%	12-15 years: 8.5 15-17 years: 17.1	No	12.8%
7.. Endo *et al.*[20]	2011	Japan	School based Study 1 (2004)	15	1721	Cross sectional survey	Subject questionnaire	Rome II (Adult)	14.6	No	12.7	16.3
			School based Study 2 (2009)	14	591	Cross sectional survey	Subject questionnaire	Rome II (Adult)	19.0	No	7.1	11.6
8. Park and Lim[21]	2011	Korea	School based		1877	Cross sectional survey	Subject questionnaire	Rome III	19		7.7	11.2*
9. Zhou *et al.* [22]	2011	China	School based	12-18	3671	stratified, randomized study	Self-reported Questionnaire	Rome III (Adult)	19.89	No	19.7	20.1
10. Zhou *et al.* [23]	2011	China (sleep)	School based	12-18	1362	Random sample	Self-reported Questionnaire	Rome III (Adult)	14.83	No	No	No
11. Alhzami *et al.* [24]	2011	Saudi Arabia	School based	15-18	1175	Cross sectional survey	Self-reported Questionnaire	Rome II	9.2	No	9.2	No
12. Devanarayana *et al.* [25]	2010	Sri Lanka	Semiurban school sample	12-16	427	Cross sectional survey	Subject questionnaire	Rome III (Child)	7.0	No	6.5	7.5
								Rome II (Child)	2.8	No	No	No

13. Zhou *et al.* [26]	2010	South China (Shanghai)	School based	10-18	2013	Randomly selected sample	Subject questionnaire	Rome III (Adults)	20.72	11 years: 17.66 13 years: 19.86 16 years: 25.92	21.06	20.88
14.. Sohrabi *et al.* [27]	2010	Iran	Population based	14-19	1436	Cross sectional survey	Subject Questionnaire	Rome II (Adults)	4.1	No	2.6	5.7*
15.Son *et al.* [28]	2008	Korea	School based	15-17	405	Cross sectional descriptive design	Subject Questionnaire	Rome II (Adults)	25.7	No	No	25.7
16. Dong *et al.* [29]	2005	China (Shanghai and Heilongjiang provinces)	School based	6-18	5403	stratified, random cluster sample	Subject questionnaire	Rome II (Child)	13.3	<=12 years: 11.86 (8-9 years: 14.78) >= 13 years: 11.44 (15-16years: 17.35	11.6	20.9*

Table 5.2 - Subtypes of IBS in Asian children

Study	Criteria	IBS-C %	IBS-D %	IBS-M or IBS- A %	IBS- Untyped%
Rajindrajith & Devanarayana (2012)	Rome III – child	27.1	28	27.1	17
Zhou *et al.*(2011)	Rome III – adult	20.11	17.8	10.3	51.1
Park *et al.*(2011)	Rome III -adult	11.0	15.7	66.0	7.3
Zhou *et al.*(2010)	Rome III – adult	20.1	18.5	10.3	51.1
Sohrabi *et al.*(2010)	Rome II – adult	52.5	11.8	18.6	-
Son *et al.*(2008)	Rome II- adult	34.6	26.9	38.5	-

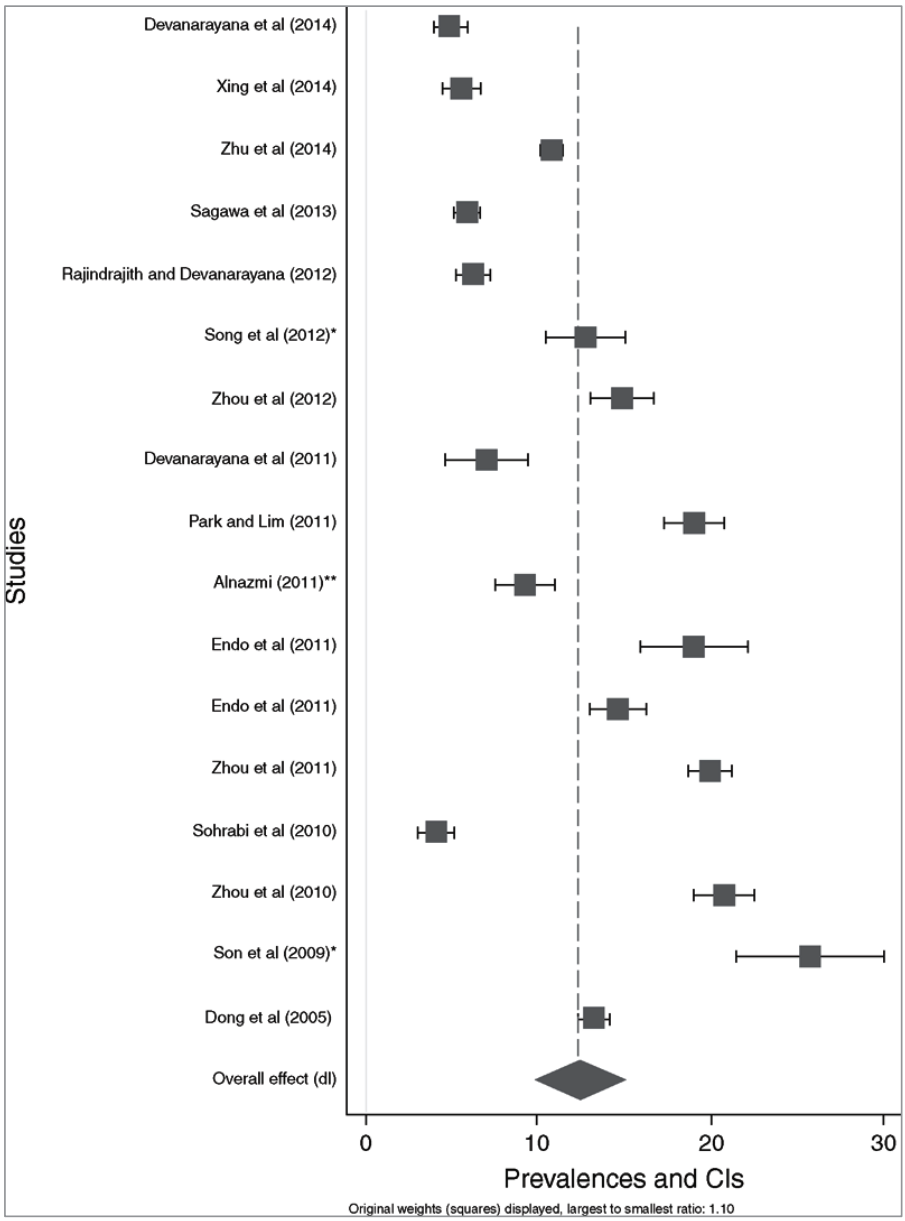

Figure 5.2 – Pooled prevalence of IBS in all of the studies. (*) Studies with only females, (**) Studies with only males. CI – confidence interval; IBS – irritable bowel syndrome

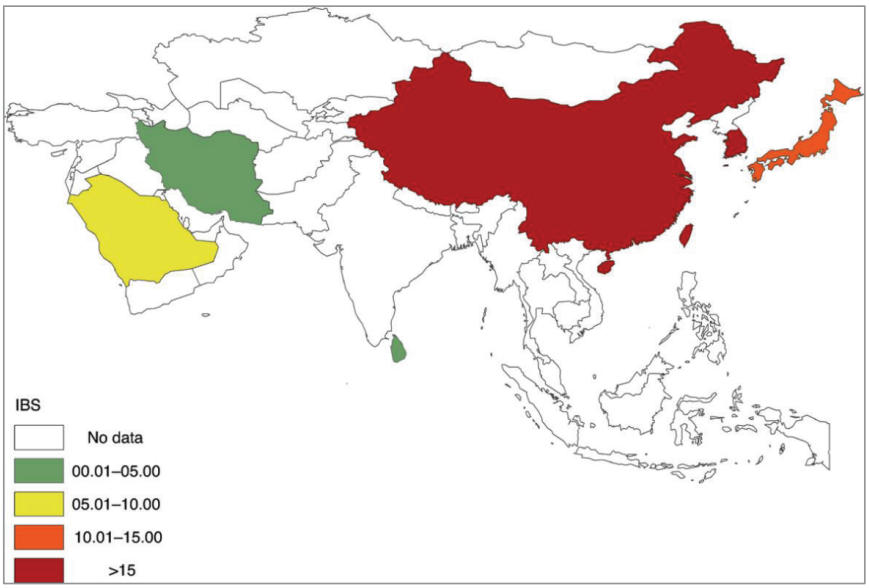

Figure 5.3 - Prevalence of IBS according to country

IBS = irritable bowel syndrome

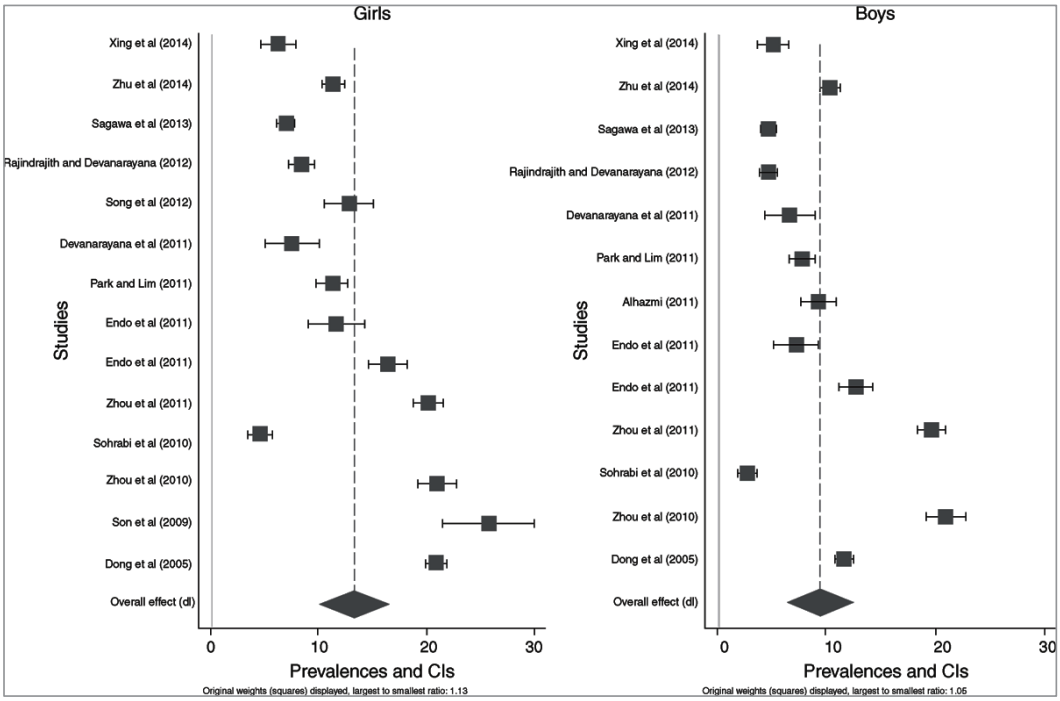

Figure 5.4 - Pooled prevalence of IBS according to gender

CI – confidence interval; IBS – irritable bowel syndrome

DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis of epidemiological studies of IBS in Asian children. The pooled prevalence in our study was 12.4 with no clear correlation with age and female sex as a risk factor of developing IBS.

IBS is a disease that affects children across the world. Epidemiological surveys from the Western countries such as UK and the USA have shown a prevalence of 2 to 14%.[8,10] Prevalence in Russian children was 14%-24%.[9] Recent studies from Colombia noted that 5.1% children suffer from IBS.[30] In this systematic review and meta-analysis the pooled prevalence was noted to be 12.4%. Our data fall within the range of Western and Russian data possibly indicating the true global prevalence. The highest prevalence was reported in Korean females and the lowest was reported from Sri Lanka (with Rome II criteria for children).[25,27]

Studies have shown a statistically significant heterogeneity. This considerable variation could be due to several reasons. First, variation of the sizes of the samples may have contributed to this variation in prevalence. Sample sizes of the studies included in this study range from 427 to 7472. In addition, obtaining precise data about prevalence was difficult because of the lack of uniform definitions and the absence of a precise biomarker. All studies in this systematic review have used standard Rome criteria (Rome II or III) for the diagnosis of IBS. However, Rome criteria itself are in an evolutionary process and criteria for the diagnosis have been changing from its first iteration to the latest Rome III classification. This is likely to affect the calculated prevalence significantly. Earlier studies have shown that the Rome II criteria are too restrictive in diagnosing FGID in children.[25] Furthermore, some studies have used adult criteria instead of pediatric criteria for diagnostic purpose.[19,20,22,23,26-28] Although the clinical features are similar, the time duration before diagnosis in adult criteria is three months whereas they are two months in the pediatric criteria. This would have underestimated the true prevalence in studies that used adult Rome criteria. It is well known that IBS status is influenced by food and food habits.[31] There are marked differences in food preparation and use of spices and other ingredients in different cultures. It is possible that these factors also influence the variation in prevalence.

Age groups included in the studies are diverse. They range from 6 to 19 years and the majority included children in their teens. Only five studies reported age specific prevalence.[6,16,19,26,29] According to them prevalence seems to be increasing with age. However the differences are not statistically significant. Contrary to this, one study from Sri Lanka has shown reduction of the mean predicted probability of prevalence with increasing age.[18] Similar meta-analysis of

epidemiology of IBS in adults have found no statistically significant difference between older and younger age groups (less than 45 against more than 45 years).[32] It is possible that there is no relationship between age and IBS contrast to other FGIDs such as functional constipation.

Asian girls have a higher tendency to develop IBS with a higher risk ratio. One study has shown a higher mean predicted probability of developing IBS in girls of 10-16 years.[18] Similar to this, in a systematic review and meta-analysis, Lovell and Ford reported that adult females have higher Odds Ratios of developing IBS.[32] This systematic review also reported a significant heterogeneity between studies, similar to our review.

Sub-typing of IBS is an important concept, especially because some of the current therapeutic options are based on the predominant bowel pattern of IBS. Sub-typing is described only for adults in both Rome II and Rome III criteria.[12,13] Although both criteria recognized IBS-C and diarrhea predominant IBS (IBS-D), Rome III criteria only recognize mixed IBS (IBS-M).[12] However, Rome II criteria recognize alternating IBS (IBS-A) which is more or less similar to IBS-M.[13] In addition, Rome III criteria appreciate untyped IBS (IBS-U).[13] Several pediatric studies have used the same classification systems to sub-type IBS in children.[18,22,25-28] Studies from Sri Lanka have shown an even distribution of all four subtypes according to Rome III criteria.[18,25] However, two studies from China noted that around 50% of their subjects had IBS-U.[22,26] IBS-C was more prevalent in Iran than the other two types.[27] Prospective studies among adults have shown that sub-types of IBS can be interchanging among patients and there is no stability in the clinical patterns.[33] This concept may be applicable to children and adolescents as well and, perhaps partly explain the diverse variability of sub-types.

There are several strengths of our systematic review and meta-analysis. We have conducted an exhaustive literature search not only through the commonly used databases but also regional databases to identify and include maximum number of studies conducted in Asia. We also used a currently accepted and reliable method to calculate pooled prevalence. In addition, all studies have used well accepted robust definitions (Rome II or Rome III) to diagnose IBS. Finally, all studies are community- or school- based studies and have a higher chance of representing the true burden of IBS in respective countries in Asia.

However, there are a few limitations as well. We included studies published only in the English language. This may have missed studies published in other languages as there is a marked diversity of languages in Asia. Two studies from Korea have only included females in their study population, possibly contributing to over-estimation of gender specific prevalence.[18,28] Studies

have used a variety of definitions of IBS in children including criteria described for adults. Some of these definitions, especially Rome II criteria and adult Rome II and Rome III criteria, would have underestimated the true prevalence of IBS in some studies.[11-13] Data from some large geographical regions are not available. Finally, it is important to realize that meeting diagnostic criteria for IBS does not necessarily exclude other possible organic diseases. Diseases such as coeliac disease and inflammatory bowel disease, although rare among the Asians, are a cause for concern. In addition, chronic gastrointestinal infections such as giardiasis and amoebiasis may mimic symptoms of IBS, especially in the developing countries of Asia.

There is a significant heterogeneity between studies included in this systematic review, as previously seen during pooling of epidemiological data.[32,34] It may possibly be due to differences in ethnicity, subtle application differences in diagnostic criteria, and cultural differences even between areas of the same country. It is not possible to appreciate these factors in a meta-analysis. However, we believe although the above factors are challenges in summarizing data in this fashion, this study is useful to get a greater epidemiological perspective of IBS in Asian children than individual study or a systematic review.

In conclusion, this systematic review and meta-analysis has demonstrated that a sizeable population of young Asians have IBS. However, the prevalence varies according to the country, diagnostic criteria, and age. It is more common among girls compared to boys. Sub-types vary between studies and countries. Further studies using pediatric criteria for IBS is needed to understand the true prevalence, especially in other parts of the Asia with large populations. These studies will help us to understand the epidemiological dynamics and risk factors in a systematic manner so that the preventive strategies could be planned. This will eventually lead the path to minimize suffering of children and young adults.

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Chapter 6

Association between functional gastrointestinal disorders and exposure to abuse in teenagers

This chapter of the thesis was published as

Devanarayana NM, Rajindrajith S, Perera MS, Nishanthanie SW, Karunanayake A, Benninga MA.
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SUMMARY

Abdominal pain predominant functional gastrointestinal disorders (AP-FGIDs) are common children and commonly attributed to exposure to child abuse. However, this relationship has not been studied in teenagers, and the main objective of the current study is to assess it.

Teenagers were recruited from four randomly selected schools in Western province of Sri Lanka. Data were collected using a validated, self-administered questionnaire. AP-FGIDs were diagnosed using Rome III criteria.

A total of 1850 teenagers aged 13-18 years were included. Three hundred and five (16.5%) had AP-FGIDs. AP-FGIDs were significantly higher in those exposed to sexual (34.0%), emotional (25.0%) and physical (20.2%) abuse, than in those not abused (13.0%, $p<0.001$). Those with AP-FGIDs exposed to abuse had a higher severity score for bowel symptoms (30.8% vs. 24.7% in not abused, $p<0.05$).

This study highlights the importance of identifying exposure to abuse in management of teenagers with AP-FGIDs.

INTRODUCTION

As in many societies around the world, a significant percentage of Sri Lankan children are exposed to many forms of physical, emotional and sexual abuse.[1] However, most of these incidences are not reported to the authorities and reported cases constituted of only the tip of the iceberg. Exposure to abuse during childhood is associated with presence of various somatic symptoms in adulthood including abdominal pain.[2-5]

Chronic abdominal pain is a common symptom seen in children. The majority of affected children have no underlying organic pathology to explain their symptoms and fulfil the Rome III criteria for functional gastrointestinal disorders.[6,7] Community based studies have shown that abdominal pain-predominant functional gastrointestinal disorders (AP-FGIDs) are a significant health problem and seen in ~12% of school children in Sri Lanka. The commonest AP-FGID reported in Sri Lanka is irritable bowel syndrome (IBS). According to previous studies, prevalence of IBS in school children in USA is ~10.5%.[8] Similarly, a school based study from Italy in children 6-19 years using Rome II criteria has reported ulcer-like dyspepsia in 3.4% and dysmotility-like dyspepsia 3.7%.[9]

Numerous studies in adults have assessed the association between child abuse and AP-FGIDs.[10-12] Most of these studies have been conducted in adult females who have been exposed to sexual abuse during childhood.[2,3,10,11,13,14] Furthermore, the majority of studies evaluated the association between sexual abuse and irritable bowel syndrome.[10,11,15-17] Therefore, the impact of child abuse on development of some AP-FGIDs which are not commonly seen in adults such as functional abdominal pain and abdominal migraine, is not known.

Only a handful of studies so far have evaluated the impact of abuse on gastrointestinal symptoms during childhood.[18-22] However, there is no detailed account of the association between exposure to different forms of child abuse and different types of AP-FGIDs in teenagers. Lack of well-designed studies to assess this association has been highlighted in a recent systematic review conducted by Sonneveld *et al.*[23]

The current study aims to fill some of these gaps of knowledge on association between AP-FGIDs and exposure to child abuse. The objectives of this study were to evaluate (i) the relationship between exposure to child abuse and presence of AP-FGIDs in teenagers; (ii) severity of symptoms of AP-FGIDs in children exposed to abuse and; (iii) somatic symptoms of teenagers with AP-FGIDs according to exposure to abuse.

METHODS

This cross-sectional study was conducted in children aged 13-18 years in Western province of Sri Lanka. For this study, four mixed schools (with both girls and boys) were randomly selected from 427 schools in this province with students in this age group. Schools were randomly selected from the list of schools available in the provincial education office using lots. From each school all classes of academic years (grades) 8-13 were selected. Children in these classes were within the age limits of 13 to 18 years. All children who were present on the day of the survey were invited to take part in the study.

Permission to conduct the study was obtained from school administration. Written, informed consent was obtained from parents and ascent was given by participants themselves.

Information regarding gastrointestinal symptoms and child abuse were collected using a self-administered questionnaire. This was an anonymous questionnaire. The questionnaire was in native language (Sinhala) and has been pretested for Sri Lankan children of this age group. It was administered in examination setting to ensure confidentiality and privacy. The questionnaire was filled under the guidance of research assistants and collected on the same day.

The questionnaire consisted of four parts. Part 1 consisted of questions of socio-demographic and family characteristics. Part 2 contained the Rome III questionnaire for pediatric functional gastrointestinal disorders (self-report form for children > 10 years)[24] and a symptom severity scale. Rome III questionnaire for pediatric functional gastrointestinal disorders has been previously translated into native language (Sinhala), pretested and used in several Sri Lankan studies involving children of same age group.[25,26] Part 3 contained information on exposure to child abuse and adverse life events. The child abuse questionnaire has been already validated and used in a previous Sri Lankan study.[27] It has questions to identify all three major forms of child maltreatment (physical, sexual and emotional abuse). Part 4 was child somatization inventory.[28] This was designed to assess somatic symptoms and their severity irrespective of their etiology. It has been translated and pretested for Sri Lankan children by the investigators before used in this study.

Scales used

Child somatization inventory consists of 24 items. Each item has scores 0 to 4 (0 = never a problem; 4 = almost always a problem). Total somatization score was obtained by adding up scores obtained for all 24 items.[28]

Severity of abdominal pain, dyspepsia and bowel symptoms were assessed using a 100mm visual analogue scale where 0% was not having symptoms at all and 100% was having very severe symptoms.

Definitions used

There are four types of AP-FGIDs (IBS, functional dyspepsia, abdominal migraine and functional abdominal pain). The current standard practice of diagnosing them is using symptom-based criteria. We used Rome III criteria defined by Rasquin *et al.* in 2006 which is the gold standard for positive diagnosis of FGIDs in children and adolescents.[29] IBS subtyping was done using criteria described by Longstreth *et al.*[30]

Ethical approval

The study was approved by the Ethical Review Committee of the Sri Lanka College of Pediatricians.

Statistical analysis

The data were analyzed using EpiInfo (EpiInfo 6, version 6.04 (1996), Centres of Disease Control and Prevention, Atlanta, Georgia, USA and World Health Organization, Geneva, Switzerland). Somatization scores were compared using unpaired *t*-test. Association between child abuse and AP-FGIDs was assessed using X^2 test. $P < 0.05$ was considered as significant.

