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Conceptual Paper

Functional Gastrointestinal Disorders in Children

Rajeev Gupta*

Department of Paediatrics, Barnsley Foundation Hospital, United Kingdom

***Corresponding Author:** Rajeev Gupta, Department of Paediatrics, Barnsley Foundation Hospital, United Kingdom.

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Introduction

Functional gastrointestinal (GI) disorders (FGIDs) are common disorders characterized by recurring GI symptoms that cannot be attributed to structural or biochemical abnormalities [1,2].

The common functional disorders seen in pediatric patients are functional dyspepsia, irritable bowel syndrome, functional abdominal pain and cyclic vomiting. There other less common conditions as well and these functional gastrointestinal disorders continue to challenge the medical professionals and have a significant emotional and economic impact. Functional gastrointestinal disorders (FGIDs) are common, the prevalence of FGIDs has been reported to range between 12% and 29% [3,4].

Our brains and our GI tracts are closely connected (the "mind-body connection"). Functional GI disorders are due to a combination of extra sensitivity of the GI tract, with changes in the motility or movement of the digestive system. Our digestive tract is moving food all the time, and some individuals feel this more intensely than others. It appears as if the "volume" has been turned up from their digestive tract. When their brains receive these sensations, its reaction can change the motion of the stomach and intestine. These conditions are common, sometimes run in families, and are usually found in individuals who are otherwise healthy.

Childhood FGIDs are perplexing and include a variable combination of often age-dependent, chronic, or recurrent symptoms not explained by identifiable abnormalities. As the child is programmed to develop, it is not unexpected that some functional disorders which occur during childhood accompany normal development (e.g. infant regurgitation or toddler's diarrhea), or may be triggered by age appropriate but maladaptive behavioral responses to internal or external stimuli (e.g. functional fecal retention often results from painful defecation and/or coercive toilet training) [5].

Definition

A functional disorder refers to a disorder or disease where the primary abnormality is an altered physiological function rather than a recognisable structural or biochemical cause. It typifies a disorder that generally can not be diagnosed in a traditional way; that is, as an inflammatory, infectious, or structural abnormality that can be seen by commonly used examination, x-ray, or blood test. In this setting, "functional" means that the symptoms occur within the expected range of the body's behavior.

Due to the lack of specific biological markers, FGIDs currently are defined according to the criteria established by the Rome Foundation, which was originally designed as Rome III and updated now to Rome IV [2,6]. The advantage of using the Rome criteria in clinical practice is that they permit a positive approach, avoiding unnecessary tests to rule out an organic cause, with a consequent beneficial effect on both patient's health and health care costs.

Rome IV 2016 gives guidelines based on a detailed clinical evaluation that must contain complete clinical history, physical examination and growth curves to help clinicians in daily practice.

Also it's important to remember that FGIDs can co-occur with other medical conditions that themselves result in GI symptoms. It thus is important to remember that a diagnosis of functional disorder should only be made if diseases that could account for the symptoms are absent or inactive.

For definition purpose, the symptoms should be present at least once a week for 2 months (previously 3 months in Rome III) for all the disorders except for the 2 cyclical ones: abdominal migraine and cyclic vomiting.

Underlying mechanism/Pathophysiology

The main symptoms described by patients with FGIDs include abdominal pain, dyspepsia, regurgitation, bloating, constipation, diarrhea, incontinence, problems in the passage of food or stool, or any combination of these symptoms. Different mechanisms have been understood to play a role in pathogenesis including disturbance in motility, altered mucosal and immune function, visceral hypersensitivity, disturbance in gut microbiota, and altered processing of visceral signals in the central nervous system (CNS) [7].

It is now well known that along with having symptoms related to the gastrointestinal tract, the patients with FGIDs also have co-existing psychosocial symptoms such as stress, anxiety and depression. FGID is considered a disorder of Gut-Brain axis [8]. A biopsychosocial model thus has been proposed for FGIDs.

We know that bidirectional communication pathways between the gut and the brain are involved in the pathogenesis of FGIDs and these are collectively known as the alteration of gut-brain axis. This communication occurs through a number of neuronal pathways and is modified by environmental and anatomical factors such as hypothalamus-pituitary axis, limbic system, autonomic nervous system, and endocrine system [9].

The brain and gut communicate continuously through a number of complex pathways involving the enteric nervous system (ENS), the autonomic nervous system (ANS), the hypothalamus-pituitary axis (HPA) and the central nervous system (CNS). Each pathway is highly integrated and regulated by inter relational neuronal and neurohumoral factors.

