

Leading Article

Functional gastrointestinal diseases in children: Stepping out of the box

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Functional gastrointestinal diseases (FGDs) are a well recognized group of diseases in children characterised by chronic or recurrent episodes of gastrointestinal symptoms for which a definitive organic cause cannot be delineated. These symptoms range from abdominal pain, vomiting, chronic nausea and abdominal bloating to disturbed defecation.

Lack of epidemiological data, poor understanding of the underlying patho-physiological mechanisms and a dearth of therapeutic modalities at primary and secondary care level, where perhaps it is most needed, has led many practising paediatricians to either reject these entities or label these diseases as possible organic diseases without evidence. However, untiring and diligent work from several research groups across the world has unravelled possible pathophysiological mechanisms and many trials are being conducted to identify effective pharmacological and non-pharmacological therapeutic interventions. In this leading article, we summarize current understanding of FGDs in children, particularly in Sri Lanka.

Three centuries ago, when the Western medical practitioners were allowed to dissect the human body, the concept of “disease” started to gather momentum. With dissecting cadavers affected by various ailments they started to find diseases with various pathological disorders based on abnormal morphological appearances. This approach, up to date, has given valuable insight into innumerable disease entities and has also helped to develop rational therapeutic approaches. Naturally, with the vast scientific basis, this “biomedical model” became the foundation of the modern curricula of medical education and helps to mould graduating young physicians’ mind that all ailments do have a demonstrable pathological basis for a given set of symptoms. The burning desire of the paediatrician to adhere to the traditional

biomedical model is often highlighted by frequent labelling of children with upper abdominal pain as having “gastritis” without clear evidence. In the early 1970’s, introduction of the “bio-psycho-social model” by Engle started to challenge the traditional “bio-medical model” of aetiology¹. In a nutshell, the bio-psycho-social model describes the integration and influence of various biological, psychological and social factors in generating illnesses. It also explains the scenario that certain illnesses cannot be explained by the traditional biological model of aetiology and therefore the currently available investigation models are unable to pinpoint an exact underlying organic pathology.

A series of epidemiological research carried out in Sri Lanka has clearly shown the magnitude of the problem. FGDs are present in nearly 30% of school children in Sri Lanka². Prevalence of abdominal pain predominant FGDs such as irritable bowel syndrome, functional abdominal pain, functional dyspepsia and abdominal migraine are 4.9%, 4.4%, 2.5% and 1% respectively³. Functional constipation is a common condition affecting 15.3% of school children⁴. About 2% of children and adolescents are suffering from functional faecal incontinence and 80% of these sufferers have constipation as the precipitating factor for their faecal incontinence⁵. In addition, conditions like rumination syndrome and aerophagia are also prevalent in 5.1% and 7.5% respectively^{6,7}. This overview gives strong evidence to suggest that FGDs are common among Sri Lankan children.

Most FGDs have significant impacts on children. Although considered as benign, quality of life of children with FGDs is lower than children with major organic diseases such as inflammatory bowel disease and gastro-oesophageal reflux⁸. A recent study from Japan found children with FGDs have poor quality of school work indicating possible long term repercussions such as stunting of their education⁹. More recent studies in Sri Lanka have also noted similar reduction in quality of life in children with abdominal pain predominant FGDs and constipation^{10,11}. Studies from other countries have

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clearly noted overall annual medical costs for children with constipation are approximately twice as high as that of controls^{12,13} indicating the burden on healthcare systems which are overstretched.

The prevailing biomedical paradigm does not entirely explain the high prevalence of FGDs in children. Gastritis is not a common disease in children presenting with abdominal pain. In a previous study in Sri Lanka, it had been shown that only 2% of children presenting with abdominal pain had *Helicobacter pylori* infection, which is the main reason for children to develop gastritis¹⁴. In addition, the notion that hypothyroidism is commonly considered to be the main reason to develop constipation in children, seems to be a misconception. A study on a large cohort of children with abnormal thyroid function tests has shown only less than 1% of children had constipation as the presenting symptom¹⁵. In addition, it had been clearly illustrated that the majority of patients with hypothyroidism had normal bowel habits¹⁶. Furthermore, studying a large number of children with irritable bowel syndrome, functional dyspepsia, and functional abdominal pain we did not find significant abnormalities in routine biochemistry, haematology, urine analysis and abdominal ultrasonography¹⁷⁻¹⁹. Consequently, the approach of hunting a specific biomarker will only lead to staggering cost for investigations together with repeated consultations and frustration of both clinician and the patient.