RESULTS

A total of 1855 questionnaires were distributed and all of them were returned. Of them, 1850 (99.7%) properly filled questionnaires were included in the analysis.

Prevalence of AP-FGIDs

There were 1000 (54.1%) males [mean age 14.4 years, SD 1.3 years]. A total of 305 (16.5%) of children had AP-FGIDs. **Table 6.1** demonstrates the prevalence of different AP-FGIDs types according to gender. Commonest AP-FGID observed in our cohort is functional abdominal pain. AP-FGIDs was significantly more prevalent in girls than in boys.

Association between child abuse and AP-FGIDs

The association between AP-FGID types and physical, sexual and emotional abuse is shown in **Table 6.2**. **Figure 6.1** shows the prevalence of AP-FGIDs according to age and exposure to abuse. The prevalence of AP-FGIDs was significantly higher in children exposed to child abuse.

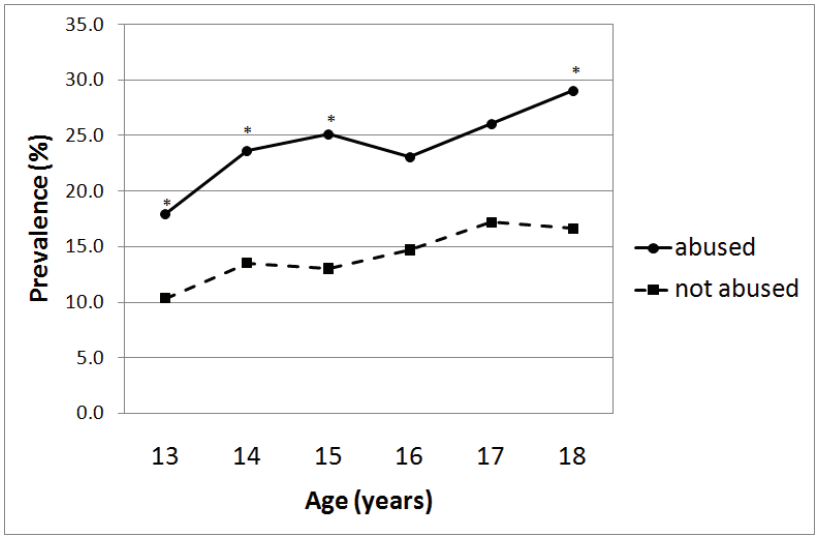

Figure 6.1 – Prevalence of abdominal pain-predominant functional gastrointestinal diseases according to exposure to abuse. *p<0.05, Z-test

Symptom severity

The mean scores obtained for severity of abdominal pain, dyspepsia and bowel symptoms in children with AP-FGIDs are demonstrated in **Figure 6.2** according to child abuse. The scores obtained for severity of bowel symptoms were significantly higher in children with AP-FGIDs, who have been exposed to abuse.

Somatization index in children with AP-FGIDs

Table 6.3 shows the mean somatization scores in children with AP-FGIDs and controls. Overall somatization score and mean scores obtained for individual somatic symptoms were significantly higher in children with AP-FGIDs compared to controls, except that for losing voice.

Children with AP-FGIDs, who have been exposed to child abuse, had a significantly higher overall somatization score (mean 17.6, SD 11.5), than those not exposed to abuse (mean 12.8, SD 10.0, p<0.0001).

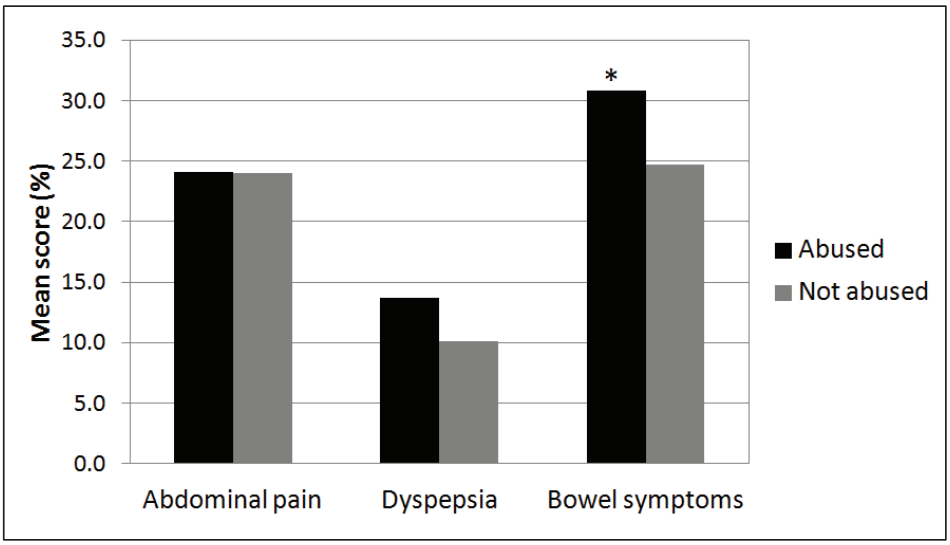

Figure 6.2 – Scores obtained for severity of symptoms in children with abdominal pain-predominant functional gastrointestinal diseases according to exposure to abuse. **p*<0.05, unpaired t-test

DISCUSSION

In this study conducted in the Western province of Sri Lanka, we found AP-FGIDs in 16.5% of 13-18 year-olds. Girls were more affected than boys. The commonest AP-FGID seen in our teenagers was functional abdominal pain, closely followed by IBS. The prevalence of AP-FGIDs was significantly higher in those exposed to physical, sexual and emotional abuse. In teenagers with AP-FGIDs, those exposed to child abuse had a significantly higher severity of bowel symptoms and higher somatization score.

In our study, the prevalence of AP-FGIDs was higher in children exposed to all three main types of abuse (physical, emotional and sexual abuse). This observation was noted across all age groups we have assessed. Very few researchers have studied the relationship between child abuse gastrointestinal symptoms during childhood, especially among teenagers. None of those previous pediatric studies have assessed the association between exposure to abuse and AP-FGIDs and impact of abuse on symptom profile in details. van Tilburg and coworkers have reported an association between child abuse and presence of abdominal pain, nausea and vomiting at the age of 12 years.[18] Two other studies evaluating stressful life events in recurrent abdominal pain have reported exposure to sexual abuse in several study subjects.[21] Similarly,

Table 6.1 – Prevalence of abdominal pain-predominant functional gastrointestinal disorders according to sex

Type of FGID	Boys		Girls		Total	
	N	(%)	*N*	(%)	*n*	(%)
IBS – Total	42	4.2%	49	5.8%	91	4.9%
IBS-diarrhea predominant	16	1.6%	17	2.0%	33	1.8%
IBS-constipation predominant	10	1.0%	20	2.4%	30	1.6%
IBS-mixed	7	0.7%	6	0.7%	13	0.7%
IBS-untyped	9	0.9%	6	0.7%	15	0.8%
Functional dyspepsia	6	0.6%	5	0.9%	11	0.6%
Abdominal migraine	8	2.7%	29**	2.5%	37	1.9%
Functional abdominal pain	76	7.6%	104*	12.2%	180	9.7%
Abdominal pain predominant FGIDs-total	130	13.0%	175**	20.1%	305	16.5%

FGID, functional gastrointestinal disorder

*p=0.001, **p<0.0001, chi-square test, girls vs. boys

Table 6.2 – Prevalence of abdominal pain-predominant functional gastrointestinal disorders according to child abuse

	Physical abuse		Emotional abuse		Sexual abuse		Any type of abuse	
	Yes	No	Yes	No	Yes	No	Yes	No
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
IBS	36 (7.7%)*	55 (4.0%)	37 (8.5%)*	54 (3.8%)	10 (18.9%)*	81 (4.6%)	59 (8.5%)*	32 (2.8%)
FD	5 (1.1%)	6 (0.4%)	3 (0.7%)	8 (0.6%)	0	11 (0.6%)	6 (0.9%)	5 (0.4%)
AM	10 (2.1%)	27 (1.9%)	16 (3.7%)*	21 (1.5%)	2 (3.8%)	35 (2.0%)	18 (2.6%)*	19 (1.6%)
FAP	49 (10.4%)	131 (9.5%)	61 (14.0%)*	119 (8.4%)	8 (15.1%)	172 (9.7%)	82 (11.8%)*	98 (8.5%)
AP-FGIDs total	95 (20.2%)*	210 (15.1%)	109 (25.0%)*	196 (13.8%)	18 (34.0%)*	287 (16.2%)	155 (22.4%)*	150 (13.0%)

IBS = irritable bowel syndrome, FD = functional dyspepsia, AM= Abdominal migraine, FAP=functional abdominal pain, AP-FGID= abdominal pain predominant functional gastrointestinal disorders

*$p<0.05$ compared to not abuses, unpaired t-test

Table 6.3 – Somatization scores for children with abdominal pain-predominant functional gastrointestinal disorders

Somatic symptom	IBS	Functional dyspepsia	Abdominal migraine	Functional abdominal pain	AP-FGIDs total	Controls
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Headache	1.7 (1.1) *	1.3 (1.1)	2.0 (1.0) *	1.6 (1.0) *	1.7 (1.0)*	1.2 (1.0)
Faintness or dizziness	0.8 (1.0) *	0.6 (0.8)	1.0 (1.1) *	0.5 (0.8) *	0.6 (0.9) *	0.3 (0.7)
Pain – heart of chest	0.9 (0.9) *	1.3 (1.4) *	1.1 (1.1) *	0.6 (0.9) *	0.8 (1.0) *	0.4 (0.8)
Low energy, slowed down	0.9 (1.0) *	0.6 (0.5)	1.1 (1.2) *	0.7 (0.9) *	0.8 (1.0) *	0.5 (0.9)
Pain –lower back	1.1 (1.2) *	0.5 (0.7)	1.5 (1.4) *	0.8 (1.2) *	1.0 (1.2) *	0.5 (0.9)
Sore muscles	0.7 (0.9) *	0.3 (0.6)	1.3 (1.2) *	0.6 (0.9) *	0.7 (0.9) *	0.4 (0.8)
Trouble getting breath	0.5 (0.9) *	0.4 (0.7)	0.7 (1.1) *	0.5 (0.9)*	0.5 (0.9) *	0.3 (0.7)
Hot or cold spells	1.0 (1.1) *	0.4 (0.7)	1.2 (1.3) *	0.5 (0.8)	0.6 (0.9) *	0.4 (0.8)
Numbness or tingling	1.0 (1.0) *	0.2 (0.4)	1.0 (1.1) *	0.6 (0.9)*	0.7(1.0) *	0.5 (0.8)
Weakness	1.0 (1.1) *	0.7 (1.2)	1.1 (1.1) *	0.7 (0.9) *	0.8 (0.9) *	0.5 (0.8)
Heavy feeing in arms, legs	0.6 (1.0) *	0.2 (0.6)	0.8 (1.1) *	0.3 (0.7)	0.4 (0.8) *	0.2 (0.5)
Nausea, upset stomach	1.1 (1.0) *	0.5 (0.5)	1.5 (1.3) *	0.5 (0.8)*	0.7 (0.9) *	0.3 (0.6)
Constipation	0.7 (1.0) *	0.3 (0.5)	0.8 (1.1) *	0.2 (0.6)	0.4 (0.8) *	0.2 (0.5)
Loose bowel movements, diarrhea	0.5 (0.9) *	0.2 (0.4)	0.7 (1.2) *	0.2 (0.5)	0.3 (0.7) *	0.2 (0.5)
Pain – stomach	1.7 (1.3) *	1.0 (1.0)	2.3 (1.4) *	1.3 (1.0)*	1.4(1.1) *	0.6 (0.8)

Heart beating too fast	0.5 (0.8) *	0.0	0.8 (1.2) *	0.5 (0.9) *	0.5 (0.9) *	0.3 (0.7)
Difficulty in swallowing	0.5 (0.9) *	0.1 (0.3)	0.3 (0.5)	0.2 (0.5)	0.3 (0.7) *	0.2 (0.5)
Losing voice	0.3 (0.7) *	0.0	0.3 (0.5)	0.2 (0.6)	0.2 (0.6)	0.2 (0.6)
Blurred vision	0.7 (1.1) *	0.5 (0.7)	1.0 (1.2) *	0.4 (0.7)	0.5 (0.9)*	0.3(0.7)
Vomiting, throwing up	0.4 (0.8) *	0.4 (0.5)	0.6 (0.9) *	0.3 (0.6) *	0.3 (0.7) *	0.2(0.5)
Feeling bloated, gassy	0.6 (1.0) *	0.5 (0.7)	0.5 (0.9) *	0.5 (0.8) *	0.5 (0.9) *	0.2(0.6)
Food makes you sick	0.3 (0.8) *	0.2 (0.4)	0.6 (1.1) *	0.1 (0.5)	0.2 (0.7) *	0.1(0.4)
Pain – Knees, elbows, joints	0.6 (1.0) *	0.2 (0.6)	0.8 (1.1) *	0.4 (0.7)	0.5 (0.8) *	0.3 (0.7)
Pain – arms, legs	1.1 (1.1) *	0.4 (0.7)	1.4 (1.4) *	0.7 (0.9)	0.9 (1.0) *	0.5 (0.9)
Total somatization score	18.9 (11.6) *	10.2 (5.5)	24.2 (13.6) *	12.8 (9.8) *	15.2 (11.1) *	8.4 (8.8)

AP-FGIDs = abdominal pain-predominant functional gastrointestinal disorders

*$p<0.05$, compared to controls, unpaired t-test

Mellon and colleagues reported a significantly higher prevalence of fecal incontinence in children exposed to abuse.[19] In contrast to this, Tam *et al.* failed to find an association between constipation and abuse.[20] The relationship between child abuse and the four main types of AP-FGIDs has not been studied in teenagers. Our findings are also similar to that previously reported in adult studies where IBS was noted to be more prevalent among adults who experienced abuse as a child.[3,12,16,17]

One previous study, conducted in 10 adult females with IBS has shown greater pain in those exposed to abuse.[31] Similarly, another adult study conducted in females attending a gastroenterology clinic has shown a significant association between greater pain severity and exposure to abuse.[3] When the relationship between exposure to abuse and symptom severity was assessed in the current study, the scores obtained for severity of bowel symptoms were significantly higher in children with AP-FGIDs who have been exposed to child abuse, than those not exposed to such events. However, severity of abdominal pain and dyspepsia had no such relationship. The exact reason for this lack of relationship is not clear.

A previous school-based study in children ages 10-16 years, using Rome III criteria, has reported AP-FGIDs in 12.5% of affected children,[26] and the prevalence AP-FGIDs in the current study is higher than that reported earlier. In addition we have also shown that the prevalence of AP-FGIDs has a positive relationship with age. Inclusion of older children may have contributed to the higher prevalence we observed in the current study. In the previous study, the commonest AP-FGIDs reported was IBS, while in the current study the most prevalent AP-FGIDs is functional abdominal pain. The exact reasons for these differences are unclear. The previous study was conducted in three provinces in the country, while the current study is conducted in only one province. In addition, the age difference in recruited children might have contributed to this difference. However, similar to the current study, a laboratory based study conducted in the same area has found functional abdominal pain as the commonest cause for abdominal pain in children aged 5-15 years.[6] The previous studies have also reported a female preponderance.[25,26]

In this study, we have assessed the somatization score in children with AP-FGIDs. Scores obtained for all somatic symptoms were significantly higher in those with AP-FGIDs than in controls, except for losing voice. Extra-intestinal somatic symptoms were also common in our children with AP-FGIDs. Headache, back pain and limb pain were the most common somatic symptoms observed in our teenagers with AP-FGIDs apart from abdominal pain. A previous Sri

Lankan study conducted in children aged 10-16 years has also reported a higher prevalence of some intestinal and extra-intestinal symptoms in children with AP-FGIDs.[26] However, the previous study has only assessed few somatic symptoms and has not used the complete somatization index. Therefore, a detailed evaluation of somatic symptoms had not been done in teenagers with AP-FGIDs previously for us to make a comparison. This novel observation indicates a number of somatic symptoms are contributing to the suffering of children with AP-FGIDs, Therefore, inquiring about the presence of somatic symptoms needs to be an integral part of clinical evaluation of children with abdominal pain.

Furthermore, total somatization score was significantly higher in children exposed to abuse than those not exposed to such events. Previous studies have also reported higher prevalence of somatic symptoms among adults exposed to abuse.[2, 4,5,13] However, there were no previous studies to evaluate this relationship in details in pediatric age group.

Exact pathophysiological mechanism explaining the association between exposure to abuse and presence of gastrointestinal symptoms are not clear. However, several possible underlying mechanisms have been postulated to explain gastrointestinal symptoms in those exposed to abuse. Functional gastrointestinal disorders including AP-FGIDs are considered as disorders of dysregulation of the brain-gut communication system or the brain-gut axis.[32] Adverse and traumatic life events such as exposure to abuse are believed to modify the brain-gut axis both at central and peripheral levels. Possible mediating mechanisms suggested are increased autonomic nervous system reactivity to stressors, visceral hypersensitivity and lower sensation threshold in the gut, altered cortico-limbic pain modulatory systems linking hypervigilance and emotions and increased repose of the hypothalamic-pituitary-adrenal axis to stress.[10]

In this study we have recruited teenagers aged 13 to 18 years. This is a crucial time period of life of any human being in terms of physical, social and emotional development and education. Presence of a chronic painful disease condition, such as AP-FGIDs, during this period, in addition to social and psychological after-effects of child abuse, would significantly impede their development and education and will have a significant negative impact on their future social, emotional and financial stability. In this context, detection of AP-FGIDs and child abuse and active intervention to minimize detrimental effects of them during early teenage period is of utmost importance to prevent long-term consequences of these conditions.

There were two main limitations in this study. In this questionnaire-based school survey, we did not investigate children to exclude organic causes for abdominal pain. In a previous study we

identified organic diseases in 10.9% of children with recurrent abdominal and nearly 89% had functional gastrointestinal diseases.[6] Similar results have been reported from other countries as well.[22,33,34] The organic diseases observed in the previous study include urinary tract infection, gastro-esophageal reflux disease, urinary calculi, antral gastritis, and intestinal amoebiasis.[6] Parasitic infestations such as giardiasis and amoebiasis have been considered to be possible mimickers of FGIDs; however, in that study, prevalence of these diseases was 1.8%, similar to several previous studies conducted in Sri Lanka.[35] The second limitation of the study is that, because this is self-administered questionnaire there is recall bias. Those exposed to abuse are reluctant to admit it. Number of reported cases of abuse is only a small percentage of actual events. Taking extensive measures to ensure confidentiality and privacy in the current study may have increased the reported incidences.

In conclusion, we found a higher prevalence of AP-FGIDs in teenagers who have been exposed to physical, sexual, and emotional abuse. Those with AP-FGIDs had other gastrointestinal-related and extra-gastrointestinal somatic symptoms and higher somatization index than controls. In addition, scores obtained for severity of bowel symptoms were significantly higher in teenagers with AP-FGIDs exposed to abuse than those not exposed to such events.

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Chapter 7

Quality of life and health care consultation in 13 to 18 year olds with abdominal pain predominant functional gastrointestinal disorders

This chapter of the thesis was published as

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ABSTRACT

Background: Abdominal pain predominant functional gastrointestinal disorders (AP-FGIDs) are commonly seen in the pediatric age group. It has a significant impact on daily activities of affected children. Main objective of this study was to assess the health related quality of life (HRQoL) in children with AP-FGIDs.

Method: This was a cross sectional survey conducted in children aged 13-18 years, in four randomly selected schools in Western province of Sri Lanka. Data was collected using a previously validated, self-administered questionnaire. It had questions on symptoms, HRQoL and health care consultation. AP-FGIDs were diagnosed using Rome III criteria.

Results: A total of 1850 questionnaires were included in the analysis (males 1000 [54.1%], mean age 14.4 years and SD 1.3 years). Of them, 305 (16.5%) had AP-FGIDs (irritable bowel syndrome = 91[4.9%], functional dyspepsia =11 [0.6%], abdominal migraine=37 [1.9%] and functional abdominal pain = 180 [9.7%]). Lower HRQoL scores for physical (83.6 vs. 91.4 in controls), social (85.0 vs. 92.7), emotional (73.6 vs. 82.7) and school (75.0 vs. 82.5) functioning domains, and lower overall scores (79.6 vs. 88.0) were seen in children with AP-FGIDs ($P<0.001$). A weak but significant negative correlation was observed between HRQoL score and severity of abdominal pain (r=-0.24, $P<0.0001$). Eighty five children (27.9%) had sought healthcare for AP-FGIDs. Factors determining healthcare seeking were presence of abdominal bloating and vomiting ($P<0.05$).

Conclusions: Children with AP-FGIDs have lower quality of life in all 4 domains. Those with severe symptoms have lower HRQoL. Approximately 28% of children with AP-FGIDs seek healthcare for their symptoms.

INTRODUCTION

The World Health Organization defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".[1] Quality of life is a term used to refer to an individual's total wellbeing. This includes all emotional, social and physical aspects of an individual's life. When the phrase is used in reference to medicine, it is called as "Health Related quality of Life (HRQoL).

Abdominal pain predominant functional gastrointestinal disorders (AP-FGIDs) such as irritable bowel syndrome (IBS), functional abdominal pain (FAP), abdominal migraine (AM) and functional dyspepsia (FD), are seen in approximately 12% of children and adolescents.[2,3] Even though not life threatening, AP-FGIDs are chronic, troublesome disorders which can have significant impact on life of the affected children. In the absence of biological measures of disease activity, HRQoL becomes an important objective measure of health status in children suffering from AP-FGIDs.

Several studies have so far assessed the quality of life in children and adolescents with AP-FGIDs and all of them have reported lower quality of life.[4-9] Most studies were conducted in young children and have assessed HRQoL using a parent report form and include children of younger age groups.[4-7] Studies reporting quality of life in teenagers with AP-FGIDs are rare.[8,9]

Abdominal pain is often an alarming symptom which leads to frequent healthcare consultation. Few studies conducted in children with abdominal pain, have reported healthcare consultation of 39 to 93% in affected children.[10-14] To date, no studies are available that have evaluated healthcare consultation in teenagers with AP-FGIDs.

HRQoL and healthcare seeking behaviors are likely to vary from country to country, community to community, depending on demographic and socio-cultural factors. HRQoL and healthcare consultation pattern in teenager are likely to be different from that of younger children. So far, no studies have assessed HRQoL and healthcare consultation in Sri Lankan teenagers with AP-FGIDs. This study was conducted with the main objective of assessing HRQoL and healthcare consultation in children aged 13-18 years in Sri Lanka and factors associated with them.

METHODS

This was a cross sectional survey conducted in in the Western province of Sri Lanka.

Data collection

Western province of Sri Lanka has 1333 functioning government schools (similar to public schools). Of them, 427 are schools with students aged 13-18 years. From the list of these 427 schools available at the Provincial Education Office, four mixed gender schools were randomly selected by drawing lots. All children aged 13 to 18 years in these schools were invited to take part in the study.

