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Functional abdominal pain is the main etiology among children referred to tertiary care level for chronic abdominal pain

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ABSTRACT – **Background** – Chronic abdominal pain (CAP) carries a significant burden of disease. The last edition of the Rome Criteria (Rome IV) allows the diagnosis of functional gastrointestinal disorders (FGIDs) according to symptoms-based criteria; however, patients continue to experience a delay in their diagnosis and to be submitted to different interventions before the establishment of a positive diagnosis. **Objective** – We aimed to characterize etiology, clinical features, and interventions in a pediatric cohort of patients with CAP secondary to FGIDs, who were referred to our tertiary care university-affiliated hospital, in Brazil. **Methods** – A retrospective descriptive study of children and adolescents (aged 20 years and younger) referred to our institution, from January/2013 to December/2018, for CAP, and who fulfilled criteria for FGIDs classified according to Rome IV criteria. **Results** – Three hundred twenty-eight patients with CAP were screened, of which 67.9% (223 patients) fulfilled the criteria for FGIDs and were included in the study. Sixty percent were female, with a mean age of 8.3 years. At the time of referral, the mean duration of symptoms was 2.8 years. Length/height for age and weight for age mean z-scores were -0.08±1.87 and -0.38±1.62, respectively. Functional abdominal pain not otherwise specified was overall the most common diagnosis (70.4%). Before establishing the diagnosis of FGIDs, multiple pharmacological interventions were described, while after, the mainstay of therapy was education/reassurance and dietary interventions. Thirty-two percent of patients did not further require specialized follow-up. **Conclusion** – Even at the tertiary care level, FGIDs were still the most common etiology of chronic abdominal pain, particularly functional abdominal pain not otherwise specified. Despite the relatively long duration of symptoms at referral, cessation of specialized care follow-up was possible in approximately a third of the cases.

Keywords – Children; adolescents; abdominal pain; functional disorders; Rome IV.

INTRODUCTION

Chronic abdominal pain (CAP) in childhood constitutes a significant time-consuming clinical problem for healthcare practitioners, and it carries an important psychosocial burden for patients and their families[1]. Among school-age children, the prevalence of CAP reported ranges widely from 10 to 45%[2-6], and it is estimated that CAP accounts for up to 5% of pediatric primary care visits[7]. It is estimated that around 90% of children with chronic abdominal pain do not have an organic cause for their abdominal pain, and even though the diagnosis of functional etiology could be established in children without any alarm symptoms or "red flags", still at least one-quarter of these children undergo diagnostic testing[8].

Functional gastrointestinal disorders (FGIDs) are diagnosed following well-established clinical principles summarized in the Rome Criteria for childhood functional gastrointestinal disorders, last updated in 2016[9,10]. The most substantial contribution of Rome IV was to present evidence and systematization of clinical criteria to support a "symptom-based diagnosis", which led to the end of an era in which the diagnosis of functional disorders had to be preceded by the exclusion of organic diseases'.

Despite the relatively benign nature of the symptoms in FGIDs and the growing evidence that supports taking away the focus on testing, in many instances patients still undergo extensive testing, receive treatments that are not supported by an evidence-based approach, and/or are referred for specialist (further) evaluation and follow up. In that context, we aimed to describe the demographics, etiology, and interventions in a pediatric cohort of patients with CAP secondary to FGIDs, referred to a tertiary care university-affiliated hospital, in Brazil.

METHODS

A descriptive retrospective cohort study of children and adolescents referred to tertiary care for CAP from January/2013 to December/2018. Patients were identified from their ambulatory visits to the divisions of General Pediatrics and/or Pediatric Gastroenterology, in the Department of Pediatrics at *Faculdade de Ciências Médicas*, *Universidade Estadual de Campinas* (UNICAMP), Campinas, SP, Brazil.

Inclusion criteria were as follows: 1) children and adolescents younger than 20 years of age, 2) reason for referral having CAP

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as the main complaint, 3) diagnosis of FGIDs following Rome IV criteria definitions for childhood FGIDs[9,10], 4) absence of chronic diseases or the use of medications that could cause abdominal pain. Patients were excluded from the analysis if on follow-up there were diagnosed with any condition known to cause abdominal pain, for example, with lactose intolerance.

