Pediatric functional abdominal pain disorders

From diagnosis to management - a clinical approach

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Publication date
2023

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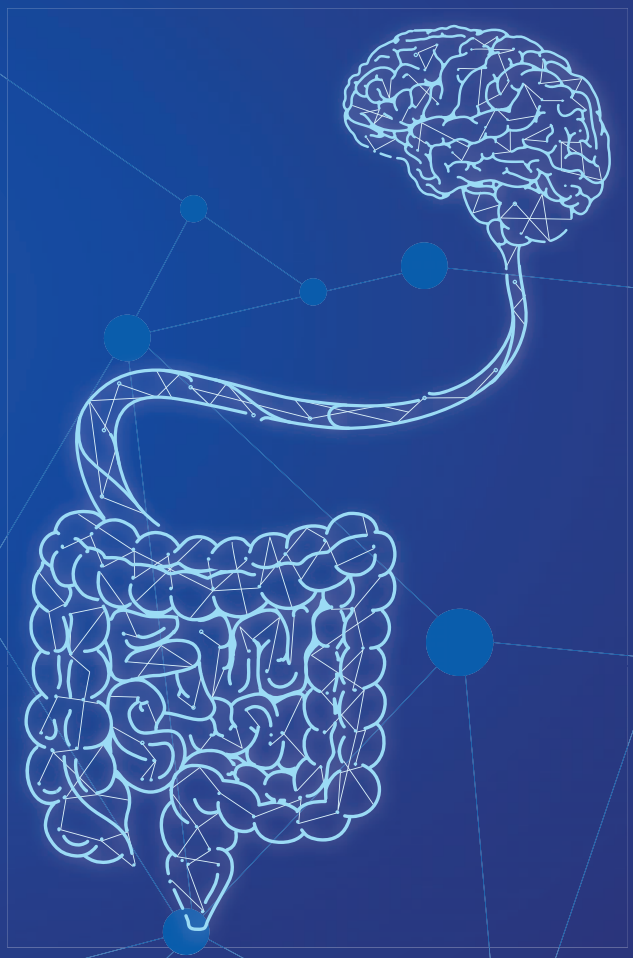

Robyn Rexwinkel

Pediatric Functional Abdominal Pain Disorders

from diagnosis to management – *a clinical approach*

Robyn Rexwinkel

Colofon

Financial support of printing this thesis was kindly provided and supported by the Amsterdam Gatroenterology Endocrinology Metabolism (AGEM) research institute, Amsterdam Reproduction & Development (AR&D) research institute, Chipsoft, Nederlandse beroepsvereniging van hypnotherapeuten, Nederlandse Vereniging voor Gastroenterologie, Nederlandse Vereniging voor Hypnose, Nutricia Specialized Nutrition, Orthica MCO Health BV, Solgar Vitamins Holland, Viatris B.V, Universiteit van Amsterdam, Will Pharma, Winclove B.V., Yakult Nederland B.V.

Cover design:	Joey Roberts
Lay-out:	Publiss | www.publiss.nl
Print:	Ridderprint | www.ridderprint.nl

Pediatric Functional Abdominal Pain Disorders

from diagnosis to management – a clinical approach

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel

op vrijdag 14 april 2023, te 10.00 uur

door

Robyn Rexwinkel
geboren te Amsterdam

Promotiecommissie

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TABLE OF CONTENTS

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Parts of this introduction have been published as:

Rexwinkel R, Vlieger AM, Saps M, Tabbers MM, Benninga MA. A therapeutic guide on pediatric irritable bowel syndrome and functional abdominal pain-not otherwise specified. Eur J Pediatr. 2022 Jul;181(7):2603-2617. doi: 10.1007/s00431-022-04459-y. Epub 2022 Apr 23. PMID: 35460383; PMCID: PMC9192445.

Pediatric functional abdominal pain disorders (FAPDs) comprise four disorders. This thesis will focus on the clinical approach of pediatric FAPDs, with a particular focus on the two most commonly diagnosed disorders: irritable bowel syndrome (IBS) and functional abdominal pain – not otherwise specified (FAP-NOS).