FGDs do not have consistently demonstrable pathological findings. However, previous studies have shown an association between pain predominant FGDs and psychological stress³. Similarly, constipation is also associated with day to day family and school related stressful life events²⁰. Childhood constipation was shown to be common in children who once lived in the war affected areas of the country, further strengthening the association of constipation and stress²¹. We have also demonstrated that constipation and pain predominant FGDs are associated with major forms of child abuse and abnormal personality traits^{10,22-24}. In addition, another series of studies have shown that pain predominant FGDs such as functional abdominal pain, irritable bowel syndrome and functional dyspepsia are associated with abnormal gastric functions and delayed gastric emptying, well correlated with the degree of psychological stress¹⁷⁻¹⁹. Furthermore, others have demonstrated presence of derailed anorectal functions in children with functional constipation²⁵. In addition, functional MRI studies have found patients with irritable bowel syndrome

with a history of abuse have greater activation of anterior midcingulate and posterior cingulate cortices with deactivation of supragenual region of the anterior cingulate cortex which is associated with down regulation of pain signals²⁶. Other researchers have also shown increased intestinal permeability, altered intestinal microbiota, changes in visceral hypersensitivity and abnormal serotonin signalling as important patho-physiological mechanisms in subsets of patients with FGDs^{27,28}. All these findings indicate that FGDs are results of complex interactions of multiple factors such as motility, psychological stress, abuse, intestinal microbes and disturbed bidirectional interactions of the brain-gut axis rather than an easily demonstrable single pathological entity.

Therefore, it should be clearly understood that most of the functional gastrointestinal diseases would not be recognized by using commonly available routine investigations. Similarly, treating with simple analgesics, antacids, a short course of laxatives and anti-helicobacter therapy will not be helpful to children suffering from FGDs. Some of the therapeutic approaches that have shown to be effective in adults such as antidepressants and probiotics failed to show any major clinically meaningful advantages in children^{29,30}. However, psychotherapy³¹ and guided imagery³² are effective in children with pain predominant FGDs and novel drugs such as polyethylene glycol and prucalopride are effective in treating constipation^{33,34}. In addition, children with refractory symptoms may need evaluation by a specialist, therapy with multiple drugs, psychological support and long term follow up.

We propose a paradigm shift. Practising paediatric colleagues need to recognize FGDs as a significant problem in our settings and not a parsimonious diagnostic entity anymore. A positive diagnosis of FGDs could easily be made using available symptom based criteria laid down by the Rome Foundation rather than sticking to popular diagnoses such as gastritis, amoebiasis and worm infestations³⁶. Most of the time, this process only requires a detailed history and a thorough physical examination. In the majority, the clinical evaluation will ensure a categorical diagnosis and identify associated clinical modifiers such as somatisation. In addition, it will also help to describe the impact of the disease on affected children and the family and outline the psychosocial modifiers of the disease. Making the correct diagnosis, identifying underlying risk factors and impact of the condition on the quality of life will make sure that optimal care is provided and prevent

unnecessary investigations such as radiological studies. The latter are sometimes invasive and potentially harmful to the child, do not add any additional information for management, and lead to higher healthcare costs to already struggling hospital budgets. Physiological studies may help to understand some patho-physiological mechanisms and are only available at specialist centres. However, timely referral of children with refractory symptoms will be helpful to families who are constantly seeking answer to the question “what’s wrong with my child’s belly?”

Although proven therapeutic options are limited for children with FGDs at the moment, studies in children, adults and animal models have ensured a rich pipeline of research in developing novel and alternative options, indicating a brighter future. In addition, identifying parental fears and addressing them to prevent illness behaviour of the child also show encouraging results³⁶. These attempts are promising and making sure that treatment options are expanding and are breaking boundaries of narrow confines of simple bio-medical model and popular approaches. Considering all these facts, we would like to encourage the readership to “step out of the box” to find new horizons in managing children with FGDs.