Data collected included gender, age, anthropometrics, clinical presentation, classification of FGIDs according to Rome IV criteria, interventions, and resolution of symptoms with discontinuation of follow-up in the tertiary care setting. Among the interventions, we collected data on additional tests used to investigate organic causes, as well as dietary changes, the use of medication and non-pharmacological measures to treat functional abdominal pain. Data were summarized with descriptive statistics.

This study was approved by our Institutional Research Ethics Board.

RESULTS

During the study period, 328 patients with CAP were referred to our center, of which 223 patients (67.9%) fulfilled the criteria for FGIDs as per Rome IV criteria definitions[9,10]. The majority of patients were female (60%), with a mean age of 8.3 years (between 2 months and 20 years old). At the time of initial evaluation in our institution, the mean duration of symptoms was 2.8 years. Length/height for age and weight for age mean z-scores were -0.08±1.87 and -0.38±1.62, respectively.

Among the FGIDs, functional abdominal pain not otherwise specified was by far the most common diagnosis, in 70.4% of cases, followed by functional constipation – 13.9%, and functional dyspepsia – 9.4%. The Rome IV diagnostic classification of all patients who fulfilled the criteria for FGIDs is summarized in TABLE 1.

TABLE 1. Rome IV diagnostic classification of 223 patients with functional gastrointestinal disorders referred to tertiary care for chronic abdominal pain.

Functional gastrointestinal disorder	Overall number (n=223)	Percentage (%)
Functional abdominal pain not otherwise specified	157	70.4%
Functional constipation	31	13.9%
Functional dyspepsia	21	9.4%
Abdominal migraine	10	4.5%
Functional diarrhea	6	2.7%
Irritable bowel syndrome	5	2.2%
Cyclic vomiting syndrome	2	0.9%
Rumination syndrome	1	0.4%
Infant colic	1	0.4%

All the 328 patients with CAP underwent additional tests to investigate organic causes. The most frequent were abdominal ultrasound in 48% of cases, complete blood count – 43%, urinalysis – 35%, upper digestive endoscopy – 35%, serum amylase – 25%, stool for ova and parasite – 25%, and abdominal radiography – 9%.

Before establishing the diagnosis of FGIDs, many treatments had been trialed, including: antiparasitic drugs, proton pump inhibitors (PPIs), and histamine H2-receptor antagonists (before ranitidine products were withdrawn from the market in Brazil) were the most common therapies used, in 18.2%, 26% and 19.2% of cases, respectively. Less commonly, the use of prokinetic agents (such as domperidone) – in 12.5%; analgesics (acetaminophen and dipyrone) – in 4.9%, and, other interventions, including *H. pylori* eradication treatments and dietary interventions – in 4.9% were also described. The relative frequency of all the main treatment modalities trialed in children with FGIDs before establishing the diagnosis of a functional disorder is presented in FIGURE 1.A.

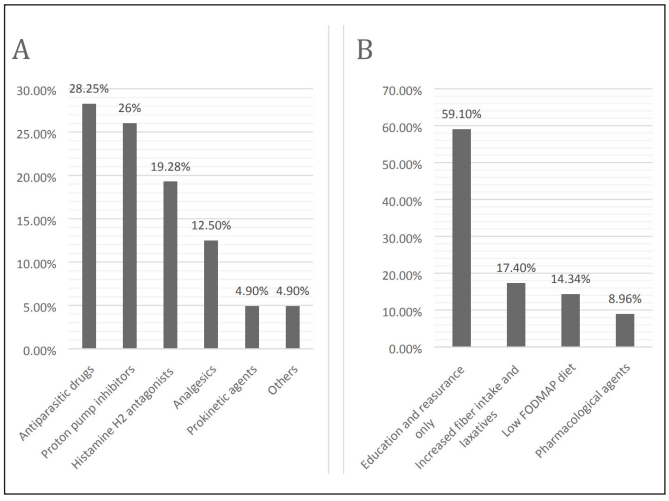

FIGURE 1. Relative frequency of the main interventions prior to establishing the diagnosis (A) of functional abdominal pain vs. interventions later established at tertiary care (B).
FODMAP: fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