Part I of this thesis zooms in on the diagnostic approach of pediatric FAPDs and **Part II** and **III** describe different clinical management strategies for pediatric FAPDs. **Part IV** evaluates a shared decision making-intervention and the development of a core outcome set (COS). The corresponding chapters are highlighted accordingly.

INTRODUCTION

FAPDs are disorders of the gut-brain interaction characterized by chronic continuous or recurrent abdominal pain, and altered bowel movements in the case of IBS.[1,2] FAPDs are defined by the Rome IV criteria and comprise four disorders: functional dyspepsia (FD), IBS, abdominal migraine (AM), and FAP-NOS (**Table 1**).[2] Four subtypes can be distinguished in IBS: predominant-diarrhea (IBS-D), predominant-constipation (IBS-C), mixed or alternating stool forms (IBS-A), and unclassified (IBS-U).[2,3]

FAPDs carry a substantial socioeconomic burden and have a profoundly negative impact on quality of life and school absenteeism rates.[4–8] Furthermore, children are at higher risk of developing depression and/or anxiety disorders compared to their healthy peers.[9] A substantial group of children continued to have FAPD-related symptoms in adulthood, highlighting the clinical significance of these disorders.[10–13]

Table 1. Rome IV criteria for functional abdominal pain disorders[2]

Functional dyspepsia (FD)[a]

Must include 1 or more of the following bothersome symptoms at least 4 days per month:

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

[a]*Criteria fulfilled for at least 2 months before diagnosis.*

Within FD, the following subtypes are now adopted:

1. Postprandial distress syndrome includes bother- some postprandial fullness or early satiation that prevents finishing a regular meal. Supportive features include upper abdominal bloating, post-prandial nausea, or excessive belching
2. Epigastric pain syndrome, which includes all of the following: bothersome (severe enough to interfere with normal activities) pain or burning localized to the epigastrium. The pain is not generalized or localized to other abdominal or chest regions and is not relieved by defecation or passage of flatus. Supportive criteria can include (a) burning quality of the pain but without a retrosternal component and (b) the pain commonly induced or relieved by ingestion of a meal but may occur while fasting.

Irritable bowel syndrome (IBS)[b]

Must include all of the following:

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

[b]*Criteria fulfilled for at least 2 months before diagnosis*

Abdominal migraine (AM)[c]

Must include all of the following occurring at least twice:

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

[c]*Criteria fulfilled for at least 6 months before diagnosis.*

Functional abdominal pain – not otherwise specified (FAP-NOS)[d]

Must be fulfilled at least 4 times per month and include all of the following:

1. Episodic or continuous abdominal pain that does not occur solely during physiologic events (e.g. eating, menses)
2. Insufficient criteria for IBS, FD, or AM
3. After appropriate evaluation, the abdominal pain cannot be fully explained by another medical condition

[d]*Criteria fulfilled for at least 2 months before diagnosis*

EPIDEMIOLOGY

Pediatric FAPDs are common, with an estimated worldwide pooled prevalence of 13.5% (range from 1.6% to 41.2%) according to the Rome II and Rome III criteria.[14] IBS is the most frequently reported subtype (8.8%, 95% CI 6.2–11.9).[14] Lower and more consistent prevalence rates are found in the adult population, with numbers ranging between 1.5–3.8% (Rome IV) and 3.5–10.1% (Rome III).[15] A likely explanation for this large variety in prevalence rates is the difference in (validated) methodologies used assessing the diagnosis. Furthermore, the diversity in cultures, dietary habits, environmental circumstances, genetics and healthcare systems may play a role.[14] Evidence regarding the prevalence of pediatric FAPDs according to the Rome IV criteria is limited. Five studies are conducted in the United States, Thailand, South-America and Dutch Caribbean islands, reporting prevalence rates ranging from 5.3–16.9%.[16–20] More prevalence studies are needed to increase understanding between different populations and potential risk factors associated with FAPDs.