Data on socio-demographic and family characteristics, symptoms, HRQoL and healthcare consultation were collected using a validated, self-administered questionnaire. Questionnaire was in native language (Sinhala). It consisted of 4 parts. First part contained questions on socio-demographic and family characteristics. Information regarding AP-FGIDs was collected using Rome III questionnaire for FGIDs (child report form for children above 10 years) (Part 2).[15] This part of the questionnaire has been translated, validated and used for Sri Lankan children previously.[2,3] Part 3 was PedsQL, Pediatric Quality of Life Inventory 4.0 (Generic Core Scales) self-report form for teens,[16-18] which has been previously translated in to native language (Sinhala) and has undergone linguistic validation by Mapi Research Trust. The investigators have obtained permission to use this questionnaire for this study. Part 4 of the questionnaire contained questions regarding healthcare consultation. This part of the questionnaire has been developed by the investigators, pretested, and used previously in a school based study in Sri Lankan children.[19]

This was an anonymous questionnaire, administered in examination setting, to ensure confidentiality and privacy. Research assistants were present and support was given during filling the questionnaire. Questionnaires were collected on the same day. Consent was obtained from school administration, teachers, parents and children themselves before administration of the questionnaire.

Scales used

The HRQoL inventory consisted of 23 items. It was used to assess the physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items) of the child. A 5-point response scale is used (0 = never a problem; 1= almost never a problem, 2= sometimes a problem, 3= often a problem, 4 = almost always a problem) to record the responses. Items were reverse scored and linearly transformed to a zero to 100 scale (0 =

100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Final HRQoL scores were computed out of 100, with higher scores indicating better HRQoL.

Symptom severity of abdominal pain, dyspepsia and bowel symptoms were recorded using a visual analogue scale (100mm) rating between 0% to 100%, where 0% is not having symptoms at all and 100% is having very severe symptoms.

Definitions used

AP-FGIDs; irritable bowel syndrome (IBS), functional dyspepsia (FD), abdominal migraine (AM) and functional abdominal pain (FAP), were diagnosed using Rome III criteria defined by Rasquin *et al.* in 2006.[20]

A child who has received treatment for abdominal pain during previous 3 months was considered as a healthcare consulter.

Ethical approval

Ethical approval was obtained from the Ethical Review Committee of the Sri Lanka College of Pediatricians.

Statistical analysis

The data were analyzed using EpiInfo (EpiInfo 6, version 6.04 (1996), Centres of Disease Control and Prevention, Atlanta, Georgia, USA and World Health Organization, Geneva, Switzerland). Total HRQoL scores were compared using unpaired t-test. Healthcare consultation between patients and controls were compared using X^2 test. Multiple logistic regression analysis was used to evaluate independent association between factors identified as significant in the univariable analysis. All correlations were done using Pearson correlation coefficient. $P < 0.05$ was considered as significant.

RESULTS

A total of 1855 questionnaires were distributed and all of them were returned. Of them, 1850 (99.7%) properly filled questionnaires were included in the analysis. There were 1000 (54.1%) boys. Mean age of the participants was 14.4 years (SD 1.3 years).

A total of 305 (16.5%) of children had AP-FGIDs. IBS was seen in 91 (4.9%), FD was seen in 11 (0.6%), AM was seen in 37 (1.9%) and FAP was seen in 180 (9.7%). Of them 13 had both IBS and AM and 1 had AM and FD. AP-FGIDs were significantly more prevalent in girls [175 (20.1%)

vs. 130 (13.0%) in boys, *P*<0.0001)]. During analysis, 1545 children without AP-FGIDs were considered as controls.

HRQoL in children with AP-FGIDs

Table 7.1 shows the mean HRQoL scores in children with all four types of AP-FGIDs and controls. Children with AP-FGIDs had lower HRQoL scores than controls in all 4 domains (physical, emotional, social and school functioning). When HRQoL scores of children with different types of AP-FGIDs were analyzed, children with IBS and AM had lower HRQoL scores for all four domains, compared to controls. Those with FAP had lower HRQoL scores only for physical and emotional functioning domains. There was no statistical difference between children with FD and controls (**Table 7.1**).

When HRQoL scores were compared between different AP-FGID types, lowest HRQoL scores were observed in children with AM (78.6%) and IBS (79.6%) (*P*<0.001, compared to FAP and FD) (**Table 7.1**).

Healthcare consultation in children with AP-FGIDs

Table 7.2 shows the percentage of healthcare consultation according to AP-FGID type. Healthcare consultation in patients with AP-FGIDs was 27.9%. In addition, 8.3% of controls have sought medical advice for abdominal pain due to other causes. When healthcare consultation between different AP-FGID types was compared, the highest rate was observed in children with AM (40.5%).

Factors affecting HRQoL in children with AP-FGIDs

As depicted in **Table 7.3**, no significant differences were found in scores obtained for HRQoL according to socio-demographic and family characteristics in children with AP-FGIDs (*P*>0.05).

HRQoL score had a weak but significant negative correlations with scores obtained for severity of abdominal pain (r= -0.24, 95% confidence interval (CI) -0.34 to -0.13, *P*<0.0001), frequency of abdominal pain (r= -0.15, 95% CI -0.26 to -0.04, *P*=0.009), severity of dyspepsia (r= -0.19, 95% CI -0.30 to -0.08, *P*= 0.001) and severity of bowel symptoms (r= -0.15, 95% CI -0.25 to 0.03, *P*=0.01) .

Table 7.1 – Health related quality of life (HRQoL) scores in children with abdominal predominant functional gastrointestinal disorders and controls

Quality of life domains	**Irritable bowel syndrome** Mean (SD)	**Functional dyspepsia** Mean (SD)	**Abdominal migraine** Mean (SD)	**Functional abdominal pain** Mean (SD)	**AP-FGIDs total** Mean (SD)	**Controls** Mean (SD)
Physical functioning (%)	84.7 (15.1)****	94.0 (7.8)	81.6 (15.2)****	89.1 (12.1)***	87.9 (13.4)****	91.5 (10.9)
Emotional functioning (%)	70.1 (21.2)****	89.5 (9.3)	68.4 (22.8)****	77.8 (19.7)****	75.6 (20.3)****	83.4 (17.0)
Social functioning (%)	85.7 (16.5)****	95.0 (9.2)	86.3 (15.6)****	92.1 (12.1)	90.0 (14.0)****	92.7 (11.6)
School functioning (%)	74.1 (18.7)****	89.5 (12.5)	72.5 (19.3)****	79.9 (16.6)*	78.0 (18.0)****	82.6 (16.8)
Total HRQoL score (%)	79.6 (13.6)****	92.3 (5.6)	78.6 (12.7)****	85.6 (10.4)**	83.8 (11.8)****	88.1 (10.9)

AP-FGIDs = abdominal pain-predominant functional gastrointestinal disorders

*P=0. 04, **P=0.006, ***P=0.003, ****P<0.0001 compared to controls, unpaired t-test

Table 7.2 – Health care consultation in children with abdominal pain predominant functional gastrointestinal disorders

	Health care consultation	
	Consulters	**Non-consulters**
	***n* (%)**	***n* (%)**
Irritable bowel syndrome	27 (29.7%)	64 (70.3%)
Functional dyspepsia	4 (36.4%)	7 (63.6%)
Abdominal migraine	15 (40.5%)	22 (59.5%)
Functional abdominal pain	44 (24.4%)	136 (75.6%)
Abdominal pain predominant FGIDs total	85 (27.9%)	220 (72.1%)
Controls	129 (8.3%)	1416 (91.7%)

FGID=functional gastrointestinal disorder

Factors determining healthcare consultation in children with AP-FGIDs

The association between socio-demographic factors and healthcare consultation is shown in **Table 7.3**. **Table 7.4** shows the association between symptom characteristics and healthcare consultation. Following multiple logistic regression analysis, abdominal bloating [adjusted odds ratio (OR) 2.1, *P*=0.04] and vomiting (adjusted OR 2.5, *P*=0.02) remained to be significantly associated with healthcare consultation.

In teenagers with AP-FGIDs, healthcare consulters had significantly higher scores for school functioning and physical functioning domains of HRQoL than non-consulters (**Figure 7.1**).

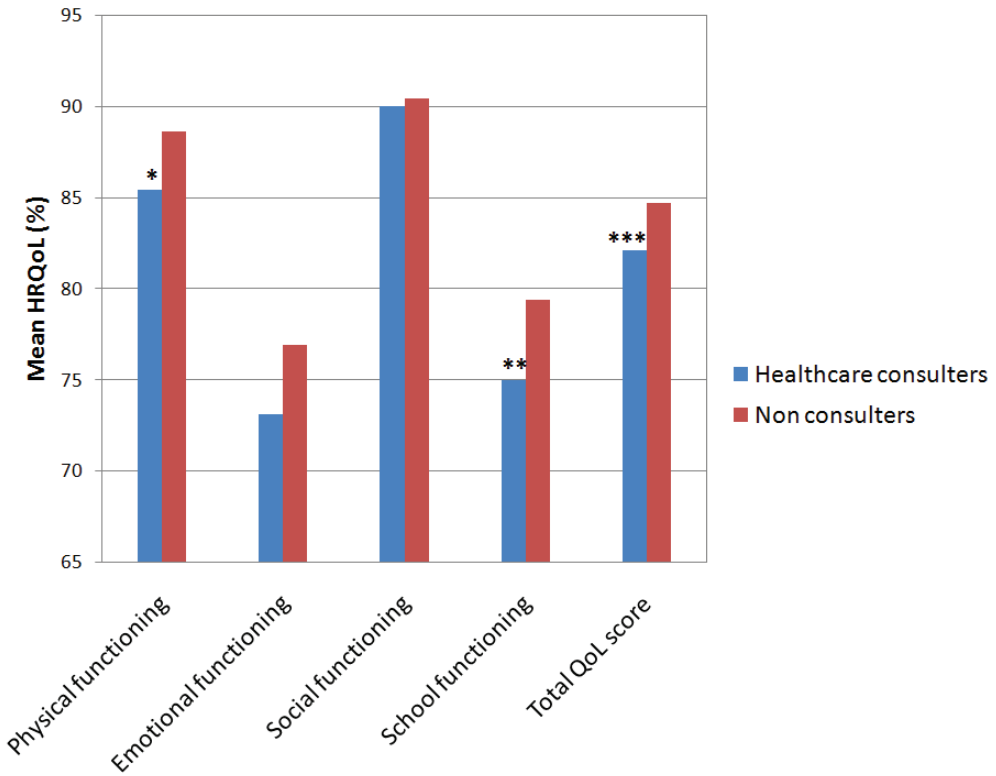

Figure 7.1 – Association between HRQOL and healthcare consultation

*p=0.03, **p=0.048, ***p=0.055, comparison between healthcare consulters and nonconsulters (unpaired t-test)

Table 7.3 – Quality of life scores and heath care consultation in children with abdominal pain predominant functional gastrointestinal disorders according to the socio-demographic and family characteristics

Variable	Health related quality of life (%) Mean (SD)	Health care consultation *n* (%)
Age		
13 years	86.5 (10.2)	26 (35.1%)
14 years	84.5 (12.7)	18 (22.8%)
15 years	82.1 (11.0)	22 (31.0%)
16 years	81.9 (11.9)	7 (15.9%)
17 years	82.3 (13.7)	8 (38.1%)
18 years	81.6 (11.8)	4 (25.0%)
Sex		
Male	84.7 (12.4)	40 (30.8%)
Female	83.1 (11.4)	45 (25.7%)
Family size		
Only child	86.2 (11.2)	11 (37.9%)
2 children	84.2 (11.7)	42 (28.0%)
3 children	83.3 (11.5)	27 (27.6%)
4 children	84.7 (11.2)	4 (19.0%)
5 or more children	67.4 (17.4)	1 (14.3%)
Birth order		
1st	83.4 (12.5)	45 (30.2%)
2nd	84.5 (10.9)	31 (28.7%)
3rd	83.7 (9.4)	5 (14.3%)
4th	85.1 (12.9)	3 (30.0%)
5th or more	68.1 (24.3)	1 (33.3%)
Father's social class		
Leading profession (e.g. doctor, engineer)	84.7 (12.3)	15 (33.3%)
Lesser profession (e.g. nurse, teacher)	83.7 (12.2)	6 (31.6%)
Skilled non-manual (e.g. clerk)	85.4 (13.3)	9 (24.3%)
Skilled manual (e.g. mason, carpenter)	83.2 (11.8)	36 (27.7%)
Unskilled/unemployed	82.4 (10.8)	11 (28.2%)
Maternal employment		
Leading profession (e.g. doctor, engineer)	83.6 (10.6)	2 (25.0%)
Lesser profession (e.g. nurse, teacher)	82.8 (15.8)	4 (28.6%)
Skilled non-manual (e.g. clerk)	84.0 (11.2)	2 (25.0%)
Skilled manual (e.g. mason, carpenter)	85.2 (11.3)	8 (22.9%)
Unskilled/unemployed	83.6 (11.8)	62 (25.8%)

Table 7.4 – Health care consultation in children with abdominal pain predominant functional gastrointestinal disorders according to symptoms

		Health care consulters *n* (%)	Non consulters *n* (%)	Odd ratio (95% Confidence Interval)	*P* value*
Frequency of abdominal pain	Once per week	61 (26.4%)	170 (73.6%)	0.8 (0.4-1.4)	0.32
	Several times per week	20 (32.8%)	41 (67.2%)	1.3 (0.7-2.6)	0.34
	Everyday	4 (30.8%)	9 (69.2%)	1.2 (0.3-4.3)	0.81
Duration of a pain episodes	Less than 1 hour	41 (27.9%)	106 (72.1%)	1.0 (0.6-1.7)	0.99
	1-2 hours	25 (34.2%)	48 (65.8%)	1.5 (0.8-2.7)	0.16
	3- 4 hours	2 (11.8%)	15 (88.2%)	0.3 (0.1-1.6)	0.13
	Most of the day	17 (25.0%)	51 (75.0%)	0.8 (0.4-1.6)	0.55
Severity of pain	Mild	14 (26.4%)	39 (73.6%)	0.9 (0.4-1.9)	0.80
	Moderate	43 (25.4%)	126 (74.6%)	0.8 (0.5-1.3)	0.29
	Severe	28 (33.7%)	55 (66.3%)	1.5 (0.8-2.6)	0.20
Location of pain	Upper abdomen	5 (38.5%)	8 (61.5%)	1.7 (0.5-5.8)	0.38
	Periumbilical	58 (33.1%)	117 (66.9%)	1.9 (1.1-3.3)	0.02
	Lower abdomen	8 (10.1%)	71 (89.9%)	0.2 (0.1-0.5)	<0.0001
	Other	14 (36.8%)	24 (63.2%)	1.6 (0.7-3.5)	0.19
Duration of the disease	2 months	26 (32.9%)	53 (67.1%)	1.4 (0.8-2.5)	0.25
	3 months	18 (30.5%)	41 (69.5%)	1.2 (0.6-2.3)	0.61
	4-11 months	12 (31.6%)	26 (68.4%)	1.2 (0.6-2.7)	0.58
	More than 12 months	29 (22.5%)	100 (77.5%)	0.6 (0.4-1.1)	0.07
Bloating	Yes	18 (43.9%)	23 (56.1%)	2.3 (1.1-4.8)	0.01
	No	67 (25.4%)	197 (74.6%)		
Early satiety	Yes	14 (31.1%)	31 (68.9%)	1.2 (0.6-2.5)	0.60
	No	71 (27.3%)	189 (72.7%)		

Loss of appetite	Yes	33 (30.3%)	76 (69.7%)	1.2 (0.7-2.1)	0.48
	No	52 (26.5%)	144 (73.5%)		
Nausea	Yes	36 (37.5%)	60 (62.5%)	2.0 (1.1-3.4)	0.01
	No	49 (26.7%)	160 (77.3%)		
Vomiting	Yes	18 (48.6%)	19 (51.4%)	2.8 (1.3-6.1)	0.002
	No	67 (25.0%)	201 (75.0%)		
Constipation	Yes	29 (37.2%)	49 (62.8%)	1.8 (1.0-3.2)	0.03
	No	56 (24.7%)	171 (75.3%)		
Loose stools	Yes	20 (34.5%)	38 (65.5%)	1.5 (0.8-2.8)	0.21
	No	65 (26.3%)	182 (73.7%)		
Sleep disturbance	Yes	32 (31.1%)	71 (68.9%)	1.3 (0.7-2.2)	0.37
	No	53 (26.2%)	149 (73.8%)		
School absenteeism	Yes	21 (32.3%)	44 (67.7%)	1.3 (0.7-2.5)	0.37
	No	64 (26.7%)	176 (73.3%)		
Disturbance in daily activities	Yes	43 (30.7%)	97 (69.3%)	1.3 (0.8-2.2)	0.31
	No	42 (25.5%)	123 (74.5%)		
Headache	Yes	38 (29.7%)	90 (70.3%)	1.2 (0.7-2.0)	0.31
	No	47 (25.4%)	130 (74.6%)		
Photophobia	Yes	16 (31.4%)	35 (68.6%)	1.2 (0.6-2.5)	0.54
	No	69 (27.2%)	185 (72.8%)		
Pallor	Yes	6 (23.1%)	20 (76.9%)	0.8 (0.3-2.1)	0.57
	No	79 (28.3%)	200 (71.7%)		

* Chi-square test

DISCUSSION

In this study, teenagers with AP-FGIDs had significantly lower HRQoL in all four domains; physical, emotional, social and school functioning. This lower HRQoL scores were significant in IBS, AM and FAP. Approximately 28% of affected children seek healthcare for their symptoms. Factors independently associated with healthcare consultation were abdominal bloating and vomiting.

In this study, we found a slightly higher prevalence of AP-FGIDs than previously reported in Sri Lanka. In a previous study conducted in children age 12-16 years in a semi-urban school, AP-FGIDs were seen in 13.8%.[2] Another study conducted in children aged 10-16 years in 8 schools of 4 provinces (out of 9 provinces of the country) has reported a prevalence of 12.5%.[3] A Colombian study conducted in a younger group of children (mean age 10 years) has reported AP-FGIDs in 10.8%. Differences between age groups and socio-geographical factors may have accounted for these differences in prevalence.[21] Contrast to previous studies, commonest AP-FGIDs in our teenagers was FAP.[2,3] We observed a significantly higher prevalence of FAP than in previous studies (9.7% in current study vs. 3.0%, 4.5% and 2.7% in previous studies).[2,3,21] Prevalence of FD is lower in the current study than previously reported in Sri Lanka (3.5%, 2.5%) and Colombia (1.7%).[2,3,21] The exact reason for this is not clear, but might be due to differences in age groups.

Very few studies have evaluated HRQoL in teenagers with AP-FGIDs. A recent school based study, conducted in 10 to 17 years old children, has reported significantly lower quality of school work in children with IBS, aerophagia and cyclic vomiting.[8] Another study conducted in high school children in Korea has also reported similar results.[9] Lower HRQoL has also been reported in younger children with AP-FGIDs. Varni *et al*.[5] have evaluated HRQoL using a generic score scale in children 2 to 18 years with IBS and reported lower scores in all 4 domains. In another study, children with FAP (mean age 11.2 years) had significantly lower HRQoL in physical and emotional domains compared to healthy controls.[4] In that study, HRQoL scores in children with FAP were similar to those with chronic organic diseases such as gastro-esophageal reflux disease and inflammatory bowel disease. Several studies conducted in preschool children and adults with AP-FGIDs have also reported lower quality of life in affected children and adults.[6,7,22-25]

We have compared HRQoL between four different types of AP-FGIDs. The lowest score was observed in those with AM. Prolonged periods of severe abdominal pain, and presence of other troublesome symptoms such as headache, may have contributed to this lower HRQoL. In

addition, children with IBS had HRQoL significantly lower than that of those with FAP and FD. Presence of bowel symptoms, in addition to abdominal pain, may have contributed to this finding. A recent study assessing school related quality of life in children 10 to 17 years reported lowest scores in those with FAP (9.0) followed by FD (10.5), IBS (11.3) and AM (11.6).[8] This is different from scores obtained for school functioning in our study (**Table 1**). The fact that the previous study has used different scale and scoring system to measure school related quality of life and the differences in ages of children recruited and socio-cultural environments may have contributed to this difference.

We observed a weak, but significant inverse relationship between severity of symptoms (severity of abdominal pain, dyspepsia and bowel symptoms, and frequency of abdominal pain) and scores obtained for HRQoL. Similar to our results, Oostenbrink and co-workers have reported significant negative correlation between severity of abdominal pain and quality of life, in preschool children in the Netherlands.[6] Another study conducted in children with defecation disorders have found a similar correlation between HRQoL and abdominal pain and bloating.[26] Previous studies conducted in adult patients with functional gastrointestinal disorders have also reported lower HRQoL in patients with more severe symptoms.[22] There is a wide individual variation in perception of symptoms including pain. Sometimes patients with severe pain have fairly good quality of life while others with mild pain have poor quality of life. In our view, these individual variations may have contributed to the weak correlation observed in the current study between symptoms and HRQoL scores.

In this study, we did not find a relationship between HRQoL and age, gender, social class, maternal employment, family size and birth order. The relationship between socio-demographic and family characteristics and HRQoL has not been evaluated in pediatric patients with AP-FGIDs. However, contrary to our results, studies conducted in adult patients with functional gastrointestinal disorders have reported lower HRQoL in females compared to males.[22]

In our study approximately 28% of affected children have sought medical advice for abdominal pain during previous 3 months. In addition, 8.3% of controls have also sought medical advice for abdominal pain due to other causes. There are no studies conducted in teenagers with AP-FGIDs on healthcare consultation. However, percentage of healthcare consultation in the current study is significantly lower than that reported in children with recurrent abdominal pain aged 5-15 years in Sri Lanka (70%),[12] and 9 -15 years in Malaysia (45-48%).[10,11] Another study conducted in German children has shown healthcare consultation of 52% in children (3-10 years) and 39% in adolescents (11-17 years).[13] Some studies have reported healthcare use as high as 93% in

children aged 4 to 17 years with non-specific abdominal pain.[14] Age groups of children included in those previous studies are lower than the teenagers we recruited in the current study. Generally, parents are more aware of the gastrointestinal symptoms and bowel habits of younger children and more worried about such symptoms when their children are younger. Therefore, younger children are more likely to seek healthcare than older children. This may have contributed to the higher prevalence of healthcare consultation seen in previous studies.

We expected higher healthcare consultations in children from higher social class, small families and those with severe symptoms and disturbances in day to day life. However, none of the other symptoms or socio-demographic and family characteristics were associated with healthcare consultation. Sri Lanka has well established government hospitals and clinics where healthcare is provided free of charge. Average distance from a home to a healthcare facility is approximately 1.4km. This may have accounted for the lack of association between healthcare consultation and socio-economic factors. Previous studies conducted in children with abdominal pain have also failed to show an association between socioeconomic factors and healthcare consultation.[10-12]

The symptoms independently associated with healthcare consultation in our study were abdominal bloating and vomiting. Similar to the current study, in the previous Sri Lankan study conducted in children aged 5 to 15 years with recurrent abdominal pain, the only symptom associated with healthcare consultation was vomiting.[12] In contrast to this, other previous studies conducted in younger children have shown significant associations between health care consultation and age of onset, severity, frequency and duration of pain episodes, school absenteeism, sleep interruption and disruption of normal activity.[10,11,27] It is parents who take the children to see a doctor. Unlike younger children, teenagers are reluctant to discuss their bodily symptoms with the parents. Some of the parents may not be aware of these symptoms in their children. That may be a reason for lack of association between healthcare consultation and some symptoms. However, a symptom like vomiting and bloating are visible to the parents and readily recognized. They are also alarming symptoms, especially in teenage girls in reproductive age. So those with bloating and vomiting are more likely to be taken to a doctor. In addition, due to variation in the perception of symptoms, the impact on the quality of life is more likely to influence healthcare consultation than the exact severity. In agreement with this, we found significantly lower scores for school functioning and physical functioning domains of HRQoL in healthcare consulters than in nonconsulters.

