The evaluation and management of recurrent abdominal pain in childhood

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Abstract

Recurrent abdominal pain (RAP) is a common complaint in children. Previously considered a single entity, RAP is now used as a descriptive term and sub-classified in the recently published Rome IV criteria, into four functional abdominal pain disorders (FAPD), including functional dyspepsia and irritable bowel syndrome. All share common pathogenic mechanisms of visceral hypersensitivity and central hypervigilance, resulting from disruption of the microbiota–gut–brain axis and abnormal enteric neuro–immune interactions. Although FAPDs are benign in nature, the persistence of symptoms and effects on everyday life can have significant secondary effects including psychosocial morbidity. The diagnosis of FAPDs is based on careful history and examination looking for 'alarm signs', although a limited battery of laboratory investigations to screen for organic disease may be of value. The management of FAPDs should be multidisciplinary and based on the bio-psychosocial model of care with careful education and engagement of patients/parents. There is currently little evidence to support the routine use of pharmacotherapy, probiotics or diet and a significant placebo effect should be considered when assessing treatment effect. Hypnotherapy has been shown to be an effective therapy. Approximately 50% of FAPDs cases will achieve resolution, especially those that have engaged with the appropriate model of management.

Keywords children; functional abdominal pain disorders; irritable bowel syndrome; microbiota–gut–brain axis; recurrent abdominal pain

How common? UK and worldwide

''Recurrent abdominal pain'' (RAP) is a common complaint in children and accounts for 2–4% of all paediatric clinic visits. In their seminal work with Bristol school children in the late 1950s two UK paediatricians, Apley and Naish found that approximately 10% of the children were reporting RAP. This ballpark figure of prevalence still stands to this day and appears to be similar across other countries worldwide.

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Definition

In the past RAP in children was considered to be a single clinical entity. In their study Apley and Naish defined RAP on the basis of four main criteria namely: (1) ≥more than or equal to three episodes of abdominal pain; (2) pain sufficiently severe to affect the child's activities; (3) episodes recurring over a period of ≥ more than or equal to three months; and (4) no known organic cause. Better classification of symptom profiles along with clinical and laboratory evaluations in more recent years, however, suggests that functional gastrointestinal disorders (FGIDs) are more complex, and include conditions with both organic and functional etiologies.

Several terms have been used interchangeably with FGIDs including "non-organic abdominal pain", "psychogenic abdominal pain", and "functional abdominal pain", causing confusion. The challenge in conditions of "chronic abdominal pain" has not only been to differentiate between organic and so-called functional etiologies but also to understand whether the many presentations of pain and its associations constitute a single phenotype.

In the late 1990s an international initiative (The Rome Foundation) established the Rome criteria for FGIDs. The aim was to improve the diagnosis and classification of these conditions. In May 2016 the latest revision of these criteria was released (Rome IV criteria). Abdominal pain-related functional gastrointestinal disorders/AP-FGIDs (Rome III), which essentially relate to RAP in children, have now been renamed as functional abdominal pain disorders (FAPDs). FAPDs have been further sub-classified into a number of disorders, namely abdominal migraine, functional dyspepsia, irritable bowel syndrome, and functional abdominal pain- 'not otherwise specified'. Each constitutes a variable combination of symptoms but with considerable overlap between the entities. By definition the disorders are not secondary to any identifiable organic condition, but may coexist with other medical conditions. For the remainder of this review the term 'FAPD' will be used to denote all references to the original term of RAP and subsequent terminologies for RAP from Rome criteria pre-Rome IV.

Epidemiology

FAPDs have a reported prevalence in western countries of between 0.3% and 19% in the paediatric population with peaks at age 4–6 years (slightly more prevalent in boys) and in early adolescence (more prevalent in girls). In a 2015 meta-analysis of 58 studies that included 196,472 children from all around the world, the pooled prevalence of FAPDs was 13.5%.

Pathology, pathogenesis and applied physiology

The two final common mechanisms involved in the pathogenesis of FAPDs, are (i) visceral hypersensitivity and (ii) central hypervigilance. In simplest terms they respectively represent a lowered threshold of sensitivity to stimuli in the bowel and

altered processing of 'pain' sensations coming into the brain from sensory fibres in the GI tract.

Visceral hypersensitivity

Visceral pain receptors (nociceptors) on afferent nerves of the inherent nervous system of the GI tract (called the enteric nervous system or ENS) respond to several stimuli, i.e. mechanical (contraction, distension) and chemical (substance P, bradykinin, serotonin, histamine) released in response to ischaemia or inflammation. Signals from stimulated afferent nerves pass through or near paravertebral ganglia on their way to the spinal cord. From here messages pass up to the brain for processing (e.g. location, context) and via reflex pathways to autonomic ganglion cells, which influence secretory and motor functions.