PATHOPHYSIOLOGY

The exact pathophysiology of FAPDs is unknown, however, an increasing body of evidence suggests that it can be best described according to the biopsychosocial model. The biopsychosocial model is based on a complex interaction of genetic, psychosocial and environmental factors.[1] Dysfunction of this model are causing disturbances in the function and/or structure of the microbiota-gut-brain axis, leading to visceral hypersensitivity and central sensitization, eventually resulting in abdominal pain and other gastrointestinal symptoms (**Figure 1**).[1] First, the core disturbances of FAPDs, visceral hypersensitivity and central sensitization, will be discussed and subsequently the other proposed multifactorial mechanisms.

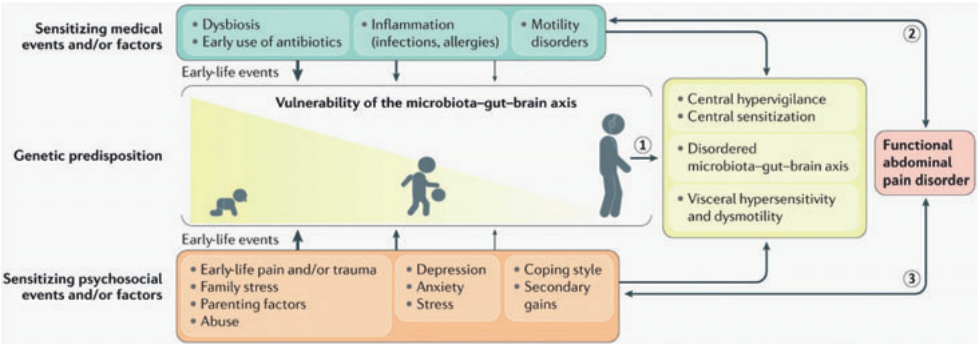

Figure 1. *Summary of the Etiopathogenesis of FAPDs.*
Reproduced with permission from Springer Nature: Thapar, N., Benninga, M.A., Crowell, M.D. et al. Paediatric functional abdominal pain disorders. Nat Rev Dis Primers 6, 89 (2020).

Visceral Hypersensitivity

Visceral hypersensitivity is described as an expanded perception of noxious (hyperalgesia) and non-noxious (allodynia) stimuli, and may be observed during distension of the bowel, such as rectal distension.[21–25] Stimuli in the gut are perceived by primary afferent neurons with their cell bodies in the dorsal root ganglia, and transduced via secondary neurons in the spinal cord to different somatosensory areas in the brain.[26] Visceral hypersensitivity is confirmed by several studies using gastric and rectal barostat, and found lower thresholds for pain in children with IBS and functional abdominal pain (FAP), compared to their healthy controls.[22,24] Children are particularly sensitive for the development of hypersensitivity early in life.[27] Studies in the adult population and animals found several triggers which possibly induce the evolvement of visceral hypersensitivity. These comprise triggers such as inflammation (infection and allergies) and stress and can basically lead to changes in mucosal permeability and an increased release of histamine, nerve growth factor (NGF), proteases, prostaglandins and neurotransmitters (such as dopamine, noradrenaline and serotonin (5-HT)) (**Figure 2**).[28–31] Recent research compared rectal biopsies of IBS patients compared with healthy controls, and found that submucosal neurons of IBS patients responded more substantially to agonists of pain-sensing receptors (TRPA1, TRPV1 and TRPV4).[32,33] Subsequently, these allogenic factors influence directly the enteric nervous system, and indirectly the brain, and are responsible for the cause of acute pain, and at the same time longer-lasting functional and structural changes.[34–37]