HRQoL is an indicator of the impact of a disease on the life of an individual and an indirect indicator of the disease severity. In this study we evaluated the impact of AP-FGIDs on physical, social, emotional and school functions of teenagers. Thirteen to eighteen years of life is a period with rapid physical, social and emotional development, and also a critical period in school education. Undesirable effects during this period are likely to have significant impact on development of the affected children and future social, emotional and financial stability. Long term and recurrent nature of the symptoms of AP-FGIDs and significantly decreased HRQoL of affected children are likely to have long term negative effects on their life. In addition, our results indicate that approximately quarter of Sri Lankan children with AP-FGIDs has sought medical advice for their symptoms during previous 3 months. Considering the high prevalence of this disease, AP-FGIDs in Sri Lankan teenagers are a significant burden on the already over-stretched healthcare system of the country. This needs to be taken in to consideration by healthcare personals, especially those looking after children with AP-FGIDs. Prompt and effective management would not only decrease the suffering of the affected children, but also reduce the short term and long term impact of the disease on their life, their families, as well as the society.

The main strengths of the current study are inclusion of large number of teenagers and using standard and validated questionnaires for data collection. We believe that these have increased the reliability of our data. However, there were few limitations in this study. First, we did not investigate children to exclude organic causes for abdominal pain in the current questionnaire based survey. In a previous study we identified organic diseases in 10.9% of children with recurrent abdominal and nearly 89% had FGIDs.[28] Similar results have been reported from other countries as well.[19-31] The organic diseases observed in the previous Sri Lankan study were urinary tract infection, gastro-esophageal reflux disease, urinary calculi, antral gastritis, and intestinal amoebiasis.[28] Parasitic infestations such as giardiasis and amoebiasis have been considered to be possible mimickers of FGIDs; however, in that study, prevalence of these diseases was 1.8%, similar to several previous studies conducted in Sri Lanka.[32] Secondly, because this is self-administered questionnaire there may be some degree of recall bias. Thirdly, we assess healthcare consultation for abdominal pain not specifically for AP-FGIDs.

CONCLUSIONS

This study has assessed HRQoL and healthcare consultation in Sri Lankan teenagers aged 13 to 18 years with AP-FGIDs. Children with AP-FGIDs have significantly lower HRQoL scores for physical, emotional, social and school functioning. Approximately 28% of affected children have sought medical advice for their symptoms during previous 3 months. The main symptoms

associated with healthcare consultation were abdominal bloating and vomiting. The health-related quality of life was an important determinant of healthcare consultation, more than the severity of individual symptoms.

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PART III

ABDOMINAL PAIN PREDOMINANT FUNCTIONAL GASTROINTESTINAL DISORDERS AND GASTRIC MOTILITY

Chapter 8

Delayed gastric emptying rates and impaired antral motility in children fulfilling Rome III criteria for functional abdominal pain

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ABSTRACT

Background: Gastric sensorimotor dysfunctions have been implicated in the pathophysiology of some functional gastrointestinal disorders such as functional dyspepsia and irritable bowel syndrome**.** Therefore, we hypothesized that abnormal gastric emptying and impaired antral motility are possible underlying mechanisms of symptoms in children with functional abdominal pain (FAP).

Methods: Hundred and two children (37 [36.3%] males, 4-14 years, mean 7.8 years, SD 2.7 years) fulfilling Rome III criteria for FAP were recruited for this study. An age and sex compatible group of healthy children (n=20) were selected as controls (8 [40%] males, 4-14 years, mean 8.4 years, SD 3.0 years). Liquid gastric emptying rate (GER) and antral motility parameters (amplitude of antral contractions, frequency of antral contractions and antral motility index) were assessed using a previously reported ultrasound method.

Results: Average GER (42.1% vs. 66.2% in controls), amplitude of antral contractions (56.5% vs. 89.0%), frequency of contractions per 3 min (8.5 vs. 9.3) and antral motility index (4.9 vs. 8.3) were significantly lower in patients with FAP compared to controls (P<0.01). Fasting antral area was higher in patients (1.4 vs. 0.6, P<0.0001). GER negatively correlated with the scores obtained for severity of abdominal pain (r=-0.29, P=0.004).

Conclusions: GER and antral motility parameters were significantly impaired in patients with FAP and GER negatively correlated with symptom severity. These findings highlight the possible role of gastrointestinal motility abnormalities in the pathophysiology of childhood FAP.

INTRODUCTION

Recurrent or chronic abdominal pain is a global health problem affecting 10-12% of school aged children,[1-4] but only less than 25% of affected children have identifiable cause for their symptoms.[5] More than 75% of children with recurrent abdominal pain suffer from functional gastrointestinal disorders (FGIDs) of which functional abdominal pain (FAP) is the commonest.[5] In community based studies, FAP is seen in 3.0% of school aged children.[6]

Exact cause for pain is unclear in children with FGIDs. The typical periumbilical pain, present in the majority of children with FAP, is suggestive of visceral pain of gastrointestinal origin.[6] Putative pathophysiological mechanisms for the pain include enhanced visceral sensitivity and gastrointestinal motility abnormalities.[7] Gastrointestinal motility has been previously assessed in children and adults with FGIDs such as functional dyspepsia (FD) and irritable bowel syndrome (IBS). These studies have reported delayed gastric emptying for liquid and solids,[8,9,10] impaired proximal stomach accommodation,[11,12] abnormal antral motility[13] and wide gastric antrum during fasting period.[14]

In contrast to FD and IBS, FAP has received little attention from researchers. Due to this, very little is known regarding motility abnormalities and their clinical significance in children with FAP whose predominant symptom is abdominal pain. Therefore, this retrospective study was conducted with the aim of looking at the abnormalities in gastric emptying and antral motility in children with FAP and the relationship between gastric motility abnormalities and clinical symptoms.

MATERIALS AND METHODS

This is a retrospective study conducted in children referred to the Gastroenterology Research Laboratory, Faculty of Medicine, University of Kelaniya, during 5 year period from 1st January 2006 to 31st December 2010.

Ethical approval

This study protocol was approved by the Ethics Review Committee, Faculty of Medicine, University of Kelaniya, Sri Lanka.

Selection of patients

All children age 4 to 14 years who have undergone gastric motility assessments in Gastroenterology Research Laboratory for diagnostic purposes were screened. Children who fulfilled Rome III criteria for FAP[15] were selected and included in this study.

Rome III criteria for FAP are as follows.

Abdominal pain once per week for at least 2 months with all of the following features,

- Episodic or continuous abdominal pain
- Insufficient criteria for other functional gastrointestinal disorders
- No evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the subject's symptoms

Screening for organic disorders

All patients recruited had been screened for organic disorders using rigorous history and comprehensive physical examination (including growth parameters) to exclude any other plausible explanation for abdominal pain. Routine investigations done in all recruited patients to rule out organic disorders, included stool microscopy, urine microscopy and culture, full blood count, C-reactive protein, liver and renal function tests. Special investigations performed in some patients based on clinical judgment included ultrasound scanning of the abdomen (*n*=54), X-ray KUB (*n*=32), serum amylase (*n*=4), upper gastrointestinal endoscopy (*n*=4), lower gastrointestinal endoscopy (*n*=1) and barium enema (*n*=3).

Symptom severity

Severity of abdominal pain was graded as mild (1 – child is able to carry out regular activities during pain episodes), moderate (2 – child stops activities and sits down during pain episodes), severe (3 – child lies down during pain episodes) and very severe (4 – child cries or screams during pain episodes). The patients were followed up for a minimum of 6 months.

Exclusion criteria

- Clinical or laboratory evidence suggesting organic pathology
- Functional gastrointestinal disorders other than FAP
- Chronic medical or surgical disease other than FAP
- Long-term medication for any illness other than FAP
- Previous abdominal surgery involving gastrointestinal tract except appendectomy
- Fever, common cold, respiratory tract symptoms, gastroenteritis or any other systemic infection during the previous month
- Subjects receiving prokinetic drugs or any other drugs that can alter gastrointestinal motility during the previous month

Selection of controls

Twenty healthy children aged 4-14 years, without symptoms related to the gastrointestinal tract (e.g. abdominal pain, abdominal distension, constipation, diarrhea etc.), were recruited as controls after obtaining written consent from a parent. Eighteen of the controls were also included in a previous study published in 2008.[16]

Laboratory methods

Gastric emptying rate and antral motility were evaluated with real-time ultrasonography by using previously reported and validated method.[13] All subjects underwent measurement of gastric emptying by a high-resolution, real-time scanner with a 3.5MHz curve linear transducer. The same investigator (NMD) performed all ultrasound examinations.

Calculation of liquid gastric emptying rate

After an overnight fast, study subjects were examined seated in a chair leaning slightly backwards. The cross sectional area of antrum was calculated in the fasting stage and after drinking a standard liquid meal heated to approximately 40^0C within 2 min (200mL of chicken soup, 54.8kJ, 0.38g protein, 0.25g fat, 2.3g sugar per serving, Ajinomoto Co., Tokyo, Japan). The ultrasound probe was positioned vertically to permit simultaneous visualization of gastric antrum, superior mesenteric artery, abdominal aorta and the left lobe of liver (**Figure 8.1**). The area of gastric antrum was measured by tracing the mucosal side of the wall using the built-in caliper and calculation program of the ultrasound apparatus. Antral cross sectional area was measured at 1min and 15min after drinking the test meal. Gastric emptying rate was calculated as the percentage reduction of gastric antral cross sectional area at 15min following ingestion of the liquid meal.

$$\text{Gastric emptying rate (\%)} = \frac{\text{Antral area at 1min} - \text{Antral area at 15min}}{\text{Antral area at 1min}} \times 100$$

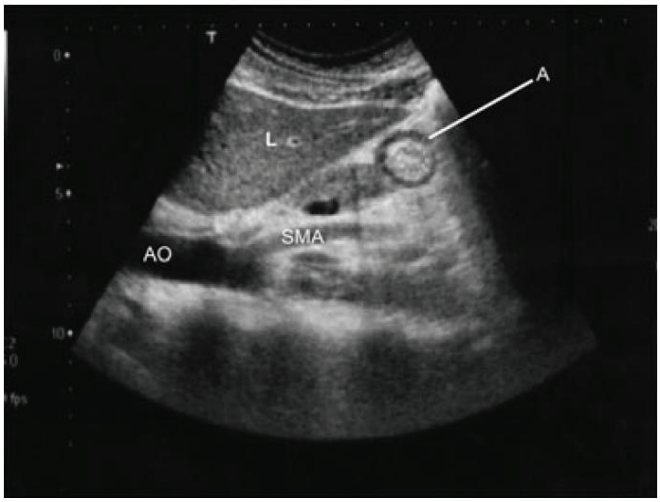

Figure 8.1 – Antral cross sectional area during fasting period

A – gastric antrum, AO – abdominal aorta, L – left lobe of the liver, SMA – superior mesenteric artery

Calculation of antral motility

These antral motility parameters were calculated within first 5 minutes after drinking the liquid meal. The minimum and maximum cross sectional areas of the antrum were measured during contractions and relaxations for at least 3 times to calculate the amplitude of antral contractions.

Antral motility parameters were calculated as follows:

Frequency of antral contractions = Number of contractions per 3 min

$$\text{Amplitude (\%)} = \frac{\text{Antral area at relaxation} - \text{Antral area at contraction}}{\text{Antral area at relaxation}} \times 100$$

Motility index = Amplitude of antral contraction X Frequency of contraction

Statistical analysis

The data were analyzed using EpiInfo (EpiInfo 6, version 6.04 (1996), Centers of Disease Control and Prevention, Atlanta, Georgia, USA and World Health Organization, Geneva, Switzerland). The statistical significance of differences of gastric motility parameters between the patient and control groups were assessed using Mann-Whitney U-test. Spearman correlation coefficient was used to assess the relationship between gastric emptying parameters and severity of abdominal pain.

RESULTS

Gastric motility data of 102 children with FAP (37 [36.3%] boys, age 4-14 years, mean 7.8 years, SD 2.7 years) and 20 healthy controls (8 [40%] boys, age 4-14 years, mean 8.4 years, SD 3.0 years) were analyzed. Abdominal pain characteristics of the study population are summarized in **Table 8.1**.

Table 8.1 – Abdominal pain characteristics in children with FAP

	Mean	Range	SD
Age at onset (years)	6.7	2.5-14.4	2.6
Duration of FAP (months)	12.9	2-72	14.9
Frequency of pain episodes (episodes/month)	30.1	4-240	34.4
Duration of a pain episode (hours)	1.31	0.05-24	4.2
Abdominal pain severity score	2.5	1-4	0.9

FAP=Functional abdominal pain

Gastric motility parameters of patients and controls

Children with FAP had significantly lower gastric emptying rate, frequency and amplitude of antral contractions and antral motility index. Furthermore, their fasting antral area was significantly higher than that of controls (**Table 8.2**).

Figure 8.2 shows the gastric emptying rates of patients and controls according to age. The majority (42 [55.3%]) of affected children had gastric emptying rates below the 10^{th} percentile of that of controls.

Furthermore, gastric emptying rate had a significant negative correlation (r= -0.29) with the scores obtained for severity of abdominal pain (**Table 8.3**).

Association between emotional stress and gastric motility

A total of 59 (57.8%) children have been exposed to at least one school and family related stressful life events during the previous 3 months. When patients with FAP who were exposed to stressful events were compared with those not exposed to such events, fasting antral area (1.5 cm^2 [SD 1.3 cm^2] vs. 1.2 cm^2 [SD 1.0 cm^2] in controls), mean gastric emptying rate (40.3% [SD 17.6%] vs. 44.5% [SD 15.6%]), mean amplitude of antral contractions (56.2% [SD 17.0%] vs. 56.9% [SD 17.0%]), frequency of antral contraction per 3 min (8.4 [SD 1.4] vs. 8.8 [SD 0.7])

and antral motility index (4.8 [SD 1.8] vs. 5.0 [SD 1.7]) were not significantly different between two groups (*P*>0.05, Mann-Whitney U test).

Table 8.3 – Correlation between abdominal pain characteristics and gastric emptying in children with FAP

Clinical parameter	Correlation coefficient*	95% confidence interval	*P* value
Frequency of abdominal pain (episodes/week)	-0.07	-0.258 to 0.129	0.506
Scores obtained for severity of abdominal pain	-0.29	-0.455 to -0.097	0.004
Average duration of a pain episode (min)	-0.03	-0.223 to 0.165	0.765
Duration of disease (months)	0.03	-0.164 to 0.224	0.757
Age at onset of the disease (years)	-0.05	-0.240 to 0.148	0.633

*Spearman's correlation coefficient

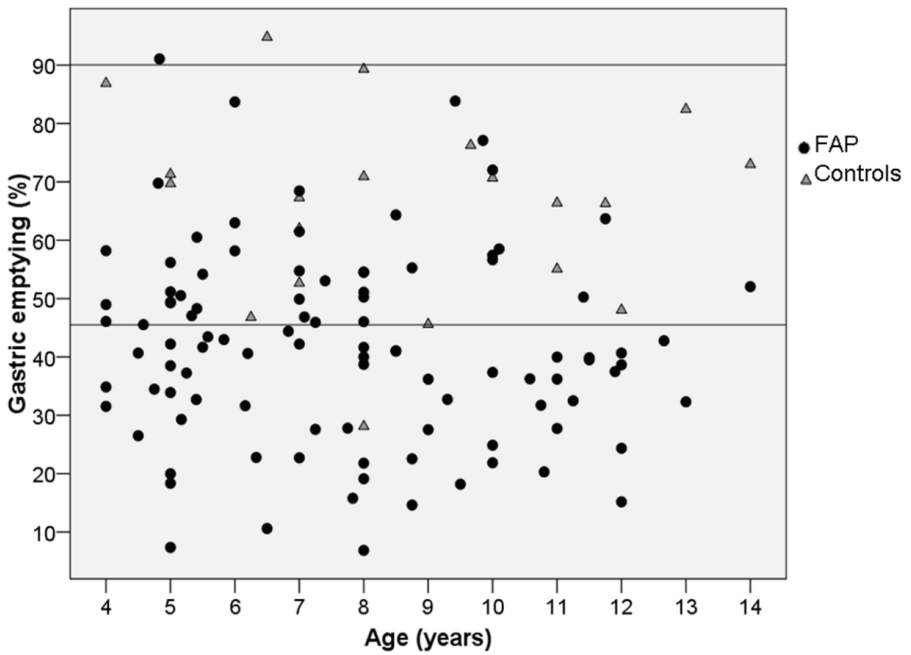

Figure 8.2 – Gastric emptying rates in patients and controls according to age

Reference lines are 10th and 90th percentiles of gastric emptying rates for healthy controls.

Table 8.2 – Gastric motility parameters in children with FAP and controls

Gastric motility parameter	Children with FAP		Healthy controls		
	Mean	SD	Mean	SD	*P*value*
Fasting antral area (cm^2)	1.4	1.2	0.6	1.0	<0.0001
Gastric emptying rate (%)	42.1	16.9	66.2	16.5	<0.0001
Amplitude of antral contractions (%)	56.5	16.9	89.0	10.1	<0.0001
Frequency of antral contraction (per 3 min)	8.5	1.2	9.3	0.8	0.004
Antral motility index	4.9	1.7	8.3	1.3	<0.0001

*Mann-Whitney U test

Table 8.4 – Correlation between gastric emptying rate and antral motility parameters

Antral motility parameter	Children with FAP		Healthy controls		Total	
	Correlation coefficient*	*P*value	Correlation coefficient*	*P*value	Correlation coefficient*	*P*value
Fasting antral area	-0.204	0.04	-0.236	0.317	-0.279	0.002
Amplitude of antral contraction	0.322	0.001	0.613	0.004	0.529	<0.0001
Frequency of antral contractions	0.292	0.003	0.342	0.140	0.364	<0.0001
Antral motility index	0.394	<0.0001	0.597	0.005	0.579	<0.0001

* Spearman's correlation coefficient

Correlation between gastric emptying rate and antral motility parameters

Table 8.4 demonstrates the relationship between gastric emptying rate and other antral motility parameters. In both patients and controls, gastric emptying rate had a significant correlation with other antral motility parameters.

DISCUSSION

This study describes, for the first time, gastric motility in children fulfilling the Rome III criteria for FAP. These children have significantly lower gastric emptying rate, lower frequency and amplitude of antral contractions and antral motility index than healthy controls. Furthermore, they had a significantly wider gastric antrum during fasting period. Gastric emptying rate reveals a negative correlation with the scores obtained for the severity of abdominal pain.

Several studies have reported abnormalities in gastric motility and prolonged gastric emptying among children with FD.[8,9,17] Furthermore, adult studies have also reported delayed gastric emptying and antral hypomotility in patients with abdominal pain predominant FGIDs such as FD and IBS.[12,18,19] Unlike FD, studies assessing gastric motility in children with FAP were almost non-existing. A previous study has reported significantly prolonged gastric emptying rate and antral motility index in children with non-organic recurrent abdominal pain.[16] In that study, the majority of children recruited had FAP. However, no subgroup analysis was performed to identify the relationship between gastric emptying parameters and the exact type of FGIDs. During the current study we have found delayed gastric emptying, decreased frequency and amplitude of antral contractions and increased fasting antral area, highlighting the gastric motility abnormalities present in children with FAP.

In our study, gastric emptying rate showed a significant negative correlation with the scores obtained for severity of symptoms. The relationship between gastric motility abnormalities and symptoms is not fully understood in patients with functional gastrointestinal disorders. While some adult studies conducted in patients with abdominal pain predominant FGIDs have failed to demonstrate a definite relationship between symptoms severity and motility abnormalities,[20,21] other studies have shown an association between delayed gastric emptying and bloating,[22] early satiety,[22] postprandial fullness,[23,24] nausea[23,24] and vomiting.[2,24] Lack of relationship between severity of clinical features and motility abnormalities has cast a doubt regarding the pathophysiological association between gastric motility and FGIDs. In this backdrop, the present study has shown a significant correlation between severity of abdominal pain and delayed gastric emptying. This relationship between clinical and physiological parameters suggests the

possibility of delayed gastric emptying playing a role in the pathogenesis of FAP in children. It is possible that delayed gastric emptying associated with poor antral contractions, leads to prolonged gastric stasis and antro-fundic dyscoordination resulting in increased wall tension in the gastric body and the fundus. This in turn may activate tension and pain receptors in the stomach to generate the characteristic periumbilical pain present in children with FAP. Furthermore, heightened visceral sensitivity in these children may also contribute to enhanced pain perception.[25,26]

Dysfunction at variety of levels of brain-gut axis has been invoked in the pathophysiology of FGIDs. Children with FGIDs are exposed to significantly more stressful events than healthy children.[1,27] Central dysfunction of brain-gut axis due to emotional stress is suggested as a precipitant of FGIDs and a cause of abnormal gastrointestinal motility.[25] Acute and chronic physical stressors, such as labyrinthine stimulation and cold pain have produced a dramatic inhibition of gastric emptying and antral motility.[28-30] In contrast to this, a previous study failed to demonstrate a significant difference in gastrointestinal motility in healthy volunteers exposed to psychological stress.[31] A pediatric study in children with recurrent abdominal pain also failed to show a significant association between exposure to stressful life events and gastric motility.[16] Similarly, we did not find a significant difference in gastric motility parameters and antral motility index between children exposed to stressful life events and those did not expose to such events in the present study.

Motility of the gastric antrum plays a pivotal role in propelling gastric contents in to the duodenum through the pylorus. Therefore, poor emptying is expected when there is impaired antral motility. Gastric emptying rate in our patients with FAP showed significant correlation with antral motility parameters. The delayed gastric emptying observed in the majority of our patients with FAP appears to be due to decreased contractile activity of the gastric antrum. Similar finding has been reported in children with recurrent abdominal pain.[16] In contrast to this, a previous adult study involving small number (n=15) of healthy volunteers have reported a significant correlation between antral motility and solid emptying, but failed show such definite association with liquid emptying.[32] However, in this study, test meal consisted of both liquids and solids, therefore, both liquid and solid emptying were assessed at the same time and the methodology of assessing gastric emptying and antral motility were different. However, in this study, a positive relationship between liquid emptying and antral motility was noted after the end of the initial lag phase for the solids.[32] The exact relationship between gastric emptying and antral motility has not been studied in children and adults with FGIDs previously.

Therefore, further studies are needed to clarify the role of abnormal antral motility in functional gastrointestinal diseases in children.