References

- Engel GL. The need for a new medical model: challenge for the biomedicine. *Science* 1977; **196**:129-36.
<http://dx.doi.org/10.1126/science.847460>
- Devanarayana NM, Adhikari C, Pannala W, Rajindrajith S. Prevalence of functional gastrointestinal diseases in a cohort of Sri Lankan adolescents: Comparison between Rome II and Rome III criteria. *Journal of Tropical Pediatrics* 2011; **57**: 34-9.
<http://dx.doi.org/10.1093/tropej/fmq039>
- Devanarayana NM, Mettananda S, Liyanarachchi C, Nanayakkara N, Mendis N, Perera N, et al. Abdominal pain predominant functional gastrointestinal diseases in children and adolescents: symptomatology and association with stress. *Journal of Pediatric Gastroenterology and Nutrition* 2011; **53**:659-65.
- Rajindrajith S, Devanarayana NM, Adhikari C, Pannala W, Benninga MA. Constipation in children: an epidemiological study in Sri Lanka using Rome III criteria. *Archives of Disease in Childhood* 2012; **97**:43-5.
<http://dx.doi.org/10.1136/adc.2009.173716>
- Rajindrajith S, Devanarayana NM, Benninga MA. Constipation-associated and non-retentive faecal incontinence in children and adolescents: an epidemiological survey in Sri Lanka. *Journal of Pediatric Gastroenterology and Nutrition* 2010; **51**:472-6.
<http://dx.doi.org/10.1097/MPG.0b013e3181d33b7d>
- Rajindrajith S, Devanarayana NM, Perera BJ. Rumination syndrome in children and adolescents: a school survey assessing prevalence and symptomatology. *BMC Gastroenterology* 2012; **12**:163.
<http://dx.doi.org/10.1186/1471-230X-12-163>
- Devanarayana NM, Rajindrajith S. Aerophagia among Sri Lankan children: Epidemiological patterns and symptom characteristics. *Journal of Pediatric Gastroenterology and Nutrition* 2012; **54**:516-20.
<http://dx.doi.org/10.1097/MPG.0b013e318236051d>
- Youssef NN, Langseder AL, Verga BJ, Mones RL, Rosh JR. Chronic childhood constipation is associated with impaired quality of life: a case-controlled study. *Journal of Pediatric Gastroenterology and Nutrition* 2005; **41**:56-60.
<http://dx.doi.org/10.1097/01.mpg.0000167500.34236.6a>
- Sagawa T, Okamura S, Kakizaki S, Shang Y, Morita K, Mori M. Functional gastrointestinal diseases in adolescents and quality of school life. *Journal of Gastroenterology and Hepatology* 2013; **28**:285-90.
- Devanarayana NM, Rajindrajith S, Karunanayake A, Nishanthini S, Perera S, Benninga MA. Abdominal pain predominant functional gastrointestinal diseases: association with child abuse, traumatic life events and quality of life. *Journal of Gastroenterology and Hepatology* 2012; **27** (Supple 5):59-438.

11. Rajindrajith S, Devanarayana NM, Weerasooriya L, Hathagoda W, Benninga MA. Quality of life and somatic symptoms in children with constipation: a school based survey. Abstract. 3rd Biennial Scientific Meeting of Asian Neurogastroenterology and Motility 2013, Pennang, Malaysia.
12. Choung RS, Shan ND, Chitkara D, Branda ME, van Tilburg MA, Whitehead WE, et al. Direct medical costs of constipation from childhood to early adulthood: a population-based birth cohort study. *Journal of Pediatric Gastroenterology and Nutrition* 2011; **52**:47-54.
<http://dx.doi.org/10.1097/MPG.0b013e3181e67058>
13. Liem O, Harman J, Benninga MA, Kelleher K, Mousa H, Di Lorenzo C. Healthcare utilization and cost impact of childhood constipation in the United States. *Journal of Pediatrics* 2000; **154**:258-62.
<http://dx.doi.org/10.1016/j.jpeds.2008.07.060>
14. Devanarayana NM, de Silva DG, de Silva HJ. Aetiology of recurrent abdominal pain in a cohort of Sri Lankan children *Journal of Paediatrics and Child Health* 2008; **44**:195-200.
<http://dx.doi.org/10.1111/j.14401754.2008.01295.x>
15. Bennett WE, Heuckeroth RO. Hypothyroidism is a rare cause of isolated constipation. *Journal of Pediatric Gastroenterology and Nutrition* 2012; **54**:285-7.
<http://dx.doi.org/10.1097/MPG.0b013e318239714f>
16. Muller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. *American Journal of Gastroenterology* 2005; **100**:232-42.
<http://dx.doi.org/10.1111/j.15720241.2005.40885.x>
17. Devanarayana NM, RajindrajithS, Rathnamalala N, Samaraweera S, Benninga MA. Delayed gastric emptying and impaired antral motility in children fulfilling Rome III criteria for functional abdominal pain. *Neurogastroenterology and Motility* 2012; **24**:420-5.
<http://dx.doi.org/10.1111/j.13652982.2011.01871.x>
18. Devanarayana NM, RajindrajithS, Bandara C, Shashiprabha G, Benninga MA. Ultrasonographic assessment of liquid gastric emptying and antral motility according to subtypes of irritable bowel syndrome in children *Journal of Pediatric Gastroenterology and Nutrition* 2013; **56**:443-8.
<http://dx.doi.org/10.1097/MPG.0b013e31827f7a3d>
19. Devanarayana NM, RajindrajithS, Perera MS, Nishanthinie SW, Benninga MA. Gastric emptying and antral motility parameters in children with functional dyspepsia: association with symptom severity. *Journal of Gastroenterology and Hepatology* 2013 Mar 21. [Epub ahead of print]
<http://dx.doi.org/10.1111/jgh.12205>
20. Devanarayana NM, Rajindrajith S. Association between constipation and stressful life events in a cohort of Sri Lankan children and adolescents. *Journal of Tropical Pediatrics* 2010; **56**:144-8.
<http://dx.doi.org/10.1093/tropej/fmp077>
21. Rajindrajith S, Mettananda S, Devanarayana NM. Constipation during and after the civil war in Sri Lanka: a paediatric study *Journal of Tropical Pediatrics* 2011; **57**: 439-43.
<http://dx.doi.org/10.1093/tropej/fmr013>
22. Rajindrajith S, Devanarayana NM, Lakmini C, Subasinghe V, Benninga MA. Constipation in Sri Lankan children: association with physical, sexual, emotional abuse. *Journal of Gastroenterology and Hepatology* 2012; **27** (Suppl 5):383.
23. Ranasinghe N, Rajindrajith S, Devanarayana NM, Warnakulasuriya T, Nishanthini S, Perera MS. Children and adolescents with constipation: Do they have different personalities? *Journal of Gastroenterology and Hepatology* 2012; **27** (Suppl 5):384.
24. Ranasinghe N, Rajindrajith S, Devanarayana NM, Warnakulasuriya T, Nishanthini S, Perera MS. Personality assessment in children with abdominal pain predominant functional gastrointestinal diseases. *Journal of Gastroenterology and Hepatology* 2012; **27** (Suppl 5):385.