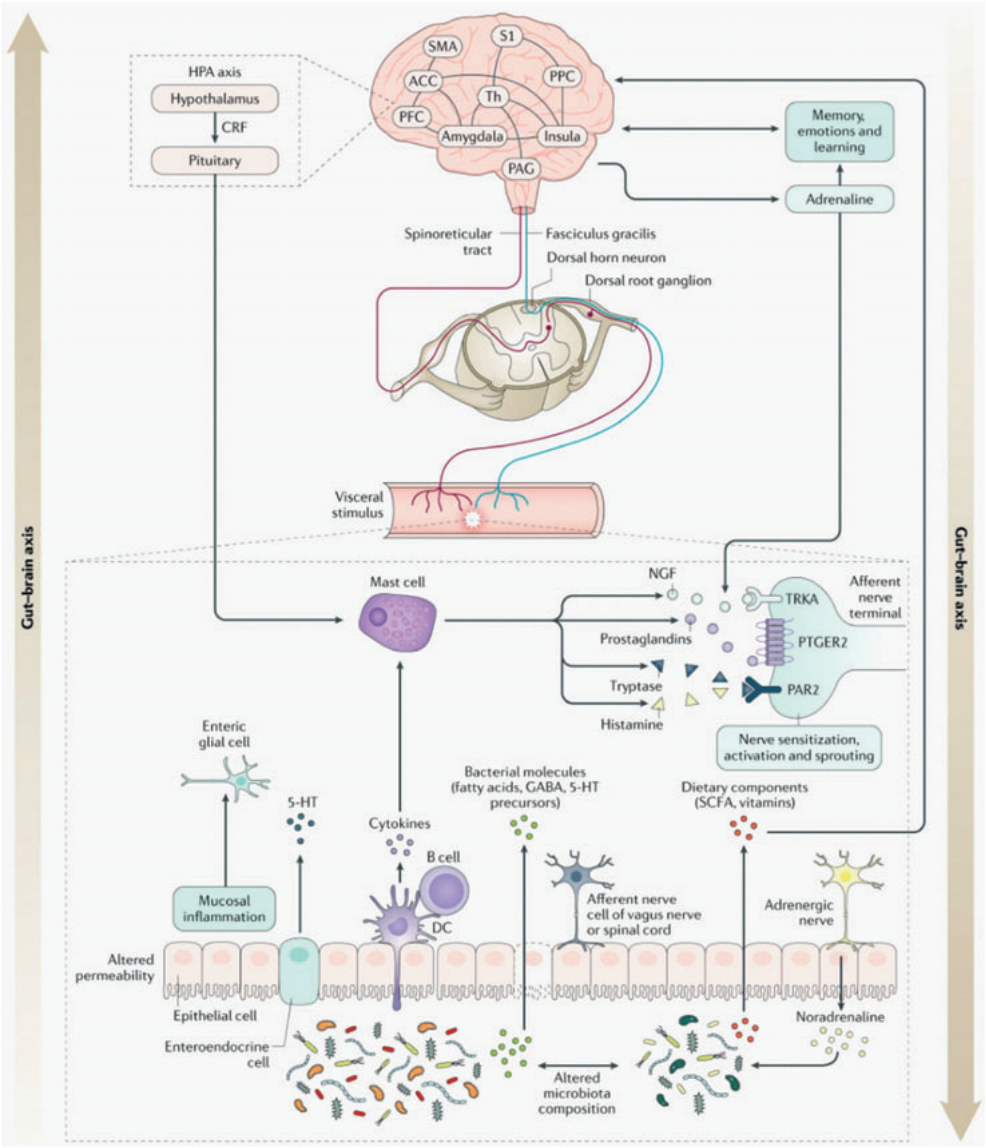

Figure 2. *Etiopathogenesis of Hypersensitivity in FAPDs.*
Reproduced with permission from Springer Nature: Thapar, N., Benninga, M.A., Crowell, M.D. et al. Paediatric functional abdominal pain disorders. Nat Rev Dis Primers 6, 89 (2020). 5-HT, serotonin; ACC, anterior cingulate cortex; DC, dendritic cell; FAPDs, functional abdominal pain disorders; HPA, hypothalamic-pituitary-adrenal; PAG, periaqueductal grey; PFC, prefrontal cortex; PPC, posterior parietal cortex; SCFAs, short-chain fatty acids; Th, thalamus.

Central Sensitization

Central sensitization is a hypersensitivity (via amplification of neural signaling within the central nervous system (CNS)) to external stimuli that are not typically painful.[38] This phenomenon can be detected by electrophysiological or imaging techniques, since it results in secondary changes in brain activity. Children with FAPDs have a higher change of developing central sensitization from an unclear source. Recent research found that secondary hyperalgesia (a centrally-mediated condition defined as increased pain sensitivity outside of the area of injury or inflammation, for example headaches, due to continuous nociceptor input from the zone of primary hyperalgesia) and altered cortical nociceptive processing is present in children with FAPDs.[39,40]