Even though delayed gastric emptying is a common finding in patients with abdominal pain-predominant FGIDs, very few studies have assessed the therapeutic value of gastro-prokinetic drugs in the management. In a previous double-blind placebo controlled trial, domperidone not only improved gastric emptying time and relieved symptoms in patients with functional dyspepsia.[10] In contrast to this, several, double-blind placebo-controlled trials on cisapride and mosapride have failed to show significant therapeutic value.[33,34] All these therapeutic trials have been conducted in adult patients with functional dyspepsia where the pathophysiology is thought to be multifactorial and the relationship between symptom severity and motility abnormalities are not clear.[35] In contrast to this, the correlation between severity of abdominal pain and delayed gastric emptying observed in our study lays a ground to investigate the therapeutic value of gastroprokinetics in the management of children with FAP.

In this study, using a simple, safe and non-invasive ultrasound method, we have shown a significant delay in gastric emptying and impairment in antral motility in children who fulfill Rome III criteria for FAP. Furthermore, we have highlighted the relationship between delayed gastric emptying and severity of abdominal pain. In this light, our findings suggest that delayed gastric emptying and impaired antral motility play a role in the pathogenesis of FAP.

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Chapter 9

Ultrasonographic assessment of liquid gastric emptying and antral motility according to the subtypes of irritable bowel syndrome in children

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ABSTRACT

Objectives: Gastric motor abnormalities have been reported in adults with irritable bowel syndrome (IBS), commonly in constipation predominant IBS (IBS-C). However, such studies are uncommon in children. Furthermore, differences of gastric motility have not been studied in children with different IBS subtypes.

Methods: Seventy six children (33 [43%] males, age 4-14 years, mean 7.9 years, SD 3.0 years) fulfilling Rome III criteria for IBS and 20 healthy controls [8 (40%) males, age 4-14 years, mean 8.4 years, SD 3.0 years] were recruited (diarrhea predominant IBS [IBS-D]=21, IBS-C=31, mixed IBS [IBS-M]=19 and unsubtyped IBS [IBS-U]=5). Liquid gastric emptying rate (GER) and antral motility were assessed using an ultrasound method.

Results: Average GER (43.8% vs. 66.2% in controls), amplitude of antral contractions (A) (56.4% vs. 89.0%), and antral motility index (MI) (5.1 vs. 8.3) were lower and fasting antral area (FA) (1.6 vs. 0.6) was higher in patients with IBS (P<0.0001). Frequency of antral contractions (F) (8.9 vs. 9.3) did not show a significant difference. Patients exposed to stressful events had a significantly lower GER, compared to those not exposed to such events (P=0.03). Gastric motility parameters had no correlation with severity of symptoms.

GER (42.6%, 46.3%, 39.6%), FA (1.4cm^2, 1.8 cm^2, 1.8 cm^2), A (53%, 58.9%, 51.8%), F (8.7, 8.9, 9.2) and MI (4.7, 5.3, 4.8) were not different between IBS-D, IBS-C and IBS-M (P>0.05).

Conclusions: GER and antral motility parameters were significantly impaired in children with IBS compared to controls. GER and antral motility parameters were not different between IBS subtypes.

INTRODUCTION

Irritable bowel syndrome (IBS) in children is characterized by chronic abdominal pain relieved by defecation, and/or associated with changing frequency and/or form of stools.[1] Prevalence of IBS varies from 5-14% in pediatric age groups in the western world and Asia.[2-5]

The current understanding of pathophysiology of IBS is based on studies conducted in adults. Pediatric studies assessing pathophysiological mechanisms in IBS are rare. Gastric motor abnormalities such as delayed gastric emptying have been reported in adult patients with IBS.[6-10] However, some of these studies have reported such abnormalities only in patients with constipation predominant IBS[8] and those with dyspepsia.[7] This led to the belief that gastric motility abnormalities in IBS occur as a result of activated colo-gastric reflex and/or concurrent functional dyspepsia. Lack of correlation with symptoms[9] has further diminished the importance of gastric motor abnormalities in pathogenesis of this condition. In contrast to adults however, the predominant symptom in children with IBS is abdominal pain.[12] Abnormalities of gastric motility such as antral hypomotility and delayed gastric emptying have been reported in several pediatric disorders, in which the predominant symptom is abdominal pain (e.g. functional dyspepsia [FD],[12,13] functional abdominal pain[14] and recurrent abdominal pain of functional origin[15]). In several of these studies, there was a significant correlation between symptom severity and reduction in gastric emptying, indicating a possible pathophysiological role. Detailed studies on gastric motility and its relationship with symptoms are not available in children with IBS. Furthermore, differences in gastric motility in different IBS subtypes (constipation predominant [IBS-C], diarrhea predominant [IBS-D], mixed [IBS-M] and unsubtyped [IBS-U] IBS) have not been studied previously.

Exploration of pathogenesis of IBS is of utmost importance in order to define treatment strategies for this common and troublesome disease condition in children. In this study, we studied gastric emptying and antral motility abnormalities in children with IBS and assessed their relationship with IBS subtypes and symptoms.

MATERIALS AND METHODS

Patients

Between January 2007 and December 2011, children referred to the gastroenterology research laboratory of a tertiary care hospital in Sri Lanka, and fulfilling the Rome III criteria for IBS were included in this study. All of them had been screened for organic diseases using history, physical examination, complete blood count, C-reactive protein, liver and renal function tests, urine microscopy and culture and stool microscopy. Specific investigations performed in some

patients based on clinical judgment included abdominal ultrasound (*n*=23), barium contrast studies (*n*=3), lower gastrointestinal endoscopy (*n*=4), upper gastrointestinal endoscopy (*n*=1) and X-ray KUB (*n*=5). None had clinical or laboratory evidence of organic diseases. In this study, IBS was diagnosed using standard Rome III criteria for children and adolescents.[1] Furthermore, demographic data, pain severity and exposure to emotional stress were recorded. A parent or a legally accepted guardian had given informed consent to carry out gastric motility studies.

Rome III criteria for IBS[1]

Abdominal discomfort or pain that occurs at least once per week for more than two months, and associated with at least two of the following three features for at least 25% of the time;

- abdominal pain improved with defecation
- onset associated with change in stool frequency
- onset associated with a change in consistency of stools.

Recruited children were divided in to IBS subtypes as follows,[16]

- Constipation predominant IBS - hard or lumpy stools $\geq$ 25% and loose (mushy) or watery stools < 25% of bowel movements
- Diarrhea predominant IBS - loose (mushy) stools or watery stools $\geq$ 25% and hard or lumpy stools < 25% of bowel movements
- Mixed IBS – hard or lumpy $\geq$ 25% and loose (mushy) or watery stools $\geq$ 25% of bowel movements
- Unsubtyped IBS – insufficient abnormality of stool consistency to meet criteria for IBS-C, IBS-D or IBS-M.

Severity of symptoms was recorded using a four point scale.

1- child is able to carry out regular activities during pain episodes
2- child stops all activities and sits down during pain episodes
3- child lies down during pain episodes
4- child cries or screams during pain episodes

Selection of controls

Twenty healthy children age 4-14 years without gastrointestinal symptoms were recruited as controls. Written consent has been obtained from parent or guardian of all controls. These controls were also described in a previous study.[14]

Assessment of gastric emptying and antral motility

The main gastric motility parameters assessed in the current study were gastric emptying rate and antral motility (frequency of antral contractions, amplitude of antral contractions and antral motility index). Gastric motility was assessed using a previously reported non-invasive, ultrasound method.[17,18] All assessments were performed using a real-time ultrasound scanner with a 3.5 MHz curve linear transducer (SD-550, Aloka, Tokyo, Japan). All motility assessments were performed between 8.30am and 9.00 am. The ultrasound probe was positioned vertically on the anterior abdomen to permit simultaneous visualization of the antrum, left lobe of liver, superior mesenteric artery and abdominal aorta. The gastric antral area was measured using the built in caliper and tracing the mucosal side of the wall. For the assessment of gastric emptying, antral cross sectional area was measured during fasting period and during 1 min and 15 min after drinking a test meal (200 mL of chicken soup, 54.8 kJ, 0.38 g protein, 0.25 g fat, 2.3 g sugar per serving, heated to approximately 40°C, consumed with in 2min) (**Figure 9.1**). For assessment of amplitude of antral contractions, the antral area was measured during three consecutive contractions and relaxations. The frequency of antral contractions was calculated for a period of 3 min. Antral motility parameters were calculated within the first 5 min after the meal.[17,18] The same experienced investigator performed all ultrasound examinations.

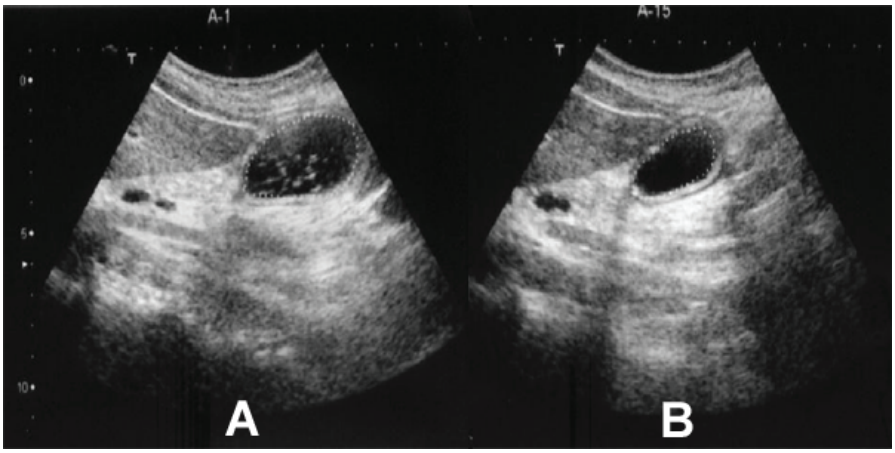

Figure 8.1 – Ultrasound assessment of gastric emptying rate

A – antral cross sectional area at 1 min, B – antral cross sectional area at 15min

Gastric emptying and antral motility were calculated as follows:

- Gastric emptying = [Antral area at 1 min - Antral area at 15 min] / Antral area at 1min X100
- Frequency of antral contractions = Number of contractions per 3min

- Amplitude of contractions = [Antral area at relaxation – Antral area at contraction] /Antral area at relaxation X 100
- Motility index = [Amplitude of antral contraction X Frequency of contraction]/100

Statistical analysis

Gastric motility parameters of patients and controls and between IBS subtypes were compared using the Mann–Whitney U-test. Gastric motility parameters and symptom scores were correlated using Spearman Correlation Coefficient. A *P* value of 0.05 or less was considered statistically significant.

Ethical approval

The ethical approval was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Kelaniya, Sri Lanka.

RESULTS

Seventy six children fulfilling the Rome III criteria for IBS (33 [43%] males, age 4-14 years, mean 7.9 years, SD 3.0 years) were included in this study. They were categorized into IBS-D (*n*=21), IBS-C (*n*=31), IBS-M (*n*=19) and IBS-U (*n*=5) according to Rome III criteria. Twenty healthy children (8 [40%] males, age 4-14 years, mean 8.4 years, SD 3.0 years) were recruited from the same area as controls.

Gastric motility parameters in patients and controls

Table 9.1 demonstrates the gastric motility parameters in children with IBS and controls. Gastric emptying rate and antral motility index were significantly impaired in children with IBS compared to controls. No significant difference observed in gastric motility parameters between different IBS subtypes.

Relationship between gastric motility parameters and symptoms

Table 9.2 shows the correlation between motility parameters and severity of symptoms. No significant correlation observed between severity of symptoms and motility parameters.

Gastric emptying rate in IBS patients with nausea (*n*=20, 26.3%) and those without nausea were respectively 40.4% and 45.1% (*P*=0.21, unpaired t test). There was no significant difference in gastric motility parameters in patients with IBS who had dyspepsia (*n*=12, 15.8%), compared to those without dyspepsia (**Table 9.3**).

Table 9.1 – Gastric motility in children with IBS and healthy controls

	IBS-D (*n*=21) *Mean (SD)*	IBS-C (*n*=31) *Mean (SD)*	IBS-M (*n*=19) Mean *(SD)*	IBS-U (*n*=5) *Mean (SD)*	IBS-total (*n*=76) *Mean (SD)*	Controls (*n*=20) *Mean (SD)*	IBS-total vs. controls *P value**
Fasting antral area (cm^2)	1.4 (1.0)	1.8 (1.5)	1.8 (1.0)	0.9 (0.7)	1.6 (1.2)	0.6 (1.0)	<0.0001
Gastric emptying rate (%)	42.6 (14.6)	46.3 (12.6)	39.6 (16.4)	50.5 (14.5)	43.8 (14.4)	66.2 (16.5)	<0.0001
Amplitude of antral contractions (%)	53.0 (14.0)	58.9 (18.7)	51.8 (11.5)	72.9 (14.5)	56.4 (16.3)	89.0 (10.1)	<0.0001
Frequency of antral contractions (/3min)	8.7 (1.0)	8.9 (1.4)	9.2 (1.0)	8.4 (1.5)	8.9 (1.2)	9.3 (0.8)	0.159
Antral motility index	4.7 (1.5)	5.3 (2.1)	4.8 (1.2)	6.0 (0.5)	5.1 (1.7)	8.3 (1.3)	<0.0001

* Mann Whitney U test

Table 9.2 – Relationship between gastric motility parameters and severity of symptoms

	Correlation*	*P* value
Fasting antral area (cm^2)	0.041	0.73
Gastric emptying rate (%)	0.086	0.46
Amplitude of antral contractions (%)	-0.107	0.36
Frequency of antral contractions (/3min)	-0.096	0.42
Antral motility index	-0.174	0.13

*Spearman correlation coefficient

Table 9.3 – Association between dyspepsia and gastric motility in children with IBS

	Dyspepsia present ***(n=12)*** **mean (SD)**	**Dyspepsia absent** ***(n=68)*** **mean (SD)**
Fasting antral area (cm^2)	1.6 (1.1)	1.6 (1.3)
Gastric emptying rate (%)	43.2 (8.9)	44.0 (15.2)
Amplitude of antral contractions (%)	55.8 (11.3)	56.5 (17.1)
Frequency of antral contractions (/3min)	8.7 (1.2)	8.9 (1.2)
Antral motility index	4.8 (1.2)	5.1 (1.8)

P>0.05 for all comparisons between two groups, Mann Whitney U test

Association between gastric motility and exposure to stressful events

Fifty children with IBS (65.6%) and 6 controls (30%) were exposed to at least one family or school related stressful life events during previous 3 months. The common stressful life events recognized by the children with IBS were preparation for the grade 5 scholarship examination (*n*=18), father or mother working abroad (*n*=14), disharmony in the family and frequent domestic fights (*n*=13), hospitalization of the child him/herself for other illness (*n*=10) and frequent punishment at school (*n*=10). Gastric motility parameters in children exposed to stressful events and not exposed to such events are shown in **Table 9.4**. Children with IBS exposed to stressful life events had significantly delayed gastric emptying compared to those not exposed to such event.

Table 9.4 – Association between exposure to stressful life events and gastric motility in children with IBS

	Exposed to stressful events *(n=50)* mean (SD)	Not exposed to stressful events *(n=26)* mean (SD)
Fasting antral area (cm^2)	1.8 (1.6)	1.5 (1.0)
Gastric emptying rate (%)	40.3 (16.9)*	45.7 (12.6)
Amplitude of antral contractions (%)	56.1 (16.7)	56.6 (16.1)
Frequency of antral contractions (/3min)	8.8 (1.7)	8.9 (0.9)
Antral motility index	4.9 (1.8)	5.1 (1.7)

*P=0.029, Mann Whitney U test

DISCUSSION

For the first time, this study has compared gastric motility in all four subtypes of irritable bowel syndrome in children. In this study we found significantly lower gastric emptying and antral motility in all four subtypes of IBS compared to controls. There was no difference in gastric emptying rate and antral motility parameters between IBS subtypes. Children with IBS, who were exposed to recent stressful life events, had a significantly lower gastric emptying rate.

We have used a simple, safe and non-invasive ultrasound method to measure liquid gastric emptying which has been previously used in children with functional gastrointestinal disorders. In addition, ultrasound methods of assessing gastric emptying have shown a good interobserver agreement,[19] and closely correlate with scintigraphic assessment of gastric emptying which is considered as the gold standard.[20] Liquid gastric emptying is reported to be abnormal in patients who have normal gastric emptying for solids, and is considered to be more sensitive to detect gastroparesis in non-diabetic patients.[21-23] Furthermore this method allows us to measure the antral motility and the fasting antral area which are also important parameters of gastric motor function.

This study showed that liquid gastric emptying measured in a cohort of children with IBS was significantly lower than that of healthy controls. Even though, there are no previously published studies assessing gastric motility in children with IBS, delayed gastric emptying have been

reported in children with other abdominal pain predominant disorders such as functional dyspepsia (FD),[12,13] functional abdominal pain[14] and recurrent abdominal pain of functional origin.[15] Previous studies conducted in adult patients with IBS have reported contradicting results. While several studies have shown significantly delayed gastric emptying in patients with IBS compared to controls,[6-10] another study has failed to demonstrate such a difference.[24] Small sample size of the latter study might have contributed to this lack of difference. .

In addition to gastric emptying, antral motility parameters (both frequency and amplitude of contraction) were also significantly lower in children with IBS in this study. Even though not reported in children with IBS, impaired antral motility is a common feature in both children and adults with functional dyspepsia,[17] functional abdominal pain[14] and recurrent abdominal pain.[15] Impaired antral motility is probably the main contributor for delayed gastric emptying observed in children with abdominal pain predominant functional gastrointestinal diseases. A previous study has reported a significant correlation between gastric emptying rate and antral motility index in children with FAP.[14]

In this study we found a higher antral area during fasting period in children with IBS. A similar result has been reported in functional abdominal pain[14] and functional dyspepsia.[25] However, a previous study conducted in adult patients with IBS failed to demonstrate a significant difference in fasting antral size.[6] A wide gastric antrum found upon ultrasonography correlates with the amount of liquid retained in the stomach.[26] Indeed children with IBS in this study retain more liquids during fasting period. An exact reason for this phenomenon is not clear, but this may possibly be due to ineffective migrating motor complexes causing poor gastric clearance and accumulation of gastric secretions in the distal stomach. In agreement with this, a previous study has reported abnormalities in small intestinal migrating motor complexes in children with recurrent abdominal pain.[27]

For the first time, we compared gastric motility in children with different IBS subtypes. Children with all four subtypes of IBS had impaired gastric emptying rates and antral motility parameters compared to controls, and there was no significant difference between different IBS subtypes. Similarly, Neilsen and colleagues did not find a significant difference in gastric emptying times in adult patients with IBS-D and IBS-C,[24] even though patients with IBS-D had faster small intestinal transit than those with IBS-C. Similarly, another adult study using Rome II criteria has reported delayed gastric emptying in 26% of IBS-C, 21% of IBS-D and 18% in IBS with alternating bowel habits (IBS-M).[7] In contrast to these, a previous study using radio-labeled technetium-99m demonstrated a significantly lower gastric emptying for solids in adults with

IBS-C than in IBS-D. However, in this study gastric emptying for liquids and indigestible solids were similar in both sub-groups[8] which is compatible with our results.

We did not observe a significant correlation between gastric motility parameters and severity of symptoms. Similar results have been reported in adult patients with IBS.[9] However, two previous studies conducted in Sri Lankan children with recurrent abdominal pain[15] and functional abdominal pain,[14] have reported significant negative correlations between severity of abdominal pain and gastric emptying rate. In contrast to previous studies, where the majority of subjects suffer from abdominal pain only, children with IBS recruited in the current study had symptoms related to defecation. Therefore, symptoms may not be completely of gastric origin, but also related to lower gastrointestinal tract. This may be the reason for lack of correlation between gastric motility and symptom severity.

The exact cause for decreased gastric motility in children with IBS is not clear. Presence of concurrent functional dyspepsia is commonly suggested as a possible reason for abnormal gastric motility observed in patients with IBS. However, the relationship between dyspeptic symptoms and delayed gastric emptying in patients with IBS is controversial. Stanghellini *et al.* reported a significant association between delayed gastric emptying and overlapping postprandial fullness and nausea,[7] while Portincasa *et al.* failed to find such an association.[6] Unlike adult patients with IBS, only 15.8% children recruited in this study had dyspeptic symptoms including epigastric pain, epigastric fullness, bloating and early satiety. Furthermore, in contrast to previous adult studies, we did not observe a significant difference in gastric motility parameters in IBS patients with dyspepsia compared to those without dyspepsia.

In addition, activation of colo-gastric reflex has been suggested as a possible reason for delayed gastric emptying in patient with IBS, since several adult studies have reported delayed gastric emptying in patients with chronic constipation and constipation associated IBS.[8,28,29] Another study, conducted in adult patients with dyspepsia, has demonstrated delayed gastric emptying in most patients with overlapping constipation and also a significant improvement in gastric emptying following administration of osmotic laxatives.[30] However, in contrast to those previous studies, decreased gastric emptying and antral motility observed in our patients with IBS are unlikely to be due to constipation and colo-gastric reflex since those with IBS-D,IBS-M and IBS-U also had similar gastric motility abnormalities to that of those with IBS-C. Therefore, the gastric motor abnormalities present in children with IBS seem to be of more complex in origin than previously believed and future studies are needed to explore these pathophysiological mechanisms.

Irritable bowel syndrome and other FGIDs in children are frequently associated with psychological factors. Several studies in children with abdominal pain have reported higher prevalence of recurrent abdominal pain, abdominal pain predominant FGIDs and constipation in those exposed to stressful life events.[5,31-33] It has been postulated that, in genetically vulnerable individuals, sustained stress can result in persistent increase in responsiveness of central stress circuits. This predisposes such individuals to develop functional gastrointestinal diseases. Emotional stress is important in altering brain-gut interactions resulting in development and exacerbation of IBS symptoms.[34] Emotional stress can significantly influence gut motility,[35] secretion and mucosal immunological functions,[36] through the brain-gut axis. However the association between emotional stress and gastric motility has not been studied in children with IBS. Previous studies conducted in children with FAP and recurrent abdominal pain, have failed to demonstrate an association between exposure to stressful events and gastrointestinal motility.[14,15] In this study, the majority of children with IBS were exposed to at least one stressful event during previous 3 months. For the first time, we found a significantly lower gastric emptying in children with IBS, who were exposed to stressful life events. Our findings give evidence on the influence of psychological factors on gastric motility through the brain-gut axis.

In conclusion, the gastric emptying rate and antral motility parameters were significantly impaired in Sri Lankan children with IBS. Furthermore, children with all four IBS subtypes had delayed gastric emptying and impaired antral motility. However, we failed to demonstrate a clear relationship between symptoms and motility abnormalities. Children exposed to recent stressful life events had a significantly lower gastric emptying rate compared to those not exposed to such events, suggesting the possibility of altered brain-gut interactions in the pathogenesis of IBS. The therapeutic value of psychotherapies, which target on reducing stress and anxiety, and gastro-prokinetic drugs, which improve of gastric motility, are needed to be explored further in management of IBS.