Meanwhile, interventions established at the tertiary care level once the diagnosis of FGIDs was established mainly focused on patient/parental education and reassurance – in all cases and reported as the only therapeutic intervention in 59.1% of cases. In selected cases, other dietary and pharmacological interventions were used, such as increased fiber intake and laxatives – in 17.4%; low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet – in 14.3%; and the use of other pharmacological agents targeting FGIDs – in 8.9%. The relative frequency of interventions established at tertiary care, after diagnosis of FGIDs is presented in FIGURE 1.B. Adjustments of dietary fiber intake and laxatives (polyethylene glycol, lactulose, and magnesium hydroxide) were reserved for cases of functional constipation; while a low FODMAP diet or reduction in the consumption of FODMAPs was recommended for selected cases in which clinical history was suggestive that the ingestion of these carbohydrates triggered the abdominal pain. Pharmacological treatment targeting FGIDs was highly individualized and included: amitriptyline, flunarizine, and cyproheptadine. Almost a third of patients (32.7%) had complete resolution of their symptoms and did not require further follow-up for this complaint.

DISCUSSION

It is well known that the overwhelming majority of children with chronic abdominal pain has no underlying organic disease – 90 to 95%[8,11]. However, it would be intuitive to expect a lower percentage among patients whose symptoms' severity, duration

and/or burden had led to a referral to tertiary specialized care. Indeed, in our study, we found that amidst 328 patients with CAP referred to a tertiary care university-affiliated hospital in Brazil, approximately 68% of patients fulfilled Rome IV criteria for FGIDs. Female predominance (60%) and the mean age of 8.3 years were compatible with previous literature reports recently summarized in a systematic review of the literature[6]. On initial assessment at specialized care, nutritional status – inferred grossly from length/height for age and weight for age z-scores – was overall normal, despite the relatively prolonged duration of symptoms (mean duration at referral of 2.8 years), as it would be expected given the benign nature of FGIDs[11]. And even though the current knowledge on FGIDs support a "symptom-based diagnosis" – well-characterized on Rome IV[9,10], we report some investigation to exclude organic causes were performed in all cases. We hypothesize that this finding could be explained by the long duration of symptoms and also a referral bias of a tertiary center.

As the majority of the studies so far have focused on epidemiology and clinical features of the general pediatric population with FGIDs, little is known about those patients who are not retained at the primary care setting and are referred to specialized care. Our study focuses on this specific setting at a tertiary care university-affiliated hospital in Brazil. By far, the most commonly observed diagnosis was functional abdominal pain not otherwise specified. Interestingly, even though the reason for referral was CAP, functional constipation not previously identified was found in 13.9% of cases. These findings differed from those previously published in a Colombian cross-sectional study, also on FGIDs diagnosed based on Rome IV criteria, which reported that functional dyspepsia and irritable bowel syndrome (IBS) were more frequent than FAP-NOS and functional constipation[12]. We hypothesize these differences are likely explained by the fact that their cohort reflected a broad pediatric population, while our study population is narrower – i.e. patients referred to tertiary care level. Our study found a relatively low prevalence of IBS (five patients – 2.2%), compared to other pediatric publications[13] – we hypothesize that this finding relates to the fact that IBS is diagnosed in older children, while our population patients had a mean age of 8.3 years. Regarding constipation, since the mean duration of symptoms before referral was 2.8 years, it is arguable whether or not it was the initial presentation or whether it developed later reflecting maladaptive behavioral responses or dietary changes. Regardless, it is important to remember that the burden of constipation is often underestimated[14], and it should be considered in the differential diagnosis even if the main complaint is abdominal pain. Functional constipation was recently reported among the most common FGIDs, especially in infants and toddlers[15]. Finally, another intriguing finding was that some of the diagnosis found (summarized in TABLE 1) were not FGIDs in which abdominal pain is typically an associated symptom but not a main complaint, such as functional diarrhea, cyclic vomiting syndrome and rumination syndrome.