25. van der Plas RN, Benninga MA, Buller HA, Bossuyt PM, Akkermans LM, Redekop WK et al. Biofeedback training in treatment of childhood constipation: a randomised controlled study. *Lancet* 1996; **348**:776-80.
[http://dx.doi.org/10.1016/S0140-6736\(96\)03206-0](http://dx.doi.org/10.1016/S0140-6736(96)03206-0)
26. Drossman DA. Abuse, trauma and GI illness: is there a link? *American Journal of Gastroenterology* 2011; **106**:14-25.
<http://dx.doi.org/10.1038/ajg.2010.453>
27. Camillari M. Peripheral mechanisms in irritable bowel syndrome. *New England Journal of Medicine* 2012; **367**:1626-35.
<http://dx.doi.org/10.1056/NEJMra1207068>
28. Faure C, Patey N, Gauthire C, Brooks EM, Mawe GM. Serotonin signalling is altered in irritable bowel syndrome with diarrhoea but not in functional dyspepsia in pediatric age patients. *Gastroenterology* 2010; **139**:249-58.
<http://dx.doi.org/10.1053/j.gastro.2010.03.032>
29. Saps M, Youssef N, Miranda A, Nurko S, Hyman P, Cocjin J et al. Multicenter, randomized, placebo-controlled trial of amitriptyline in children with functional gastrointestinal disorders. *Gastroenterology* 2009; **137**:1261-9.
<http://dx.doi.org/10.1053/j.gastro.2009.06.060>
30. Horvath A, Dziechciarz P, Szajewska H. Meta-analysis: *Lactobacillus rhamnosus* GG for abdominal pain-related functional gastrointestinal disorders in childhood. *Alimentary Pharmacology and Therapeutics* 2011; **33**:1302-10.
<http://dx.doi.org/10.1111/j.13652036.2011.04665.x>
31. Levy RL, Langer SL, Walker LS, Romano JM, Christie DL, Youssef N et al. Twelve-month follow-up of cognitive behavioural therapy for children with functional abdominal pain. *JAMA Pediatrics* 2013; **167**:178-84.
<http://dx.doi.org/10.1001/2013.jamapediatrics.282>
32. van Tilburg MA, Chitkara DK, Palsson OS, Turner M, Blois-Martin N, Ulshen M et al. Audio-recorded guided imagery treatment reduces functional abdominal pain in children: a pilot study. *Pediatrics* 2009; **124**:e890-7.
<http://dx.doi.org/10.1542/peds.2009-0028>
33. Hoekman DR, Benninga MA. Functional constipation in childhood: current pharmacotherapy and future perspectives. *Expert Opinion on Pharmacotherapy* 2013; **14**:41-51.
<http://dx.doi.org/10.1517/14656566.2013.752816>
34. Winter HS, Di Lorenzo C, Benninga MA, Gilger MA, Kearns GL, Hyman PE, et al. A multicenter open-label study of oral prucalopride in children with functional constipation *Journal of Pediatric Gastroenterology and Nutrition* 2013 Mar 26. [Epub ahead of print].
<http://dx.doi.org/10.1097/MPG.0b013e318292f9ea>
35. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2006; **130**:1527-37.
<http://dx.doi.org/10.1053/j.gastro.2005.08.063>
36. Levy RL, Langer SL, Walker LS, Romano JM, Christie DL, Youssef N, et al. Cognitive-behavioural therapy for children with functional abdominal pain and their parents decreases pain and other symptoms. *American Journal of Gastroenterology* 2010; **105**:946-56.
<http://dx.doi.org/10.1038/ajg.2010.106>