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Chapter 10

Gastric emptying and antral motility parameters in children with functional dyspepsia: association with symptom severity

This chapter of the thesis was published as

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ABSTRACT

Background and aims: Functional dyspepsia (FD) is an important gastrointestinal problem with obscure aetiology. Abnormal gastric motility is suggested as a possible pathophysiological mechanism for symptoms. The main objective of this study was to assess gastric motility in Sri Lankan children with FD.

Methods: Forty one children (19 [46.3%] males, age 4-14 years, mean 7.5 years, SD 2.6 years) referred to the Gastroenterology Research Laboratory, Faculty of Medicine, University of Kelaniya, from January 2007 to December 2011, were screened. Those fulfilling Rome III criteria for FD were recruited. None had clinical or laboratory evidence of organic disorders. Twenty healthy children were recruited as controls (8 [40] males, age 4-14 years, mean 8.4 years, SD 3.0 years). Liquid gastric emptying rate (GE) and antral motility parameters were assessed using an ultrasound-based method.

Results: Average GE (45.6 vs. 66.2% in controls), amplitude of antral contractions (58.2% vs. 89.0%) and antral motility index (5.1 vs. 8.3) were lower and fasting antral area (1.5cm^2 vs. 0.6cm^2) was higher in patients with FD (P<0.01). Frequency of antral contractions (8.8 vs. 9.3) did not show a significant difference (P=0.07). Scores obtained for severity of abdominal pain negatively correlated with GE (r=-0.35, P=0.025). Children with FD, exposed to stressful events had higher fasting antral area (1.9cm^2) than those not exposed to stress (1.0cm^2) (P=0.02).

Conclusions: GE and antral motility parameters were significantly impaired in children with FD compared to controls. GE negatively correlated with severity of symptoms. This study points to disturbances in gastric motility as an aetiological factor for FD.

INTRODUCTION

Dyspepsia (epigastric pain, epigastric burning, postprandial fullness and early satiation) is a common gastrointestinal symptom in children. It was initially thought that the majority of children with dyspeptic symptoms were suffering from gastroduodenal inflammation. However, previous hospital based studies have shown gastroduodenal ulceration and *Helicobacter pylori* infection in only a minority of children with dyspepsia.[1] Subsequent studies have demonstrated that the majority of children suffering from dyspeptic symptoms have functional dyspepsia (FD).[2,3] Prevalence of FD in children and adolescents around the world varies from 0.3%- 7.1%.[4, 5] In Sri Lankan children, a prevalence of 2.5-3.5% has been noted in previous studies.[6, 7]

The pathophysiology of FD is often unknown. Visceral hypersensitivity, gastrointestinal motility abnormalities, such as abnormal meal induced gastric accommodation,[8,9] abnormal electrogastrography,[10, 11] abnormal gastroduodenal manometry,[12, 13] and modulation of the gut immune system have been suggested as possible pathophysiological mechanisms for this condition.[14, 15] Gastric emptying rates of solids and liquids have also been studied in the past as potential pathophysiological mechanism of FD. Two studies have shown delayed liquid gastric emptying in children with FD[11, 16] and two more studies have found abnormalities in solid gastric emptying.[17, 18] However, these studies included only a small number of children and no correlation was found between symptom severity and motility parameters.

Ultrasonography has been widely used to assess gastric emptying rates and shown to have a good correlation with that measured by radionuclear scintigraphy, the "gold standard".[19] In addition, liquid gastric emptying has been shown to be sensitive to detect abnormalities of gastric emptying in otherwise healthy individuals.[20,21] Previous Sri Lankan studies, using ultrasound techniques, have reported gastric motility abnormalities in children with other abdominal pain predominant functional gastrointestinal disorders (FGIDs) such as functional abdominal pain and irritable bowel syndrome.[22, 23] In some of these studies gastrointestinal motility abnormalities correlated with severity of symptoms.[22] However, gastrointestinal motility has not been assessed in Sri Lankan children with FD.

Therefore, the aims of this study were to

a) assess liquid gastric emptying of children with FD using a non-invasive ultrasound method

b) assess the relationship between gastric emptying and symptoms of FD

and

c) study the effects of psychological stress on gastric emptying in children with FD.

METHODS

Study subjects

Selection of patients

Forty one consecutive children with FD were selected from patients referred to the Gastroenterology Research Laboratory, University of Kelaniya, Sri Lanka, from 1st January 2007 to 31st December 2011. A parent or guardian had given informed consent to conduct gastric motility studies.

Selection of controls

Twenty healthy children aged 4-14 years without gastrointestinal symptoms were recruited as controls after obtaining written consent from a parent or guardian.

Study protocol

In this study, FD was diagnosed using Rome III criteria for children and adolescents.[21] The demographic data, symptom characteristics and exposure to stressful life events were recorded in a data sheet.

Rome III diagnostic criteria for FD

Must include **all** of the following:

1. Persistent or recurrent pain or discomfort centred in the upper abdomen (above the umbilicus)
2. Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel syndrome)
3. No evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the subject's symptoms

Above criteria need to be fulfilled at least once a week, for at least 2 months, prior to making the diagnosis.

Screening of patients for organic disorders

All recruited children with FD had been investigated for organic diseases (using history, physical examination and investigations). Routine investigations performed in all patients included complete blood count, C-reactive protein, liver and renal function tests, urine microscopy with culture and stool microscopy. Specific investigations performed in some patients included ultrasound scanning of the abdomen (n=22), barium contrast studies (n=8), upper gastrointestinal endoscopy (n=18), serum amylase (n=7), Screening for *Helicobacter*

pylori infection *(n=5)* and abdominal X-ray kidney, ureter, bladder (*n*=3). None of the recruited patients had clinical or laboratory evidence of an organic disease.

Assessment of gastric motility

Gastric motility was assessed using a previously reported ultrasound method.[24] Main motility parameters assessed were antral area during fasting period, gastric emptying rate, frequency of antral contractions, amplitude of antral contractions and antral motility index.

All gastric motility assessments were performed using a real-time ultrasound scanner with a 3.5 MHz curve linear transducers (SD-550, Aloka, Tokyo, Japan). All motility assessments were started at 9.00am in the morning. The ultrasound probe was positioned vertically to permit simultaneous visualization of the gastric antrum, left lobe of liver, superior mesenteric artery and abdominal aorta. The area of gastric antrum was measured tracing the mucosal side of the wall.

For the assessment of gastric emptying, antral cross sectional area was measured at fasting, 1 min and 15 min after drinking the test meal (200 mL of chicken soup, 54.8 kJ, 0.38 g protein, 0.25 g fat, 2.3 g sugar per serving, heated to approximately 40°C). The test meal was consumed within 2 minutes. For the assessment of amplitude of antral contractions, the antral area was measured during consecutive contraction and relaxation for a minimum of three times **(Figure 10.1).** The number of antral contractions was calculated for a period of 3 minutes. Antral motility parameters were calculated within the first 5 min after the meal. The same investigator performed all ultrasound examinations.

Gastric emptying and antral motility were calculated as follows;

1) Gastric emptying = [Antral area at 1 min - Antral area at 15 min] / Antral area at 1min X 100
2) Frequency of antral contractions = Number of contractions per 3min,
3) Amplitude of contractions = [Antral area at relaxation – Antral area at contraction] /Antral area at relaxation X 100
4) Motility index = [Amplitude of antral contraction X Frequency of contraction]/100

Statistical analysis

The gastric motility parameters of patient and control groups were compared using the Mann–Whitney U-test. Gastric motility parameters and symptom scores were correlated using Spearman Correlation Coefficient. A *P* value of 0.05 or less was considered statistically significant.

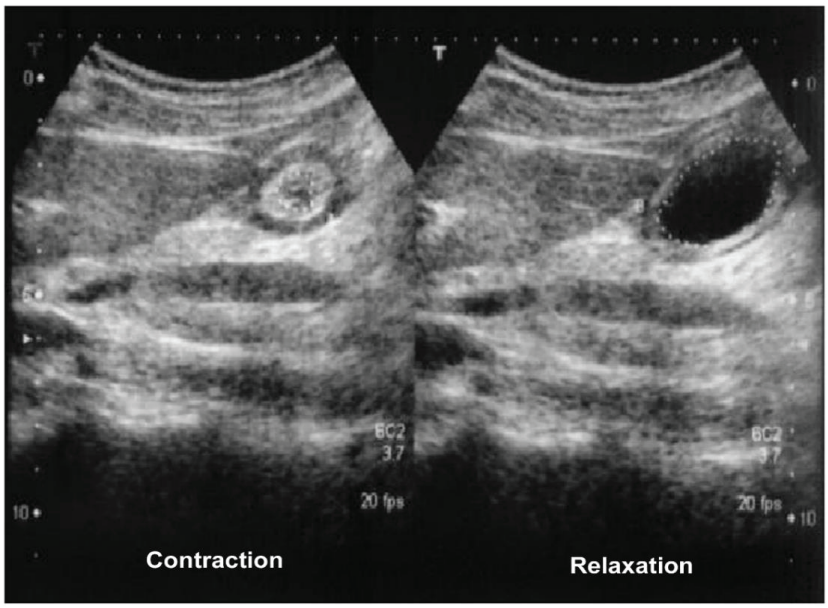

Figure 10.1 – Utrasonographic assessment of antral motility

Ethical approval

Ethical approval was obtained from the Ethical Review Committee of the Faculty of Medicine, University of Kelaniya, Sri Lanka.

RESULTS

Forty one children with FD were included in this study (19 [46.3%] males, age 4-14years, mean 7.5 years, SD 2.6 years). An additional 20 healthy children (8 [40%] males, age 4-14 years, mean 8.4 years, SD 3.0 years) were recruited as controls.

Gastric motility parameters in patients and controls

Mean gastric emptying rates of children with FD and controls are shown in **Figure 10.2**. **Table 10.1** shows antral motility parameters in children with FD and controls. Gastric emptying rate and antral motility index were significantly impaired in those with FD compared to controls.

Relationship between gastric motility parameters and symptoms

Table 10.2 shows the correlation between motility parameters and severity of symptoms. Scores obtained for severity of abdominal pain had a negative correlation with gastric emptying rate (r=-0.35, p=0.025).

Table 10.1 – Gastric motility parameters in children with FD and controls

Gastric motility parameter	Children with FD		Controls		
	Mean	SD	Mean	SD	*P* value†
Fasting antral area (cm^2)	1.5	1.3	0.6	1.0	0.01
Amplitude of antral contractions (%)	58.2	19.6	89.0	10.1	<0.0001
Frequency of antral contraction (per 3 min)	8.8	1.0	9.3	0.8	0.074
Antral motility index	5.1	1.8	8.3	1.3	<0.0001

†Mann-Whitney U test, FD = Functional dyspepsia

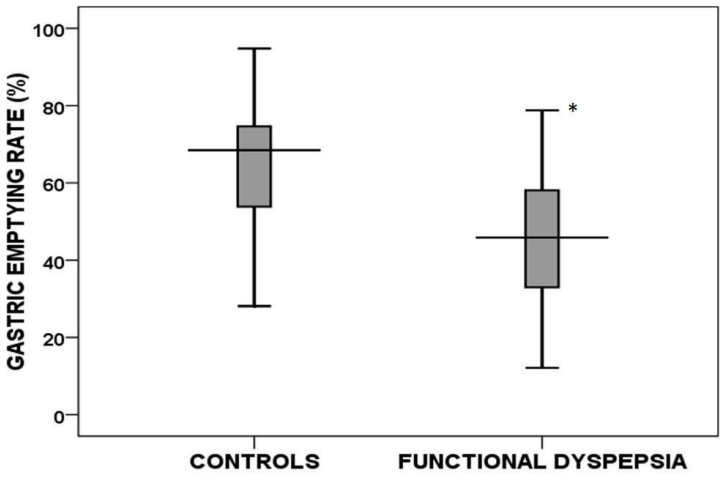

Figure 10.2 – Mean gastric emptying in children with functional dyspepsia and controls. *P<0.001, Mann-Whitney U test

Table 10.2 – Correlation between gastric motility parameters and severity of functional dyspepsia

Clinical parameter	Correlation coefficient†	Pvalue
Fasting antral area	-0.30	0.06
Gastric emptying rate	-0.35	0.026
Amplitude of antral contractions	-0.04	0.82
Frequency of antral contractions	0.20	0.22
Antral motility index	-0.01	0.96

†Spearman's correlation coefficient

Association between gastric motility and exposure to stressful life events

Gastric motility parameters in children exposed to stressful life events and those not exposed to such events are shown in **Table 10.3**. Children exposed to stressful events had a larger fasting antral area (1.9cm^2) than those not exposed to stress (1.0cm^2) (P=0.02).

Table 10.3 – Relationship between gastric motility parameters and exposure to emotional stress

Motility parameter	Children with FD exposed to stressful events		Children with FD not exposed to stressful events		*P*value†
	Mean	*SD*	Mean	*SD*	
Fasting antral area (cm^2)	1.9	1.5	1.0	0.7	0.02
Gastric emptying rate (%)	40.6	18.0	50.9	16.1	0.06
Amplitude of antral contraction (%)	53.6	18.8	63.0	19.7	0.13
Frequency of antral contractions (/3min)	8.9	1.1	8.7	0.9	0.43
Antral motility index	4.8	1.8	5.4	1.8	0.26

† Mann Whitney U test, FD=functional dyspepsia

DISCUSSION

This study reports gastric emptying and antral motility in children with FD, using a validated ultrasonographic method. It shows that gastric emptying is significantly prolonged in children with FD and that they have impaired antral motility together with a larger fasting antral cross sectional area. The gastric emptying rate had a significant negative correlation with severity of symptoms.

Liquid gastric emptying has been previously studied in pediatric and adult patients with FD. Similar to our results, Cucchiara *et al*., studying 11 children with upper gastrointestinal symptoms, have reported significantly prolonged liquid gastric emptying.[13] In addition, three studies have also shown delayed gastric emptying for solids in children with FD.[10, 17, 18] On the other hand, Riezzo *et al.* failed to show a significant difference in half emptying time between patients and controls.[25] However, the test meal used in this study was a mixed solid and liquid meal compared to our study which used a liquid meal. Similarly, adult studies have also reported equivocal results. While many previous adult studies have reported delayed gastric emptying in patients with FD,[26-32] some other studies have failed finding such a difference.[33] A few have even reported accelerated gastric emptying.[34]

Both frequency and amplitude of antral contractions are easily measured using ultrasound techniques and have been shown to be more sensitive than manometry in detecting antral contractions.[19] Very few studies have assessed antral motility after a meal in patients with FD and all those have been done in adult patients. These studies have reported antral hypomotility in 8.6% to 29% of patients.[35, 36] In addition, Kusunoki *et al*, using an ultrasound method, reported decreased antral motility in adult patients with FD.[24] In the current study, for the first time in the literature, we have demonstrated significantly lower antral motility index in children with FD. Decreased antral motility has also been found in children with other abdominal pain predominant FGIDs and recurrent abdominal pain.[24, 37]

In this study, children with FD had significantly larger antral size during the fasting period. Hausken and Berstad also reported a wide gastric antrum in adult patients with FD.[38] Previous studies in children with functional abdominal pain have also reported similar results.[22, 37] This may be due to poor gastric clearance during interdigestive periods. Wilmer *et al*, have reported antroduodenal motility abnormalities in 70% patients with FD during fasting periods.[35] Similarly, Piñeiro-Carrero *et al*. have reported abnormal migrating motility complexes in children with recurrent abdominal pain.[39] .

The exact reason for gastric motility abnormalities observed in patients with FGIDs is unknown. Activation of brain-gut axis due to psychological factors such as emotional stress is considered as one of the main mechanisms for altered motility in FD.[40] Some previous studies have reported an inhibition of gastric emptying and antral motility, after acute and chronic stressors such as labyrinthine stimulation and cold pain.[41-43] However, another study, conducted in healthy volunteers exposed to psychological stress, failed to demonstrate a significant difference in gastrointestinal motility.[44] In addition, two previous studies conducted in children with functional abdominal pain also failed to find a significant association between exposure to emotional stress and gastric motility.[22, 37] In the current study, the patients with FD, who were exposed to stressful life events, had a significantly larger antral size during the fasting period. Other motility parameters did not show a significant difference.

In this study we found a significant negative correlation between gastric emptying rate and severity of abdominal pain. Similar results have been reported in children with functional abdominal pain.[22, 37] In contrast, Friesen *et al.* failed to find such an association,[10] while, Riezzo *et al.* reported a significant correlation between antral dilatation and symptoms in children with FD.[11] A number of studies conducted in adults with FD have failed to find a relationship between gastric motility and symptoms.[28, 31, 35, 45, 46] In contrast to this, two follow up studies among adults have shown improvement of motility parameters in patients who had improvement of symptoms after treatment.[29, 47]

Whether delayed gastric emptying causes symptoms of dyspepsia, or is an epiphenomenon, is a matter of ongoing controversy.[48] Emptying of liquids from the stomach is controlled by coordinated motor activity of the entire stomach and is driven by the proximal gastric tone.[48] Therefore, delayed liquid gastric emptying in our study suggests the possibility of pan gastric dysfunction. It is possible that reduction in gastric emptying and antral motility lead to gastric stasis. When gastric stasis reaches a critical volume, stimulation of stretch receptors in the wall of the stomach could generate pain and discomfort. Presence of visceral hypersensitivity is likely to further enhance the perception of pain and discomfort. This could possibly explain the association between delayed gastric emptying and symptom severity in our children with FD. Our findings would favor a pathophysiological relationship rather than a mere epiphenomenon.

An important limitation of this study is that we recruited children referred to a tertiary care center. Therefore, it is possible that we studied a group of children with symptoms severe enough to be referred for specialized evaluation. The other limitation is we only measured liquid gastric emptying and it may differ from solid emptying. However, it has been shown that

ultrasound measurement of liquid gastric emptying correlates well with scintigraphic measurements.[19] Furthermore, liquid gastric emptying is shown to be more sensitive than solid emptying to detect abnormalities of gastric motility in non-diabetic individuals.[20, 21]

In conclusion, this study reports the presence of significant delays in gastric emptying and impaired antral motility in children with functional dyspepsia. There is a significant negative correlation between severity of abdominal pain and gastric emptying to indicate the clinical relevance of these findings. Our findings provide a scientific basis to evaluate gastroprokinetics in children with functional dyspepsia.

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Chapter 11

Abdominal migraine in children: association between gastric motility parameters and clinical characteristics

Unpublished data

Devanarayana NM, Rajindrajith S, Benninga MA

Under review in BMC Gastroenterology

ABSTRACT

Background: Approximately 0.2-1% of children suffers from abdominal migraine (AM). Pathophysiology of AM has not been completely assessed nor studied. This study evaluated gastric motility in children with AM.

Methods: Seventeen children (6 boys), within an age range of 4-15 years, referred to a tertiary care hospital in Kelaniya, Sri Lanka, from 2009 to 2013, were screened. Those fulfilling Rome III criteria for AM were recruited. None had clinical or laboratory evidence of organic disorders. Twenty healthy children (8 boys), with an age range of 4-14 years, were recruited as matched controls. Liquid gastric emptying rate (GE) and antral motility parameters were assessed using an ultrasound method.

Results: Average GE (41.6% vs. 66.2%, in controls), amplitude of antral contractions (A) (57.9% vs. 89.0%) and antral motility index (MI) (5.0 vs. 8.3) were lower and fasting antral area (1.8cm^2 vs. 0.6cm^2) was higher in children with AM (P<0.01). No significant difference in the frequency of antral contractions (F) (8.8/3min vs. 9.3/3min, p=0.08) was found between the two groups. Scores obtained for severity of abdominal pain had a negative correlation with A (r=-0.55, P=0.03). Average duration of abdominal pain episodes correlated with GE (r=-0.58, P=0.02). Negative correlations were observed between duration of AM and A (r=-0.55), F (r=-0.52), and MI (r=-0.57) (P<0.05).

Conclusions: GE and antral motility parameters were significantly lower in children with AM. A significant correlation was found between symptoms and gastric motility. These findings suggest a possible role of abnormal gastric motility in the pathogenesis of AM.

INTRODUCTION

Recurrent abdominal pain is a common symptom in children worldwide.[1-5] Majority of these children suffer from functional gastrointestinal disorders (FGIDs) [6-8] and only a minority have an identifiable organic cause.[2, 7, 9, 10] Previous studies have shown that approximately 10 to 12% of children and adolescents suffer from abdominal pain predominant functional gastrointestinal disorders (AP-FGIDs).[11-13] AP-FGIDs in children include irritable bowel syndrome (IBS), functional abdominal pain (FAP), abdominal migraine (AM) and functional dyspepsia (FD).[6-8]

AM is an uncommon pain-predominant FGIDs in children. It is characterized by episodes of severe, intense periumbilical pain lasting for hours, associated with other intestinal and extra-intestinal symptoms such as headache, nausea, vomiting, photophobia and pallor.[14] Prevalence of AM varies from 0.2% to 4.1% in community studies.[11-13, 15, 16] In hospital-based studies, AM is seen in 2.2% to 23% of children with non-organic abdominal pain.[7, 17-20]

Similar to other FGIDs, the exact underlying pathophysiology of AM is not clear. Various mechanisms, including gastrointestinal motility abnormalities, have been suggested as possible pathophysiological mechanisms for symptoms of FGIDs. Gastric motility abnormalities have been reported in children with other AP-FGIDs such as FD,[21-23] IBS,[24] and FAP.[25] However, there are no currently available data on gastric motility parameters in children with AM. In such a context, we attempted to study gastric emptying and antral motility parameters in children with AM and their correlation with symptoms.

MATERIALS AND METHODS

Selection of patients with AM

This study was conducted in the Gastroenterology Research Laboratory, Faculty of Medicine, University of Kelaniya, Sri Lanka. All children aged 4 to 15 years, referred to this laboratory from 1st January 2009 to 31st December 2013 and fulfilling the Rome III criteria for abdominal migraine,[14] were recruited. They were screened for organic diseases using detailed history and comprehensive physical examination (including growth parameters) and relevant investigations. Routine investigations done in all recruited patients to rule out organic disorders included stool microscopy, urine microscopy and culture, full blood count, C-reactive protein, liver and renal function tests. Special investigations performed in some patients based on clinical judgment included ultrasound scanning of the abdomen (*n*=13), X-ray KUB (*n*=4), serum amylase (*n=5*), upper gastrointestinal endoscopy (*n=2*) and lower gastrointestinal endoscopy (*n*=1). None of the patients had evidence of organic disorders. The patients were followed up for a minimum of 3 months.

Exclusion criteria were clinical or laboratory evidence suggesting organic pathology, FGIDs other than AM, chronic medical or surgical diseases other than AM, children on long-term medications, previous abdominal surgery involving gastrointestinal tract, fever, common cold, respiratory tract symptoms, gastroenteritis or any other systemic infection during the previous month and subjects receiving drugs that can alter gastrointestinal motility during the previous month.

Selection of controls

Twenty healthy children with an age range of 4 to 14 years were recruited as controls after obtaining written consent from a parent. None of the controls had symptoms related to the gastrointestinal tract, such as abdominal pain, abdominal distension, constipation, diarrhea etc.