Other Multifactorial Mechanisms

Genetics and Early-life Events

Studies within families support the hypothesis that genetic predisposition contribute to the pathophysiology of FAPDs.[41] Research has shown that adults with IBS have a higher change of having siblings with a functional gut disorder compared to healthy controls.[42] Similarly, a genetic contribution to IBS was almost twofold higher in monozygotic twins than for dizygotic twins.[41,43] Also a parental history (especially the mother) of a FAPD has proven to be a strong predictor.[44] Furthermore, environmental and social influences, such as parental illness beliefs and behaviors, play a major role in the development of FAPDs, through social learning of illness behavior.[43,45,46] However, environmental and genetic factors are not conclusive, since they both play a role in the development of FAPDs, but seems to be insufficient on its own to contribute.[47] For instance, a genome-wide association study found a significant correlation between anxiety, depression and neuroticism and the risk of developing IBS. However, this is more likely due to shared pathogenic pathways, than an contribution of these symptoms causing abdominal pain on its own.[48] Other factors such as cultural aspects and socioeconomic status, or early-life events such as emotional, physical and sexual abuse, are also indicated to contribute to the pathophysiological factors of FAPDs.[46,49–55]

Gastrointestinal Motility Abnormalities

Bloating, constipation, diarrhea and abdominal distension are symptoms caused by a disrupted gastrointestinal motility.[1] Colonic transit time and muscle contractility are factors of motility which can generate these symptoms.[56] In the gastrointestinal tract, via de gut-brain axis, various stressors may lead to (1) a decreased motility, causing a delayed colonic transit (e.g., constipation in IBS-C), delayed gastric emptying, poor antral motility or stomach fullness, and (2) an accelerated colonic transit time (e.g., diarrhea in IBS-D), or both.[40,57,58] To date, there is no evidence if disturbed gastrointestinal motility contributes to the effect or the cause of abdominal pain in children.[59] For example, in clinical practice, treatment focusing on improving colonic transit, such as laxatives, does not provide sufficient relief of abdominal pain in children with IBS-C.[2,40]

Microbiota

It is assumed that composition and diversity of gut microbiota possibly influence the pathophysiology of FAPDs, especially in IBS, by altering the gut-brain axis.[56,60–67] The diversity of the microbiota from patients with IBS is either decreased or unchanged, and can develop FAPD symptoms.[60,67] Still, the role of the microbiota is questioned, particularly because it is unclear what comprises a healthy microbiome. To date, no significant association has been found between FAPD symptoms and cross-sectional gut microbiota dysbiosis in the adult and pediatric population. A recent systematic review compared gut microbiota composition in children and adults with IBS compared to health controls.[68] A significant decrease of the genus *Bifidobacterium* was found in patients with IBS compared with healthy controls. Furthermore, the potentially harmful bacteria genus *Bacteroides*, family *Enterobacteriaceae* and family *Lactobacillaceae* were increased in IBS patients compared with healthy individuals. Still, there are some limitations concerning the methodology used in the included studies and therefore results should be interpreted with caution. More studies are needed using a standardized approach for microbiota sample collection, identification and processing to elucidate the role of the microbiome in IBS. Fecal microbiota transplantation (FMT) may be a potential future therapeutic strategy in IBS patients.[69,70] However, results in adult IBS studies have shown conflicting results and data in the pediatric population is lacking. Therefore, no valid conclusions on the efficacy of this treatment for pediatric IBS can be drawn. Furthermore, stool donor recruitment, screening,

follow-up, and high costs associated with FMT intervention trials are challenging. In a recent Dutch cohort study, only 10% of the potential stool donors could be enrolled. The presence of the protozoa *Dientamoeba fragilis* and *Blastocystis* spp. often caused the exclusion of the participants.[71]