Multiple mechanisms have been proposed and studied among the different disorders that fall under the umbrella of FGIDs. To this date, no single mechanism can explain its pathogenesis – and it is unlikely that we will ever find an isolated explanation: these disorders are heterogeneous, and seem to result from a complex interaction between genetics and environmental factors, such as gastrointestinal infections and inflammation, visceral hypersensitivity, psychological stressors, abnormal intestinal motility, among others[16]. The understanding of these specific pathophysiologic mechanisms is an evolving area: while earlier studies focused on alterations in motility and visceral hypersensitivity, more recently the focus has changed to the underlying role of the intestinal microbiota and host immune responses, the bidirectional communication between the central and the enteric nervous systems and genetic factors[17,18].

Our current knowledge does not allow the precise indication of specific interventions to target-directed mechanisms when treating FGIDs. It is, however, well documented that some of the commonly used pharmacological interventions used in this context have minimal or no effect[19-21], and therefore, should not be routinely recommended. Some of these therapies, such as PPIs, ranitidine, domperidone and others, were often used in our cohort of patients before to establishing the diagnosis of FGID. Specifically, regarding *H. pylori* eradication, the joint North American and European Societies for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN, respectively) guidelines recently published categorically affirmed that studies in children do not support a role for *H. pylori* infection in functional disorders, and strongly recommended against diagnostic testing for *H pylori* infection in children with functional abdominal pain, based on high-quality evidence[22].

On a different note and as a reality which is more specific to resource-limited countries, the use of antiparasitic drugs was very common in our cohort – even though such practice should be directed only to cases when the cause of abdominal symptoms is proven to be related to a parasitic infection[23], hence not to treat FGIDs.

With a well-established diagnosis of FGID and under specialized care, less than 10% of patients in our study received any pharmacological treatment – amitriptyline, cyproheptadine and flunarizine were used in selected patients. The evidence for the use of those drugs remains controversial – for example, there is data supporting the use of low-dose amitriptyline to treat functional gastrointestinal disorders[24], while other studies have shown results similar to placebo[20,25,26].

General principles for the management of functional gastrointestinal disorders must include first and foremost the establishment of a "positive diagnosis" (i.e. not based on the need to exclude other gastrointestinal conditions), reassurance of patients and families, with education on the benign nature of the diagnosis, appropriate adjustment of expectations, and acknowledgment of the symptoms and their impact in the quality of life; beyond that, lifestyle, dietary, pharmacological and non-pharmacological interventions should be established in an individualized basis[17,27]. Failing to provide or delaying the diagnosis, following the "traditional diagnostic approach" of ruling out a series of other conditions leads to inappropriate tests and treatments, and adds to parental concerns and frustration, increasing the burden of the disease and health care costs.

Among the non-pharmacological interventions, cognitive behavioral therapy (CBT) is the most studied. It has been demonstrated that CBT is effective to address dysfunctional emotions, maladaptive behaviors, and cognitive processes in FGIDs[16,28]. Unfortunately, at our center, as most centers in the Public Health System in Brazil, we cannot offer CBT – the reason why this modality of treatment was not reported in our study.

A healthy lifestyle and diet are always recommended as part of a "well-child" visit and these recommendations deserve special attention in the evaluation of children with FGIDs, as often pitfalls

and triggers can be identified. Despite the recognition of the role of diet in the treatment of childhood FGIDs, a recent study reported that most patients do not receive dietary recommendations, and that there is great variability in the guidance provided when these recommendations are given[29]. The most common dietary interventions are high-fiber diet or dietary fiber supplementation and low-FODMAP diet[20,29,30]. However, the overall data on fiber supplementation is functional abdominal pain disorders is inconclusive. Recently, special attention has been devoted to low FODMAPs diet as a strategy to treat FGIDs: it is hypothesized that these poorly absorbed short-chain carbohydrates may trigger gastrointestinal symptoms in patients with visceral hypersensitivity, as they exert osmotic effects in the intestinal lumen, and are rapidly fermented by bacteria[31]. In our cohort, all patients had an assessment of their diet and were provided some general guidance/education on their diet, but fiber supplementation or low-FODMAP diet were recommended on an individualized basis, in 17.4% and 14.3% of cases, respectively.