Assessment of symptom severity

All children with AM underwent gastric motility assessment during a period of abdominal pain. Severity of abdominal pain was graded as mild (1 – child is able to carry out regular activities during pain episodes), moderate (2 – child stops activities and sits down during pain episodes), severe (3 – child lies down during pain episodes) and very severe (4 – child cries or screams during pain episodes).

Laboratory methods

For this study, gastric motility was assessed using a previously validated ultrasound method.[26] All ultrasound measurements were done by the same investigator (NMD).

All gastric motility measurements were done after an overnight fast, using a high-resolution, real-time scanner with a 3.5MHz curve linear transducer. All subjects were examined seated in a chair, slightly leaning backwards.

The cross sectional area of antrum was measured in the fasting stage and after drinking a standard liquid meal heated to approximately 40^0C (200mL of chicken soup, 54.8kJ, 0.38g protein, 0.25g fat, 2.3g sugar per serving, Ajinomoto Co., Tokyo, Japan). The meal was ingested within 2 minutes. The ultrasound probe was positioned vertically to permit simultaneous visualization of gastric antrum, superior mesenteric artery, abdominal aorta and the left lobe of the liver. The area of gastric antrum was measured by tracing the mucosal side of the wall using the built-in caliper and calculation program of the ultrasound apparatus.

Main gastric motility parameters assessed were fasting antral area, gastric emptying rate, frequency and amplitude of antral contractions and antral motility index.

Calculation of liquid gastric emptying rate

Antral cross sectional area was measured at 1min and 15min after drinking the test meal. Gastric emptying rate was calculated as the percentage reduction of gastric antral cross-sectional area at 15 minutes following ingestion of the liquid meal.

$$\text{Gastric emptying rate (\%)} = \frac{\text{Antral area at 1mins.} - \text{Antral area at 15mins.}}{\text{Antral area at 1min.}} \times 100$$

Calculation of antral motility

These antral motility parameters were calculated within the first 5 minutes after drinking the liquid meal. The minimum and maximum cross sectional areas of the antrum were measured during contractions and relaxations for at least 3 times to calculate the amplitude of antral contractions.

Antral motility parameters were calculated as follows:

Frequency of antral contractions = Number of contractions per 3 minute period

$$\text{Amplitude (\%)} = \frac{\text{Antral area at relaxation} - \text{Antral area at contraction}}{\text{Antral area at relaxation}} \times 100$$

Motility index = Amplitude of antral contraction X Frequency of contraction

Ethical approval

This study protocol was approved by the Ethics Review Committee, Faculty of Medicine, University of Kelaniya, Sri Lanka.

Statistical analysis

The data were analyzed using EpiInfo (EpiInfo version 6.04 (1996), Centres of Disease Control and Prevention, Atlanta, Georgia, USA and World Health Organization, Geneva, Switzerland). The statistical significance of differences of gastric motility parameters between the patient and control groups were assessed using Mann-Whitney U-test. Spearman correlation coefficient was used to assess the relationship between gastric emptying parameters and severity of abdominal pain.

RESULTS

Gastric motility parameters were calculated in 17 children with abdominal migraine (6 [35.3%] boys, age range 4-15 years, mean 9.5 years, SD 3.1 years) and 20 healthy controls (8 [40%] boys, age range 4-14 years, mean 8.4 years, SD 3.0 years).

Characteristics of children with AM

Out of 17 children recruited, 12 (60.6%) had severe abdominal pain and 5 (29.4%) had very severe abdominal pain. The mean age at onset of symptoms was 8.3 years (SD 3.4 years), whereas the mean duration of AM was 15.1 months (SD 14.8 months). The mean duration of pain episodes were 1.6 hours (range 1-48 hours) and the mean frequency of abdominal pain episodes was 20.4 per month (SD 23.7/month). Some children had several attacks of abdominal pain several times per day. Mean symptom free period in children with AM varied from 1.8 weeks to 22.3 weeks. Fourteen (82.4%) children had abdominal pain localized in the periumbilical area while 3 (17.6%) children had pain in a wider area of the abdomen including the umbilical area. Symptoms were aggravated by meals in 4 (23.5%) children, stress in 2 (11.8%) and physical activity in 1 (5.9%). None of the children reported any relieving factors. Other intestinal related and extra-intestinal symptoms associated with abdominal pain in children with AM are summarized in **Table 11.1**.

Table 11.1 – Intestinal related and extra-intestinal symptoms in children with abdominal migraine

Symptom	Number	(%)
Headache	11	64.7
Photophobia	8	47.1
Pallor	2	11.8
Dizziness	3	17.6
Lethargy	1	5.9
Joint pain	5	29.4
Nausea	8	47.1
Vomiting	5	29.4
Loss of appetite	5	29.4
Weight loss	5	29.4
Hard stools	2	11.8
Loose stools	5	29.4
Sleep disturbances	1	5.9

Seven (41.2%) children with AM reported chronic gastrointestinal disorders in first degree relatives while chronic headaches were present in first degree relatives of five (29.4%) children.

Gastric motility parameters of children with AM and controls

The results are depicted in **Table 11.2.** Children with AM had significantly lower gastric emptying rate, amplitude of antral contractions and antral motility index. Furthermore, their fasting antral area was significantly larger than that of controls.

Table 11.2 – Gastric motility parameters in children with abdominal migraine (AM) and controls

	AM *(n=17)* *Mean (SD)*	**Controls** *(n=20)* *Mean (SD)*	*P value**
Fasting antral area (cm^2)	1.8 (1.3)	0.6 (1.0)	0.005
Gastric emptying rate (%)	41.6 (13.4)	66.2 (16.5)	<0.0001
Amplitude of antral contractions (%)	57.9 (16.2)	89.0 (10.1)	<0.0001
Frequency of antral contractions (/3min)	8.8 (0.8)	9.5 (0.8)	0.08
Antral motility index	5.0 (1.5)	8.3 (1.3)	<0.0001

*Mann Whitney U test

Correlation between gastric motility parameters and symptom characteristics

The relationship between gastric motility parameters and symptom characteristics are shown in **Table 11.3**. Gastric emptying rate had a significant negative correlation with the average duration of pain episodes, while amplitude of antral contractions negatively correlated with scores obtained for severity of abdominal pain. No significant correlations observed between gastric motility parameters and headache, photophobia, vomiting, nausea and pallor.

Association between emotional stress and gastric motility

Six (35.3%) children were exposed to stressful life events during the previous 3 months. When gastric motility parameters between children exposed to stressful events and those not exposed to such events were compared, there was no significant difference (**Table 11.4**).

Table 11.3 – Correlation between gastric motility parameters and abdominal pain characteristics in patients with abdominal migraine

	Scores obtained for severity of abdominal pain	Average duration of a pain episode (min)	Frequency of pain episodes (/month)	Duration of the disease (months)	Age at onset of the disease (years)
Fasting antral area (cm^2)	0.28	0.30	-0.14	0.08	0.30
Gastric emptying rate (%)	-0.26	-0.58*	0.16	-0.04	-0.34
Amplitude of antral contractions (%)	-0.55*	-0.43	-0.10	-0.55*	0.04
Frequency of antral contractions (/3min)	-0.33	0.17	0.05	-0.52*	0.22
Antral motility index	-0.45	-0.36	-0.17	-0.57*	0.07

* *P<0.05*, Spearman correlation coefficient

Table 11.4 – Gastric motility parameters in children with abdominal migraine according to exposure to stress

	Stressful event positive *Mean (SD)*	Stressful events negative *Mean (SD)*	*P value**
Fasting antral area (cm^2)	1.5 (0.5)	1.9 (1.6)	0.8
Gastric emptying rate (%)	43.8 (6.1)	40.2 (16.3)	0.6
Amplitude of antral contractions (%)	50.2 (12.1)	63.1 (17.1)	0.2
Frequency of antral contractions (/3min)	8.7 (0.5)	8.8 (1.0)	0.7
Antral motility index	4.3 (1.0)	5.5 (1.7)	0.2

*Mann Whitney U test

DISCUSSION

The current study describes clinical characteristics of children with AM and their gastric motility abnormalities.

In conformity with an earlier study,[14] the majority of children with AM recruited for this study were girls. The mean age of onset of the symptoms of AM (8.3 years) in our study is similar to the observations made in previous studies (7 years).[14] All children had severe abdominal pain lasting for more than 1 hour. The average duration of symptoms (1.6 hours) was significantly shorter and average frequency of pain episodes (20.4 episodes/month) was significantly higher in our children with AM than previously reported symptoms in adult patients with this condition (41.6 hours and 2.0/month respectively).[27] Although classically pain in AM occurs around the periumbilical area, some of our children had pain extending to a wider area of the abdomen. Meal-related symptoms are usually seen in children with FD and IBS. In this sample a sizeable proportion (24%) of children reported exaggerated pain with meals. Some children had altered bowel habits as well, although they did not fulfil the criteria for IBS or constipation. Commonest associated symptoms were headache, photophobia and nausea. A previous study conducted in the United Kingdom in children aged 5-15 years has reported anorexia, nausea and pallor as commonest associated symptoms.[16]

Despite 0.2 to 23 per cent of children suffering from AM,[7, 11-13, 15-20] the precise mechanism of symptoms remains unknown. Although, the main symptom in children with AM is abdominal pain, they also have symptoms related to dysfunction of the central nervous system such as visual disturbances. Therefore, it is likely that the underlying pathophysiology of AM involves both peripheral and central nervous system dysfunction.[28]

Several hypotheses have been investigated to determine the pathophysiology of AM. Factors suggested as underlying mechanisms of pain include IgE-mediated diet induced allergy, gut mucosal immune responses, phenol sulfotransferase enzyme M and P catabolism of catecholamines and monoamines, permeability of the gut mucosal surface and altered relationship between the gut and the central nervous system.[29-31] The enteric nervous system of the gut and the central nervous system arise from the same embryologic tissues. So, it is likely that they have direct effects on each other. Some investigators have proposed that psychological factors such as emotional stress increases central nervous system arousal, which in turn, could lead to dysregulation of gastrointestinal functions.[31]

Gastrointestinal motility abnormalities have been suggested as a possible underlying mechanism for AP-FGIDs. Gastric motility abnormalities have been commonly reported in children with IBS, FD and FAP.[23-25, 32-35] This is the first time gastric motility has been assessed in patients with AM. In this study, we found significantly larger fasting antral area and lower gastric emptying rate and antral motility parameters in a cohort of Sri Lankan children with AM. In addition, we observed significant correlation between some gastric motility parameters and abdominal pain. This is consistent with previous studies conducted in children with FD and FAP, which have reported correlations between abdominal pain and gastrointestinal motility abnormalities.[21, 23, 25, 36, 37] However, we did not observe a similar correlation between headache, nausea, vomiting, photophobia and gastrointestinal motility parameters. All these findings tend to indicate abnormal gastric motility as a potential mechanism that contributes to the pathophysiology of abdominal pain but not to other associated symptoms of AM.

We also assessed the relationship between exposure to stressful life events and gastrointestinal motility in children with AM. We did not observe any significant difference in gastrointestinal motility parameters in children exposed to emotional stress and those not exposed to such events. Previous studies conducted in children with FAP and recurrent abdominal pain also failed to show a difference in gastric motility parameters in children exposed to stress.[25, 38] However, two studies conducted in children with FD and IBS have reported a higher gastric antral area during fasting period and lower gastric emptying rate in those exposed to stressful life events.[23, 24]

The exact reason for delay in gastric emptying and abnormal antral motility of AM is not clear. Alterations in brain-gut axis have been commonly suggested as the main pathophysiological mechanism for FGIDs.[39] Psychological factors are proposed to influence gastric functions including sensation, motility, secretion and immunological functions via brain-gut axis.[40] Associated dys-coordination of the antrum and the fundus may partly contribute to impaired gastric emptying. That in turn leads to stasis of fluid, gases and other contents in the stomach and cause gastric dilatation, which may produce intense pain through stimulated stretch and pain receptors. Hypersensitivity of both central and peripheral neural receptors and pathways may have enhanced perception of pain and further increased the pain severity. These physiological phenomena may also contribute to nausea and vomiting. The bi-directional dialogue between brain-gut neurons through the connecting neural and hormonal circuits may have led to the changes in the central nervous system to generate other symptoms such as headache and photophobia. Arousal of autonomic nervous system may give rise to features of sympathetic hyperactivity such as pallor.

Our study has several strengths. We have investigated children with AM to rule out possible organic diseases causing abdominal pain. Furthermore, significant correlation between motility parameters and symptoms suggest an association between symptoms and physiological correlates. One drawback in our study is inclusion of only a relatively small number of patients. However, AM is not a common disorder and therefore it was not possible to include a very large sample. The other potential limitation is that we included children from a referral center. One can argue that they may not represent patients in the general population. However, the proposed possible pathophysiological mechanisms are not likely to be altered by selecting the sample from a referral center. In addition, the investigator who performed the ultrasound measurements was not blinded and was aware that she was scanning a patient with gastrointestinal problem, even though she did not know the exact diagnosis at the time of scanning. However, the ultrasound measurements done in the current study are objective measurement involving calculations. Therefore we believe that this will reduce the operator bias.

In conclusion, gastric emptying rate and antral motility were significantly lower in children and adolescents suffering from abdominal migraine. In addition, we also observed a significant correlation between gastric motility abnormalities and symptoms. Lack of such correlation with extra-intestinal symptoms indicates that gastric motility abnormalities may play a pathophysiological role in the origins of abdominal pain in affected children. More studies are needed to assess the exact relationship between gastrointestinal functions and symptoms in AM.

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PART IV

SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

SUMMARY

Abdominal pain is the second common painful health problem in children, only second to headache. Abdominal pain can be acute or recurrent in origin. Chronic abdominal pain is a misnomer since episodes of abdominal pain in children are distinct and separated by periods of wellbeing. Numerous organic disorders lead to recurrent abdominal pain (RAP). However, in Sri Lanka, and also in developed countries, common causes for RAP are functional gastrointestinal disorders (FGIDs) such as irritable bowel syndrome (IBS), functional abdominal pain (FAP), functional dyspepsia (FD), and constipation.

John Apley, the British pediatrician is the first person to study abdominal pain among children. He gave the initial definition for RAP. Apley's criteria has been used frequently to diagnose non-organic RAP in children until Rome criteria for abdominal pain predominant functional gastrointestinal disorders (AP-FGIDs) are released. Main AP-FGIDs recognized by Rome III definition are IBS, FD, abdominal migraine (AM) and FAP.

Childhood FGIDs are a worldwide health problem. With growing population trends and increasing predisposing factors such as psychological stress and obesity, it can be predictable that the incidence of FGIDs will increase further and become a significant healthcare problem. Although FGIDs are not life threatening, research shows that children suffering from FGIDs tend to have a lower quality of life than their healthy peers and frequently miss school. In addition many FGIDs such as constipation and IBS has high healthcare expenditure and are becoming a major challenge on already overstretched healthcare budgets. **Chapter 1** of this thesis introduces these key aspects of FGIDs in children including definitions, global epidemiology and burden of the disease.

Chapter 2 of this thesis gives a detailed account on possible underlying pathophysiological mechanisms for AP-FGIDs and available treatment modalities. In the currently accepted biopsychosocial model, the interplay of genetic, physiological, psychological and immunological factors are considered to give rise to FGIDs in children. The prevailing viewpoint is that the pathogenesis of functional pain syndromes involves the inter-relationship between changes in visceral sensation, so-called visceral hyperalgesia or hypersensitivity, and altered gastrointestinal motility. Potential targets for pharmacological and nonpharmacological therapy are arising from this model. To date, high-quality efficacy studies of treatment in pediatric AP-FGIDs are scarce. Available evidence indicates beneficial effects of hypnotherapy and combined behavior therapy. Evidence for diets low in fermentable oligosaccharides, disaccharides, monosaccharaides and polyols (FODMAP) and probiotics is promising, as well as

for drug treatment such as peppermint oil, cyproheptadine or famotidine, but well-designed trials with long-term follow-up are needed to confirm these preliminary results.

Chapter 3 describes the prevalence and risk factors for development of AP-FGIDs in Sri Lanka. AP-FGIDs are seen in 12.5% of Sri Lankan children ages 10 to 16 years. IBS is the most common AP-FGID diagnosed, followed by FAP and FD. AP-FGIDs are significantly higher in girls compared with boys. There is a negative correlation between the age and prevalence of AP-FGIDs, with highest prevalence observed in children aged 10 years. Intestinal-related symptoms and extraintestinal symptoms are more frequent in affected children, compared with controls. Exposure to home- and school-related stressful life events are significantly associated with AP-FGIDs.

The distribution of IBS subtypes in 10-16 year olds, their symptom characteristics, and bowel habits are described in details in **chapter 4** of this thesis. Constipation predominant IBS (IBS-C), diarrhea predominant IBS (IBS-D) and mixed IBS (IBS-M) have almost equal distribution while untyped IBS (IBS-U) has a relatively lower prevalence. IBS is more frequent in girls than in boys. Several intestinal-related and extraintestinal symptoms are significantly associated with all four subtypes of IBS, indicating higher occurrence of somatization among affected children.

Asia is the home for over 50% of the world's childhood population. In addition, most of Asian countries are going through a rapid change in socio-economic status and their cultural foundations are constantly being challenged by globalization. In that light, we believed that studying epidemiological patterns of IBS in Asian children in a systematic way will provide a greater perspective for understanding the burden of IBS, its epidemiological distribution, and patterns of subtypes in this continent. **Chapter 5** is a systematic review and meta-analysis which has demonstrated that a sizeable population of young Asians have IBS. The prevalence of IBS varies widely depending on the country, diagnostic criteria, and age of the participants. It is more common among girls compared to boys. There is a significant difference in the prevalence of sub-types in different studies. This systematic review concluded that further studies using pediatric criteria for IBS are needed to understand the true prevalence, especially in other parts of the Asia with large populations.

It is believed that exposure to abuse as a child may subsequently result in abdominal pain. However, only a handful of studies have evaluated the impact of abuse on AP-FGIDs in children and none in teenagers. Results of a study conducted to assess this association between exposure

to child abuse and AP-FGIDs in teenagers is presented as **Chapter 6**. The prevalence of AP-FGIDs is significantly higher in teenagers who have been exposed to physical, sexual, and emotional abuse. In addition, scores obtained for severity of bowel symptoms were significantly higher in teenagers with AP-FGIDs exposed to abuse than those not exposed to such events.

Chapter 7 describes the health related quality of life (HRQoL) and healthcare consultation in Sri Lankan teenagers aged 13 to 18 years with AP-FGIDs. Children with AP-FGIDs have significantly lower HRQoL scores for physical, emotional, social and school functioning. Approximately 28% of affected children have sought medical advice for their symptoms during previous 3 months. The main symptoms associated with healthcare consultation were abdominal bloating and vomiting. The HRQoL was an important determinant of healthcare consultation, more than the severity of individual symptoms.

Chapter 8, chapter 9, chapter 10 and chapter 11, using a simple, safe and non-invasive ultrasound method, we have shown a significant delay in gastric emptying and impairment in antral motility in children who fulfil Rome III criteria for all 4 main types of AP-FGIDs, namely FAP, IBS, FD and AM. Furthermore, there is a significant negative relationship between delayed gastric emptying and severity of symptoms in children with FAP, FD and AM. In addition, children with IBS who were exposed to recent stressful life events, had a significantly lower gastric emptying rate compared to those not exposed to such events, suggesting the possibility of altered brain-gut interactions. In this light, our findings suggest that delayed gastric emptying and impaired antral motility play a role in the pathogenesis of AP-FGIDs.

CONCLUSIONS

This thesis clearly shows that AP-FGIDs are common among Sri Lankan children, especially those exposed to psychological factors such as school and home related stressful events and abuse. The commonest AP-FGID type is IBS of which IBS-D, IBS-C and IBS-M have almost equal prevalence. Affected children have a poor HRQoL in physical, emotional, social and school functioning domains. Only approximately a quarter of children with this troublesome symptom have received healthcare. Affected children have significant abnormalities in their gastric motility functions, and in some, the abnormal motility correlates with the severity of symptoms.

FUTURE PERSPECTIVES

Exposure to school and family related stressful life events is a major risk factor for development of AP-FGIDs. As a result of rapid westernization and exposure to global environment, Asian societies including Sri Lanka, have become very complex, exerting tremendous strain on life of

school aged children. In addition, due to limited opportunities for higher education, the current educational system is highly competitive, which has further increased the burden on children. With increasing psychological risk factors, prevalence of functional gastrointestinal diseases such as IBS and FD are likely to increase further in the future. High prevalence of these disorders will further impair HRQoL and education of school aged children, and increase the burden on healthcare systems of developing countries like Sri Lanka with limited healthcare budgets.

However, without clear understanding of underlying pathophysiology and evidence based therapeutic guidelines, the management of AP-FGIDs still remains a major challenge to the Pediatricians and Family Care Physicians. To date, exact underlying pathophysiological mechanisms for the association between exposure to stressful life events and abnormal gastrointestinal motility have not been described. Some studies conducted in adults with IBS have revealed stress-induced alterations in gastrointestinal motility, visceral sensitivity, autonomic dysfunctions and hypothalamo-pituitary-adrenal (HPA) axis dysfunction. Therefore, it is possible that, through the same mechanisms, abuse and stress lead to the alteration of both the HPA and brain–gut neural axes, predisposing individuals to develop FGIDs. However, further physiological studies are needed to explain the exact underlying pathophysiological mechanisms and to find new, more effective therapeutic targets, especially in children.

With clear evidence on the association between AP-FGIDs and psychological stress and abnormal gastric motility, psychological therapies and treatment modalities improving gastric motility are likely therapeutic targets that should be evaluated for AP-FGIDs in future randomized controlled treatment trials.

Impaired gastrointestinal motility is a universal finding in children with AP-FGIDs. However, treatment trials targeting gastrointestinal prokinetics are not available for children with AP-FGIDs and double blind randomized controlled trials will be helpful to determine the exact therapeutic value motility normalizing drugs. Real time ultrasound technique we use to assess gastric emptying and antral motility is risk free and non-invasive and can be applied to even young children. In addition, ultrasound scanners are available worldwide and an individual test costs less than 5.00 US dollars. Only limitation is that this technique needs trained and skilled ultrasound technician or radiologist.

Previously, non-pharmacological treatment options such guided imagery, progressive relaxation and hypnotherapy have shown promising results in the management of children with

FGIDs. However, in Sri Lanka, there is a limited number of psychiatrist and very few psychologists, of which, less than a handful have specialized in child care. Furthermore, all of them are busy dealing with patients suffering from more severe psychological problems and psychiatric disorders and have little or no time to administer these time consuming psychological treatments. Therefore, availability of psychotherapies for children with AP-FGIDs is very limited. In addition, since Sri Lanka is a country with a different cultural and social background, it is difficult to administer therapies developed in western countries directly. The time has come to develop easily administrable and culturally accepted psychological and behavioral therapies for Sri Lankan children suffering from AP-FGIDs. With Buddhist culture, Sri Lankans have been practicing different meditation techniques to relax their minds for centuries. Some Sri Lankan children learn simple meditation techniques in their schools. In addition, well trained meditation instructors are widely available in the country. Therefore, psychological therapy based on modified, non-religious meditation program would be a likely therapeutic target for children with AP-FGIDs.