Inflammation and Immune Activation

The activation of immune cells, altered membrane permeability and the development of low-grade gut inflammation are proposed to be part of the pathophysiology of FAPDs.[72] This is supported by studies in adults and children, which found an association between the development of IBS after an episode of acute gastroenteritis.[73–75] This is also known as post-infectious IBS (PI-IBS): persisting gastrointestinal symptoms after an gastrointestinal infection with predominantly *Campylobacter* species, *Escherichia coli*, and *Salmonella* species.[74,76] Up to 10% of patients with infectious gastroenteritis develop PI-IBS.[77,78] Two mechanisms are regarded as the basis of PI-IBS: (1) changes in immune function, and (2) changes of tight junctions which leads to an increased permeability.[79,80] This results in stimulation of the immune system, causing an aggravate release of inflammatory cytokines and low-grade mast cell activation.[81–84] Mast cells play a major role in allergic reactions and food-induced abdominal pain. Mast cells are directly activated by psychological stress as well as by bacterial or food-derived products, by binding Immunoglobulin E (IgE) and releasing neurotropic mediators such as histamine and NGF.[29,30,85] The role of mast cells in food-induced abdominal pain will be discussed subsequently.

Nutrition

The role of diet in the pathogenesis of pediatric FAPDs has been of great interest in the last decade, with up to 90% of patients reporting that at least one food and/or food type is associated with aggravation of their gastrointestinal symptoms.[86] Consequently, children often avoid a long list of specific foods.[86–90] Reactions to food that potentially trigger IBS symptoms can be divided into two groups: (1) immune reactions and (2) non-immune reactions.[91] Immune reactions comprise a complex interaction of various mechanisms including the patient's diet, immune system and the microbiota, which activate different intestinal pain pathways.[92] The immune response to specific foods can activate the production of local dietary-antigen-specific IgE antibodies and mast cell dependent mechanisms, inducing

visceral hypersensitivity.[93,94] The difference between food-induced abdominal pain and classic food allergy, is that IgE-antibodies are only observed in colonic tissue, creating a local, instead of an systemic immune response against dietary antigens.[94] For example, an unfavorable effect of gluten is frequently reported.[95] A clinical condition that has not been studied sufficiently in children is non-celiac gluten sensitivity. This condition is defined as worsening or triggering of gastrointestinal symptoms in the absence of a diagnosis of celiac disease.[96] Therefore, new therapeutic strategies to target mast cells and allergies have been proposed and have already shown promising results. These include the H1R-antagonist ebastine, by blocking the effects of mast cell mediators, IgE (by omalizumab), mast cell inhibition (lirentelimab) and mast cell depletion (anti-c-Kit antibody).[33,94,97–99]

Non-immune reactions to food can be induced by products such as insoluble fibers, short chain fatty acids (SCFAs) and fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). These products are already used as target of FAPD treatment.[91] Soluble fibers may be particularly useful in the management of IBS-C, since they attract water into stools and therefore may relieve symptoms of constipation.[100,101] However, increased gas production may also occur due to fiber fermentation.[102] Inadequate fiber intake has also been proposed as a risk factor for developing FAPDs in children, as it can potentially increase intracolonic pressure, accelerate gut transit time and aggravate abdominal pain.[103–106] Last but not least, studies in adults have shown beneficial effects of a diet low in FODMAPs for the treatment of IBS.[107] It is hypothesized that one of the mechanisms of action involves a reduction in gas production and subsequently in luminal distention, resulting in a decrease in pain.[107–109]

Psychological Factors

Psychological factors, such as anxiety and depression, coping style, (family) stress, somatization, catastrophizing and sexual or physical abuse history, are known to be associated with childhood FAPDs.[110] Both afferent and efferent pathways (such as neural and endocrine) are included in the complex physiology of the gut-brain axis, which all this together implies that gut-brain interactions involve both top-down as bottom-up processes.[111–113] The vagus nerve (VN) is a key component of neural communication between microbes of the gut and the brain. The VN modulates especially gastrointestinal motility and secretion, and has an

anti-inflammatory role.[114,115] Psychological factors, such as stress, inhibits the VN. Furthermore, an increased VN sensitivity has been described in IBS patients, which enlarge the risk of peripheral inflammation.[116] Stress causes alterations in the gut-brain axis and central pain processing, leading to abnormal visceral sensitivity.[111,112]

It has been suggested that the hypothalamic-pituitary-adrenal (HPA) axis, an endocrine pathway, plays also an important role in gut-brain interactions by regulating psychological stress and state.[111] Either in the neonatal period or later in life, stressful events stimulate the HPA axis, which stimulates cortisol release, mast cell activation and inflammation, causing a dysregulation in the microbiota-gut-brain axis and changes in gut permeability.[117]