In children with FAPDs, both types of afferent neurons (i.e. those that respond to low-pressure stimuli (nociceptors) and to high-pressure stimuli) become sensitized and show altered patterns of excitation evoked at lower thresholds. In children suffering from Irritable Bowel Syndrome (IBS) this can be shown by rectal barostat studies by reports of discomfort at lower rectal distention pressures compared to control patients.

Central hypervigilance

The co-ordination of gut functions with overall body homoeostasis requires continuous communication between the CNS and the GI tract. The processing of visceral pain signals is also performed by the CNS and provides contextual information and determining appropriate responses. Evidence suggests that altered central processing underlies FAPDs, by influencing the perception of pain in these individuals (hyperalgesia). Studies with functional brain MRI suggest that in adults with FAPD there appears to be increased metabolic activity in cortical areas that are concerned with the processing of pain.

Overall, the enhanced responsiveness described above results not only in heightened pain sensation and awareness but also in dysregulation of gut epithelial (i.e. immune, permeability) and neuromuscular function, which in turn produce characteristic symptoms of FAPDs e.g. irritable bowel syndrome symptoms.

Although, both these states appear to involve alterations in the function of neural pathways or processing areas, these seem to occur as a result of insults to components of the so-called gut–brain–microbiota axis as well as neuro–immune interactions within the gut itself. The relatively recent recognition of the gut–brain–microbiota axis, a complex cross-talk between these elements, has heralded not only a better understanding of the pathogenesis of FAPD in children including the potential of 'early life programming' but has also given us insights into the pathogenesis of a whole spectrum of human diseases. A plethora of factors e.g. genetic (e.g. family history of IBS), early life events (e.g. pyloric stenosis, gastroschisis/gastric surgery and nasogastric tube suction), environmental triggers (e.g. cow's milk protein allergy, post-enteritis syndrome), gastrointestinal factors (e.g. inflammation/infections, trauma, early exposure to antibiotics/altered gut microbiome) as well as psychosocial triggers (e.g. abuse, stress, anxiety), may contribute in the complex uncharted pathways that interact and ultimately alter the 'gut microbiome–brain–CNS-immune' axis and the perception of pain (see Figure 1).

Course of the disease

As mentioned before, the term FAPD embodies a spectrum of conditions under the umbrella of abdominal pain-related functional GI disorders. Each may vary in course and severity, and have different presentations in different age groups. In the majority of patients, no organic cause is identified. FAPDs usually develop gradually and are benign in nature, but the persistence of symptoms and their effects on everyday life, cause significant secondary distress and ultimately psychosocial dysfunction to patients and their families. Long-term follow-up of children with FAPD reveals that approximately 50% of them will eventually progress to complete resolution of their symptoms. In those that do not recover persistence of symptoms and ultimately progression to psychological and psychiatric disorders is a concern.

Diagnosis

Given that in the majority of cases no significant pathology can be identified, even following extensive and often interventional investigation, the diagnosis of FAPD is dependent on careful history and examination. The Rome Foundation has taken on the challenge of establishing symptom-based diagnostic criteria for FGIDs because of a current lack of diagnostic biologic markers. The Rome III, and most recently the Rome IV criteria are largely based on findings from published literature and suggest that FGIDs should be considered as a positive diagnosis and not one of exclusion.

The Rome IV criteria for the four subgroups of abdominal pain-related FGIDs are summarized below. They are further divided, on the basis of differences in symptoms, into two age groups; one for the functional disorders of the infant/toddler (up to 4 years old) and one for the disorders of the child/adolescent. For both of the sub-groups the criteria are similar, varying in regards to the duration of symptoms and/or structural or biochemical and behavioural differences in between the two age groups.

The FAPDs for the child/adolescent group are divided into four sub-groups:

(i) *Functional dyspepsia* (*FD*): when one or more of the following symptoms occur (postprandial fullness, early satiety, epigastric pain or burning sensation not related with defaecation), for at least 4 days per month, and for a period of more than or equal to 2 months prior to diagnosis, and the symptoms cannot be fully explained by other medical condition. FD incorporates two subtypes; a. Postprandial distress syndrome (i.e. fullness or early satiety, with or without upper abdominal bloating, nausea or excessive belching) and b. Epigastric pain syndrome (severe pain or burning sensation localized in the epigastrium or to abdominal/chest regions that is not relieved by defaecation, and may be accompanied by a burning quality of pain of non-retrosternal nature, or pain induced or relieved by eating, but may occur while fasting).

(ii) *Abdominal migraine* (*AM*): when there are paroxysms of intense and acute periumbilical, midline or diffuse abdominal pain, (with duration more than or equal to 1 hour) that can affect the child's normal activities and are associated with more than or equal to two of the following