LIST OF PUBLICATIONS AND CO-AUTHORS

CONTRIBUTING AUTHORS OF THIS THESIS

Amaranath Karunanayake
Department of Physiology
Faculty of Medicine, University of Ruhuna
Sri Lanka

Arine Vlieger
Department of Pediatrics
St. Antonius Hospital, Nieuwegein
Netherlands

Arunasalam Pathmeswaran
Department of Public Health
Faculty of Medicine, University of Kelaniya
Sri Lanka

Chandrika Bandara
Department of Physiology
Faculty of Medicine, University of Kelaniya
Sri Lanka

Chathurangi Liyanarachchi
Department of Pediatrics
Faculty of Medicine, University of Kelaniya
Sri Lanka

Chitra Abegunasekara
Medical Library
Faculty of Medicine, University of Kelaniya
Sri Lanka

Gayani Shashiprabha
Department of Physiology
Faculty of Medicine, University of Kelaniya
Sri Lanka

Judith Korterink
Department of Pediatric Gastroenterology and Nutrition
Emma Childre's Hospital, Academic Medical Centre
Amsterdam, Netherlands

M.S. Perera
Department of Physiology
Faculty of Medicine, University of Kelaniya
Sri Lanka

Marc Alexander Benninga
Department of Pediatric Gastroenterology and Nutrition
Emma Childre's Hospital, Academic Medical Centre
Amsterdam, Netherlands

Nadeeka Rathnamalala
Department of Physiology
Faculty of Medicine, University of Kelaniya
Sri Lanka

Navoda Nanayakkara
Department of Pediatrics
Faculty of Medicine, University of Kelaniya
Sri Lanka

Nimnadi Perera
Department of Pediatrics
Faculty of Medicine, University of Kelaniya
Sri Lanka

Nipul Kithsiri Gunawardena
Department of Parasitology
Faculty of Medicine, University of Kelaniya
Sri Lanka

Niranjala Mendis
Department of Pediatrics
Faculty of Medicine, University of Kelaniya
Sri Lanka

S. W. Nishanthanie
Department of Physiology
Faculty of Medicine, University of Kelaniya
Sri Lanka

Sachith Mettananda
Department of Pediatrics
Faculty of Medicine, University of Kelaniya
Sri Lanka

Savithri Samaraweera
Department of Physiology
Faculty of Medicine, University of Kelaniya
Sri Lanka

Shaman Rajindrajith
Department of Pediatrics
Faculty of Medicine, University of Kelaniya
Sri Lanka

LIST OF PUBLICATIONS AND CONTRIBUTION OF CO-AUTHORS

1. ***Chapter 1– Global prevalence and international perspective of paediatric gastrointestinal disorders.*** Rajindrajith S, Devanarayana NM, Benninga MA. In: *Paediatric Gastrointestinal disorders: a psychosocial perspective.* Editors. Martin C, Dovey T. Radcliffe Publishing. London. 2014; pp 11-23.
   ISBN: 13:978 184619 995 0

   Contribution of co-authors:
   S Rajindrajith and NM Devanarayana collected the data and wrote the initial manuscript. MA Benninga contributed to the concept and final manuscript by critically analysing it.

2. ***Childhood functional abdominal pain: mechanisms and management.*** Korterink J, Devanarayana NM, Rajindrajith S, Villeger A, Benninga MA. *Nature Review Gastroenterology and Hepatology* 2015;12:159-71.

   Contribution of co-authors:
   J. Korterink, NM Devanarayana and S. Rajindrajith researched data for this article and drafted the initial manuscript. All authors contributed equally to substantial discussions of content and reviewing/editing the manuscript before submission.

3. ***Abdominal pain predominant functional gastrointestinal diseases in children and adolescents: prevalence, symptomatology and association with emotional stress.*** Devanarayana NM, Mettananda S, Liyanarachchi C, Nanayakkara N, Mendis N, Perera N, Rajindrajith S. *Journal of Pediatric Gastroenterology and Nutrition* 2011;53:659-65.

   Contribution of co-authors:
   NM Devanarayana contributed to the concept and data collection, analysed the data and wrote the initial manuscript. S Rajindrajith contributed to the concept and data collection and to the final manuscript by critically analysing it. S Mettananda contributed to the validation of reaserch tool. N Mendis and N Perera contributed to validation of research tool, data collection and data entry. C Liyanarachchi and N Nanayakkara entered data.

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Contribution of co-authors:

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   Contribution of co-authors:

   NM Devanarayana and S Rajindrajith contributed to the concept, data collection and writing of the manuscript. A Pathmeswaran analysed the data. C Abegunasekara contributed to data collection. NK Gunawardena prepared the maps. MA Benninga contributed to the concept and final manuscript by critically analysing it.

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   Contribution of co-authors:

   NM Devanarayana and S Rajindrajith contributed to concept, data collection. NM Devanarayana wrote the initial manuscript. MS Perera, SW Nishanthanie and A Karunanayake contributed to data collection and data entery. S Rajindrajith and MA Benninga contributed to the final manuscript by critically analysing it.

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   Contribution of co-authors:

   NM Devanarayana and S Rajindrajith developed initial concept and collected the data. NM Devanarayana analysed the date and wrote the initial version of the manuscript. MA Benninga and S Rajindrajith contributed to the final version of the manuscript by critically analysing it.

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    NM Devanarayana contributes to the study design, collected and analysed the data and wrote the initial manuscript. S Rajindrajith contributed to study design and the final manuscript. N Rathnamalala and S Samaraweera contributed to study design and data entry. MA Benninga contributed to the final manuscript by critically analyzing it.

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SUMMARY OF THE THESIS, IN DUTCH

Epidemiologische en pathofysiologische aspecten van buikpijn-gerelateerde functionele gastro-intestinale aandoeningen bij kinderen en adolescenten: een Sri Lankaans perspectief

SAMENVATTING

Buikpijn is na hoofdpijn de meeste voorkomende pijnaandoening bij kinderen. Buikpijn kan acuut ontstaan maar is ook vaak chronisch van origine. Chronische buikpijn (CB) bij kinderen is eigenlijk een verkeerde term, want periodes van buikpijn worden afgewisseld met periodes van welbevinden. Ook vele organische aandoeningen kunnen overigens leiden tot CB. In Sri Lanka echter, maar ook in vele andere ontwikkelingslanden, is de meest voorkomende oorzaak voor CB een van de zogenaamde functionele gastro-intestinale pijnsyndromen (FGIP) zoals prikkelbaredarmsyndroom (PDS), functionele buikpijn (FB), functionele dyspepsie (FD) en obstipatie.

John Apley, een Britse kinderarts, was de eerste onderzoeker die studies deed naar buikpijn bij kinderen. Hij introduceerde de eerste definitie voor chronische buikpijn bij kinderen. Deze klassieke definitie van chronische buikpijn is: in een periode van tenminste 3 maanden tenminste 3 episoden van buikpijn die voldoende ernstig zijn om het kind te hinderen in zijn dagelijks functioneren. Deze zogenaamde “Apley criteria” werden in het verleden vaak gebruikt om niet-organische oorzaken voor CB te diagnosticeren. Inmiddels wordt deze definitie minder vaak gebruikt en worden de Rome criteria aangehouden om buikpijn-gerelateerde FGIP (BP-FGIP) te diagnosticeren. De Rome III-definities voor BP-FGIP zijn PDS, FB, FD en abdominale migraine (AM).

FGIP op de kinderleeftijd komen wereldwijd veel voor. Door het toenemen van de wereldpopulatie en een toename van predisponerende factoren zoals obesitas en psychologische stress is het zeer aannemelijk dat de incidentie van FGIP alleen maar zal toenemen en zal leiden tot een nog groter gezondheidsprobleem. Ook al zijn FGIP niet levensbedreigend, onderzoek toont aan dat deze kinderen een lagere kwaliteit van leven rapporteren in vergelijking met gezonde kinderen van dezelfde leeftijd en een groter schoolverzuim hebben. Daarnaast leiden FGIP zoals obstipatie en PDS tot hoge zorguitgaven en worden daarom een steeds grotere uitdaging op de al-overbelaste gezondheidszorgbudgetten.

Hoofdstuk 1 van dit proefschrift beschrijft de belangrijkste aspecten die betrekking hebben op FGIP bij kinderen met inbegrip van definities, mondiale epidemiologie en de variëteit aan problemen waar deze aandoeningen mee gepaard gaan.

Hoofdstuk 2 van dit proefschrift geeft een gedetailleerde beschrijving over de onderliggende pathofysiologische mechanismen die mogelijk aan BP-FGIP ten grondslag liggen. Tevens worden de beschikbare behandelingen voor BP-FGIP besproken. In het huidige aanvaarde biopsychosociaal model wordt gedacht dat de interactie van genetische, fysiologische, psychologische en immunologische factoren leidt tot FGIP bij kinderen. Op dit moment is de huidige hypothese dat de pathogenese van functionele pijnsyndromen de onderlinge relatie betreft tussen het ontwikkelen van viscerale hyperalgesie of overgevoeligheid van de darm, en veranderde gastro-intestinale motiliteit. Potentiële targets voor farmacologische en nonfarmacologische behandelingen zijn op dit model gebaseerd. Tot op heden, zijn er slechts weinig hoge-kwaliteit effectiviteitstudies verricht met betrekking tot de behandeling van BP-FGIP bij kinderen. Enkele gerandomiseerde studies waarbij gebruikt maakt werd van cognitieve gedragstherapie of hypnotherapie laten goede effecten zien. Wetenschappelijk bewijs voor diëten laag in fermenteerbare oligosacchariden, disacchariden, mono- en polyolen (FODMAP) en probiotica is veelbelovend bij volwassenen met prikkelbaredarmsyndroom. Echter grote gerandomiseerde studies met lange follow-up bij kinderen met dezelfde klachten ontbreken nog om deze goede resultaten te bevestigen. Kleine gerandomiseerde studies met geneesmiddelen zoals pepermuntolie, cyproheptadine of famotidine, hebben ook positieve resultaten laten zien maar moeten door middel van grote gerandomiseerde studies bevestigd worden.

Hoofdstuk 3 beschrijft de prevalentie en de risicofactoren voor het ontwikkelen van BP-FGIP in Sri Lanka. 12.5% van de kinderen in Sri Lanka in de leeftijdscategorie 10 tot 16 jaar heeft één van de BP-FGIP. PDS wordt het vaakst gediagnosticeerd, gevolgd door FBP en FD. BP-FGIP komen significant vaker voor bij meisjes dan bij jongens. Tevens is er een negatieve correlatie tussen leeftijd en de prevalentie van BP-FGIP. Intestinaal-gerelateerde symptomen en extra-intestinale symptomen zijn vaker aanwezig bij deze kinderen dan bij gezonde controles.
Blootstelling aan huiselijk- en met school gerelateerde stressvolle gebeurtenissen zijn significant geassocieerd met BP-FGIP.

De verschillende PDS subtypes bij 10-16 jarigen, de additionele gastro-intestinale symptomen die bij PDS voorkomen, inclusief het defecatiepatroon wordt beschreven in **Hoofdstuk 4** van dit proefschrift. Obstipatie-predominante PDS (PDS-O), diarree-predominante PDS (PDS-D) en mixed-PDS (PDS-M) komen ongeveer evenveel voor. Het ongedefinieerde PBS subtype (PDS-O)

komt relatief minder voor. PDS komt meer voor bij meisjes dan bij jongens. Intestinale- en extra-intestinale symptomen komen bij alle 4 de subtypes van PDS significant meer voor dan bij gezonde controles. Deze bevindingen wijzen er op dat er meer somatisatie voorkomt bij kinderen met PDS.

Ongeveer 50% van alle kinderen woont in Azië. De meeste Aziatische landen maken een snelle verandering door met betrekking tot hun sociaaleconomische status. Daarnaast wordt hun culturele achtergrond voortdurend uitgedaagd door de globalisering. In dat licht, wilden wij op een systematische manier de epidemiologie bestuderen van PDS bij kinderen in Azië. Hiermee wordt getracht de belasting van PDS en het voorkomen van de verschillende subtypes van PDS in Azië te bestuderen. **Hoofdstuk 5** is een systematische review en meta-analyse waarin wordt aangetoond dat een aanzienlijk deel van de Aziatische adolescenten PDS heeft. De prevalentie van PDS varieert echter per Aziatisch land, de verschillende diagnostische criteria die werden gebruikt en de leeftijd. PDS komt meer voor bij meisjes dan bij jongens. Het voorkomen van de verschillende BP-FGIP subtypes variëren per studie en per land. Deze systematische review onderstreept dat toekomstige studies gebruik moeten maken van eenduidige definities, zoals de pediatrische Rome criteria, om de echte prevalentie van BP-FGIP op de kinderleeftijd in Azië in kaart te brengen.

Vaak wordt gedacht dat misbruik (fysiek, seksueel, emotioneel) op de kinderleeftijd tot chronische buikpijnklachten kan leiden. Tot op heden zijn er echter slechts een paar studies verricht die de invloed van misbruik onderzochten bij kinderen met BP-FGIP. Er bestaat geen onderzoek dat deze relatie bij tieners tot op heden heeft onderzocht. **Hoofdstuk 6** presenteert de resultaten van een onderzoek dat de associatie tussen blootstelling aan misbruik op de kinderleeftijd en BP-FGIP op de tienerleeftijd beschrijft. De prevalentie van BP-FGIP is significant hoger bij tieners die blootgesteld werden aan fysiek, seksueel en emotioneel misbruik. Bovendien, waren er significant meer gastro-intestinale klachten bij kinderen die misbruik ondergingen in vergelijking met kinderen waar dit niet was gebeurd.

Hoofdstuk 7 beschrijft de gezondheid gerelateerde kwaliteit van leven (Health Related Quality of Life HRQoL) en het gebruik van gezondheidszorg bij Sri Lankaanse tieners (13-18 jaar) met BP-FGIP. Kinderen met BP-FGIP hebben een significant lagere HRQoL op de domeinen fysiek, emotioneel, sociaal en school functioneren. Slechts 28% van de kinderen met BP-FGIP zocht medische hulp voor hun gastro-intestinale symptomen. De belangrijkste symptomen om

medische advies te vragen waren een opgezette buik en braken. HRQoL was een belangrijke determinant voor medische advies, meer dan de ernst van de klachten.

In **hoofdstuk 8 tot en met hoofdstuk 11** wordt gebruik gemaakt van een simpele, veilige en non-invasieve echografische methode om de maaglediging en de antrale motoriek in beeld te brengen. Met behulp van deze methode wordt aangetoond dat de maaglediging significant vertraagd is en dat er bovendien sprake is van een gestoorde antrale motiliteit bij kinderen die voldoen aan de Rome III criteria voor alle BP-FGIP, namelijk PDS, FB, FD en AM. Daarnaast wordt ook een negatieve relatie gevonden tussen vertraagde maaglediging en de ernst van de klachten bij kinderen met FB, FD en AM. Bij kinderen met PDS, die blootgesteld waren aan recente stressvolle life events, wordt een significante tragere maaglediging gevonden in vergelijking met kinderen die geen stressvolle gebeurtenissen hadden meegemaakt. Mogelijk ligt een veranderde brein-darminteractie aan deze bevinding ten grondslag. Deze bevindingen suggereren dat vertraagde maaglediging en gestoorde antrale motiliteit een rol spelen in de pathogenese van BP-FGIP.

CONCLUSIES

Dit proefschrift toont duidelijk aan dat buikpijn gerelateerde functionele gastro-intestinale pijnsyndromen (BP-FGIP) veel voorkomen bij Sri Lankaanse kinderen. Vooral bij die kinderen die zijn blootgesteld aan psychologische factoren, zoals huiselijke- en school gerelateerde stressvolle gebeurtenissen en misbruik. Het meest voorkomende subtype van deze BP-FGIP is PDS, waarbij PDS-D, PDS-C en PDS-A bijna even vaak voorkomen. Deze kinderen met chronische buikpijn hebben vaak een slechte kwaliteit van leven en scoren duidelijk slechter op fysiek, emotioneel, sociaal gebied en school functioneren. Opvallend is dat slechts een kwart van de kinderen met dit hinderlijke en frustrerende symptoom gebruik maakt van de gezondheidszorg. Tenslotte wordt in dit proefschrift aangetoond dat een deel van de kinderen met BP-FGIP, significante afwijkingen heeft ten aanzien van hun maagmotoriek en dat bij sommige van deze kinderen de gestoorde maagmotoriek correleert met de ernst van de symptomen.

SUMMARY OF THE THESIS, IN ENGLISH

Epidemiological and pathophysiological aspects of abdominal pain predominant functional gastrointestinal disorders in children and adolescents: a Sri Lankan perspective

SUMMARY

Abdominal pain is the second common painful health problem in children, only second to headache. Abdominal pain can be acute or recurrent in origin. Chronic abdominal pain is a misnomer since episodes of abdominal pain in children are distinct and separated by periods of wellbeing. Numerous organic disorders lead to recurrent abdominal pain (RAP). However, in Sri Lanka, and also in developed countries, common causes for RAP are functional gastrointestinal disorders (FGIDs) such as irritable bowel syndrome (IBS), functional abdominal pain (FAP), functional dyspepsia (FD), and constipation.

John Apley, the British pediatrician is the first person to study abdominal pain among children. He gave the initial definition for RAP. Apley's criteria has been used frequently to diagnose non-organic RAP in children until Rome criteria for abdominal pain predominant functional gastrointestinal disorders (AP-FGIDs) are released. Main AP-FGIDs recognized by Rome III definition are IBS, FD, abdominal migraine (AM) and FAP.

Childhood FGIDs are a worldwide health problem. With growing population trends and increasing predisposing factors such as psychological stress and obesity, it can be predictable that the incidence of FGIDs will increase further and become a significant healthcare problem. Although FGIDs are not life threatening, research shows that children suffering from FGIDs tend to have a lower quality of life than their healthy peers and frequently miss school. In addition many FGIDs such as constipation and IBS has high healthcare expenditure and are becoming a major challenge on already overstretched healthcare budgets. **Chapter 1** of this thesis introduces these key aspects of FGIDs in children including definitions, global epidemiology and burden of the disease.

Chapter 2 of this thesis gives a detailed account on possible underlying pathophysiological mechanisms for AP-FGIDs and available treatment modalities. In the currently accepted biopsychosocial model, the interplay of genetic, physiological, psychological and immunological factors are considered to give rise to FGIDs in children. The prevailing viewpoint is that the pathogenesis of functional pain syndromes involves the inter-relationship between changes in visceral sensation, so-called visceral hyperalgesia or hypersensitivity, and altered gastrointestinal motility. Potential targets for pharmacological and nonpharmacological therapy

are arising from this model. To date, high-quality efficacy studies of treatment in pediatric AP-FGIDs are scarce. Available evidence indicates beneficial effects of hypnotherapy and combined behavior therapy. Evidence for diets low in fermentable oligosaccharides, disaccharides, monosaccharaides and polyols (FODMAP) and probiotics is promising, as well as for drug treatment such as peppermint oil, cyproheptadine or famotidine, but well-designed trials with long-term follow-up are needed to confirm these preliminary results.

Chapter 3 describes the prevalence and risk factors for development of AP-FGIDs in Sri Lanka. AP-FGIDs are seen in 12.5% of Sri Lankan children ages 10 to 16 years. IBS is the most common AP-FGID diagnosed, followed by FAP and FD. AP-FGIDs are significantly higher in girls compared with boys. There is a negative correlation between the age and prevalence of AP-FGIDs, with highest prevalence observed in children aged 10 years. Intestinal-related symptoms and extraintestinal symptoms are more frequent in affected children, compared with controls. Exposure to home- and school-related stressful life events are significantly associated with AP-FGIDs.

The distribution of IBS subtypes in 10-16 year olds, their symptom characteristics, and bowel habits are described in details in **chapter 4** of this thesis. Constipation predominant IBS (IBS-C), diarrhea predominant IBS (IBS-D) and mixed IBS (IBS-M) have almost equal distribution while untyped IBS (IBS-U) has a relatively lower prevalence. IBS is more frequent in girls than in boys. Several intestinal-related and extraintestinal symptoms are significantly associated with all four subtypes of IBS, indicating higher occurrence of somatization among affected children.

Asia is the home for over 50% of the world's childhood population. In addition, most of Asian countries are going through a rapid change in socio-economic status and their cultural foundations are constantly being challenged by globalization. In that light, we believed that studying epidemiological patterns of IBS in Asian children in a systematic way will provide a greater perspective for understanding the burden of IBS, its epidemiological distribution, and patterns of subtypes in this continent. **Chapter 5** is a systematic review and meta-analysis which has demonstrated that a sizeable population of young Asians have IBS. The prevalence of IBS varies widely depending on the country, diagnostic criteria, and age of the participants. It is more common among girls compared to boys. There is a significant difference in the prevalence of sub-types in different studies. This systematic review concluded that further studies using pediatric criteria for IBS are needed to understand the true prevalence, especially in other parts of the Asia with large populations.

It is believed that exposure to abuse as a child may subsequently result in abdominal pain. However, only a handful of studies have evaluated the impact of abuse on AP-FGIDs in children and none in teenagers. Results of a study conducted to assess this association between exposure to child abuse and AP-FGIDs in teenagers is presented as **Chapter 6**. The prevalence of AP-FGIDs is significantly higher in teenagers who have been exposed to physical, sexual, and emotional abuse. In addition, scores obtained for severity of bowel symptoms were significantly higher in teenagers with AP-FGIDs exposed to abuse than those not exposed to such events.

Chapter 7 describes the health related quality of life (HRQoL) and healthcare consultation in Sri Lankan teenagers aged 13 to 18 years with AP-FGIDs. Children with AP-FGIDs have significantly lower HRQoL scores for physical, emotional, social and school functioning. Approximately 28% of affected children have sought medical advice for their symptoms during previous 3 months. The main symptoms associated with healthcare consultation were abdominal bloating and vomiting. The HRQoL was an important determinant of healthcare consultation, more than the severity of individual symptoms.

Chapter 8, chapter 9, chapter 10 and chapter 11, using a simple, safe and non-invasive ultrasound method, we have shown a significant delay in gastric emptying and impairment in antral motility in children who fulfil Rome III criteria for all 4 main types of AP-FGIDs, namely FAP, IBS, FD and AM. Furthermore, there is a significant negative relationship between delayed gastric emptying and severity of symptoms in children with FAP, FD and AM. Furthermore, children with IBS who were exposed to recent stressful life events had a significantly lower gastric emptying rate compared to those not exposed to such events, suggesting the possibility of altered brain-gut interactions. In this light, our findings suggest that delayed gastric emptying and impaired antral motility play a role in the pathogenesis of AP-FGID.

CONCLUSIONS

This thesis clearly shows that AP-FGIDs are common among Sri Lankan children, especially those exposed to psychological factors such as school and home related stressful events and abuse. The commonest AP-FGID type is IBS of which IBS-D, IBS-C and IBS-M have almost equal prevalence. Affected children have a poor HRQoL in physical, emotional, social and school functioning domains. Only approximately a quarter of children with this troublesome symptom have received healthcare. Affected children have significant abnormalities in their gastric motility functions, and in some, the abnormal motility correlates with the severity of symptoms.

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