Serotonin functions as a key neurotransmitter at both terminals of this network, the central nervous system and the gastrointestinal tract. Accumulating evidence points to a critical role for the gut microbiome in regulating normal functioning of this axis. In particular, it is becoming clear that the microbial influence on tryptophan metabolism and the serotonergic system may be an important node in such regulation [10].

Brain - gut interaction is important and the psychological stress has been postulated to cause FGID; probably due to changes in the 'brain-gut axis', altering the perception of visceral sensation [11,12]. This may lead to a phenomenon known as 'visceral hyperalgesia'. There is agreement that altered gastrointestinal function is the root cause of various FGIDs, and these could stem from motility abnormality, visceral or central hypersensitivity, altered mucosal immune function, altered gut mucosa composition, Brain-Gut dysregulation etc

Types of FGID

Rome IV has redefined functional gastrointestinal disorders (FGIDs) for children.

H category is for Functional disorders: children and adolescents:

H1. Vomiting and aerophagia

- Adolescent rumination syndrome
- Cyclic vomiting syndrome
- Aerophagia

H2. Abdominal pain–related FGIDs

- Functional dyspepsia
- Irritable bowel syndrome
- Abdominal migraine
- Childhood functional abdominal pain
- Childhood functional abdominal pain syndrome

H3. Constipation and incontinence

- Functional constipation
- Nonretentive fecal incontinence.

Common symptoms in FGID

The symptoms are dependent on the type of FGID, however the common symptoms are:

- Abdominal pain
- Abdominal distention
- Nausea
- Vomiting
- Chronic diarrhea or constipation
- Fecal soiling

- Bloating
- Belching
- Nausea
- Retching
- Vomiting,
- Regurgitation
- Heartburn
- Food refusal.

Presentation of FGID

Individual conditions may have different presentations, with redefined symptomatology and grouping in Rome IV Functional dyspepsia is now considered commonest presentation.

Functional dyspepsia

Functional dyspepsia has been defined by the Rome IV criteria and must include 1 or more of the following bothersome symptoms at least 4 days per month for at least 2 months before the diagnosis is made:

- Postprandial fullness
- Early satiation
- Epigastric pain or burning not associated with defecation
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

Irritable bowel syndrome

IBS has been defined by the Rome IV criteria and all these must be fulfilled for at least 2 months before a diagnosis of IBS can be made:

- Abdominal pain at least 4 days per month associated with one or more of the following:
  - Related to defecation
  - A change in frequency of stool
  - A change in form (appearance) of stool
- In children with constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not irritable bowel syndrome)
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition.

Abdominal migraine

Rome IV criteria have specified certain characteristics for diagnosis of abdominal migraine and all these criteria should be fulfilled at least twice in the preceding 6 months:

- Paroxysmal episodes of intense, acute periumbilical, midline or diffuse abdominal pain lasting 1 hour or more (should be the most severe and distressing symptom)
- Episodes are separated by weeks to months.
- The pain is incapacitating and interferes with normal activities
- Stereotypical pattern and symptoms in the individual patient
- The pain is associated with 2 or more of the following:
  - Anorexia
  - Nausea
  - Vomiting
  - Headache
  - Photophobia
  - Pallor
- After appropriate evaluation, the symptoms cannot be cannot be fully explained by another medical condition.

Functional abdominal pain – Not otherwise specified epidemiology

This has been described in the Rome IV criteria for FGIDs and is characterised by a set of criteria all of which should be fulfilled at least 4 times per month for at least 2 months before diagnosis is made:

- Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g. eating, menses)
- Insufficient criteria for irritable bowel syndrome, functional dyspepsia, or abdominal migraine
- After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition.

RED flag signs in FGID

- Abdominal pain or diarrhea that wakes the child from sleep
- Delay in onset or progression of puberty
- Faltering growth
- Family history of inflammatory bowel disease, celiac disease

- History of significant weight loss
- Multiple episodes of bleeding per rectum
- Pain abdomen in right upper/lower quadrant
- Persistence of severe vomiting or diarrhea
- Persistent joint pains
- Recurrent unexplained fever
- Stools that may be difficult to flush away
- Unexplained pallor.

Management

A Comprehensive approach is needed for pediatric functional GI disorders. Thus a multidisciplinary treatment approach that combined gastrointestinal, pain and psychologic factors helped improve symptoms in children with functional gastrointestinal disorders.

Many pharmacologic and non-pharmacologic interventions are proposed, however we suggest a multipronged approach with strong emphasis on a biopsychosocial explanation for FGIDs may have positive effect and enable recommendations previously not perceived as helpful to the families.

