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