Our study limitations include the well-known weaknesses of retrospective and single-center studies. Given the retrospective nature, we have to recognize that documentation, especially of non-pharmacological interventions and education may be underestimated. Furthermore, our study reflects the practice of a single pediatric healthcare tertiary institution, and therefore, our findings should be confirmed in additional similar healthcare settings. However, the strengths of this study include our relatively large sample size, and the novelty of focusing on a population of patients different than the typically described in studies on childhood chronic abdominal pain or FGIDs, since all the patients had previously been evaluated in the primary healthcare setting.

In conclusion, functional gastrointestinal disorders still represented the majority of the cases of chronic abdominal pain referred to tertiary care, particularly functional abdominal pain not otherwise specified – this is an intriguing finding, which can be perhaps explained by the fact it is probably easier to give a positive diagnosis of a "well-defined" functional abdominal pain disorder (such as functional dyspepsia or irritable bowel syndrome) rather than a less specific one. Despite the relatively long duration of symptoms at referral, cessation of specialized care follow-up was possible in approximately a third of the cases.

Authors' contribution

Martins GP and Bellomo-Brandão MA: conceptualized the manuscript and obtained REB approval. Martins GP: collected the data and drafted the initial manuscript. Sandy NS and Alvarenga LR: supported data curation, production of the manuscript, and revision of the manuscript. Lomazi EA and Bellomo-Brandão MA: supported supervision of all stages, reviewed and edited the manuscript. All authors approved the final version as submitted.

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Martins GP, Sandy NS, Alvarenga LR, Lomazi EA, Bellomo-Brandão MA. Dor abdominal funcional é a principal etiologia em crianças encaminhadas ao nível de atenção terciária por dor abdominal crônica. Arq Gastroenterol. 2022;59(1):97-101.

RESUMO – Contexto – A dor abdominal crônica (DAC) pode acarretar importante morbidade. A última edição dos Critérios de Roma (Roma IV) permite o diagnóstico de distúrbios gastrointestinais funcionais (DGIFs) de acordo com critérios baseados em sintomas; no entanto, esses pacientes continuam a apresentar atraso no diagnóstico e a serem submetidos a diferentes intervenções antes do estabelecimento de um diagnóstico. **Objetivo** – Caracterizar a etiologia, características clínicas e intervenções de crianças com DAC que não são mantidas na atenção primária e que foram encaminhadas ao nosso hospital universitário de nível terciário, no Brasil. **Métodos** – Estudo retrospectivo descritivo de crianças e adolescentes (com idade igual ou inferior a 20 anos) encaminhados a nossa instituição, entre janeiro/2013 e dezembro/2018, por DAC e que preenchiam os critérios para DGIFs conforme o consenso de Roma IV. **Resultados** – Trezentos e vinte e oito pacientes com DAC foram triados, 67,9% (223 pacientes) preencheram os critérios para DGIFs e foram analisados. Sessenta por cento do sexo feminino, com idade média de 8,3 anos. A duração média dos sintomas no encaminhamento era de 2,8 anos. Os escores z médios de estatura para idade e peso para idade foram -0,08±1,87 e -0,38±1,62, respectivamente. Dor abdominal funcional sem outra especificação foi o diagnóstico mais comum (70,4%). Antes do diagnóstico de DGIFs, múltiplas intervenções farmacológicas foram descritas, enquanto depois, a base da terapia foi a educação, passar segurança à família e intervenções dietéticas. Trinta e dois por cento dos pacientes apresentaram resolução dos sintomas e receberam alta do acompanhamento especializado. **Conclusão** – Mesmo no nível terciário, as desordens gastrointestinais funcionais ainda constituem a etiologia mais comum da DAC, particularmente a dor abdominal funcional não especificada. Apesar da duração longa dos sintomas, alta do serviço especializados foi possível em aproximadamente um terço dos casos.

Palavras-chave – Crianças; adolescentes; dor abdominal; distúrbios funcionais; Roma IV.

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