Pharmacological treatment

The pharmacological interventions are based on symptoms and although commonly implemented, the outcomes variable as it doesn't address the root cause.

In fact, the evidence for pharmacological treatment in children with FGIDs is 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.

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.

The role of placebo in functional disease in general is substantial but need to be carefully planned.

Non-pharmacological treatment strategies

Non-pharmacological therapies are found effective and these include (1) dietary modification, (2) probiotic supplementation, and (3) bio-psychosocial intervention [13].

Dietary modification

Dietary modification is one of the most frequently used strategy to approach a child with FGIDs and is generally easily accepted by both children and parents. Dietary intervention may involve excluding or significantly reducing a specific ingredient or a group of foods from the diet, such as lactose; fructose; dairy products; fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs); and gluten, or even increasing the daily intake of other foods, such as fiber-rich food and water.

The typical low-FODMAP diet is a two-step intervention, step 1 is 2 to 6 week complete elimination of all slowly absorbed or indigestible short-chain carbohydrates, followed by-if symptoms have decreased substantially a structured reintroduction of specific FODMAPs, according to tolerance. Although, the efficacy of a low-FODMAP diet is well-established, but the success of maintaining this regimen for the long term in children, as for other similar dietary intervention, remains contentious [14].

Another part of a useful dietary intervention is the elimination of foods and drugs that specifically are known to cause problems. Chocolate, caffeine, spicy and fatty foods; nitrite- and amine-containing foods; and non-steroidal anti-inflammatory drugs may trigger abdominal symptoms in children with FAPS.

Fiber **-** The importance of the amount of fiber in the diet of children with FAPS has been proposed for long [15]. The proposals include soluble and non-soluber fibres, solubles being slightly better. A randomized, double-blind pilot study in 60 children (aged 8–16 years) with FAP demonstrated that a specific type of fiber, called partially hydrolyzed guar gum (PHGG), probably has beneficial effects on symptom control [16]. The mechanisms involved however seem to be modulation of the intestinal microbiota, similar to prebiotics, and normalization of stool frequency.

Probiotics supplementation

The human microbiota have drawn a lot of interest in the recent

years. It is assessed to be composed of more than 1×10^{14} bacterial cells, ten times the number of human cells. Fortunately or unfortunately, the majority of the human microbiota lives in the gut lumen and there is plenty of evidence to suggest that our intestinal microbes carry out the many important functions: (1) enhancing gut barrier function; (2) inhibiting pathogen binding by binding themselves to small and large bowel epithelium and producing substances that inhibit the growth of other pathogenic organisms; (3) modulating the gut inflammatory response by modulating the gastrointestinal lumen towards an anti-inflammatory state; (4) reducing visceral hypersensitivity associated with both inflammation and psychological stress; and (5) altering colonic fermentation by converting undigested carbohydrates into short-chain fatty acids and improving gut function.

Research over past few years has suggested a strong association between modification of the intestinal microbiota and IBS, constipation, diarrhea, and FAP [17-19]. Over time, several different strains of probiotics have been tested as potential treatments for children with FGID, with the most commonly used being *Lactobacilli* and *Bifidobacteria*.

Bio-psychosocial interventions

Cognitive Behavior Therapy - CBT demonstrates its psychotherapeutic effect by addressing dysfunctional emotions, maladaptive behaviors and cognitive processes and contents through a number of goal-oriented, explicit systematic procedures. Behavioral procedures include identification of verbal and non-verbal pain behavior and how family members, teachers and caregivers react to it and are addressed by interventions such as physical exercise to promote relaxation, breathing exercises and muscle relaxation techniques taught by trained therapists. Several RCTs have demonstrated the effectiveness of psychological therapies for pediatric FAP [20,21].

Hypnotherapy has also been found effective. Gut-directed hypnotherapy is a trance-based therapy in which a therapist gives the child suggestions aimed at changing intestinal hypersensitivity, ego-strengthening and stress reduction. Evidence suggests 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 [22].

Yoga has been increasingly sought after natural remedy for FIGD [23]. Even young children can be taught general relaxation exercises, breathing exercises, focused training for abdominal muscle relaxation and positive reinforcement and may be considered as a form of behavioral therapy. It can be considered as a sport-like activity and may be attractive option for older children to stay fit. Yoga is well known to calm the mind and the beneficial effect is thought to be related to a positive influence on Brain-Gut axis which is deranged in FGID.

It's important for the paediatrician, paediatric gastroenterologists as well as primary care physician to be aware of the multifaceted dimensions of FGIDs so that they can manage these more effectively.

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