To date, there is no evidence that psychological symptoms alone lead to abdominal pain in children, although they seem to play an important role in moderating etiology, maintenance and exacerbation of pediatric FAPDs.[118] For instance, anxiety and depression, somatization and catastrophizing may be related with an increase in symptom severity, disability and lower quality of life.[9,110,119] However, it has been proven that anxiety and depression are not the greatest predictors for disease severity. Coping behaviors and specific pain-related cognitions are straightly linked to disability and pain. A study showed that anxiety and depression scores on abdominal pain was mediated by catastrophizing and somatization.[120] These findings point out not to focus on anxiety and depression alone, but to examine pain-specific psychological factors.

DIAGNOSIS AND CLINICAL EVALUATION

Pediatric FAPDs are diagnosed according to the Rome IV criteria, which supports a positive diagnosis instead of a diagnosis based on ruling out other (organic) causes of disease.[2] A thorough patient medical history and physical examination are the first steps. However, in clinical practice, adequate description of symptoms by (especially young) children might be challenging and is potentially hampered by a communication barrier between the patient, the parent(s) and healthcare professional (HCP). The use of Patient Reported Outcome Measures (PROMs), by using pictograms, may overcome this barrier and could enhance the comprehension of medical information.[121–124] Therefore, in **chapter 1**, we evaluated whether the use of pictograms improves symptom evaluation for children with FAPDs.

Also, it is important to look for potential alarm symptoms or '*red flags*', such as a gastrointestinal blood loss or a positive family history of inflammatory bowel disease (IBD), that can increase the chance of an organic cause of abdominal pain (**Table 2**).[58,125–127] Special attention should be given to psychosocial history taking such as life events (i.e., sexual, physical and emotional abuse) and anxiety or depressive symptoms. This is not distinguishing between FAPDs or organic disease, but helpful in treatment-decision and concomitant comorbidities.

Table 2. Alarm signs/red flags for organic disease[127]

Patient history	Positive family history of IBD/celiac disease/FMF Chronic diarrhea Gastrointestinal blood loss Involuntary weight loss Recurrent vomiting Joint pain (Unexplained) fever
Physical examination	Anemia Aphthous ulcer Fever Perianal complications Impaired growth Arthritis Erythema nodosum Hepatosplenomegaly Uveitis Icterus

FMF, familial Mediterranean fever; IBD, inflammatory bowel disease

Additional non-invasive laboratory testing, even in the absence of alarm symptoms, is almost regularly done by the child's threating physician. These include standard serological testing such as complete blood count and C-reactive protein (CRP), and more targeted tests such as serological testing for celiac disease. It is well known that children with IBS have a fourfold risk of having celiac disease than children without IBS.[96] Therefore, it is also recommended to measure anti-tissue transglutaminase (anti-tTG) antibodies.[128] Final, if a child has symptoms of both abdominal pain and diarrhea, fecal testing for *Giardia lamblia* is indicated.[58,129] In the last decade, evaluation of fecal calprotectin is being increasingly utilized as non-invasive screening measure of intestinal mucosal inflammation.[127] Thus, fecal calprotectin has been shown to be a valuable measure to differentiate between IBD and non-IBD.[130] It even seems to be superior to common blood parameters or CRP in terms of sensitivity and

specificity.[130–133] The current recommendations and evidence, although limited, supports targeted and limited initial diagnostic testing. However, in clinical practice a combination of different diagnostic tests is regularly performed, even if this supports overdiagnostics. Therefore, in **chapter 2,** the additional value of common laboratory blood parameters (hemoglobin, CRP, erythrocyte sedimentation rate), to anti-tTG, fecal calprotectin, and *Giardia lamblia* was investigated, to distinguish between a functional and an organic cause of chronic abdominal pain in children.

The additional value of endoscopy and imaging, such as abdominal radiographs, in children with FAPDs is limited and therefore not recommended.[40] **Figure 3** gives an detailed overview of the Rome IV diagnostic workflow of pediatric FAPDs.

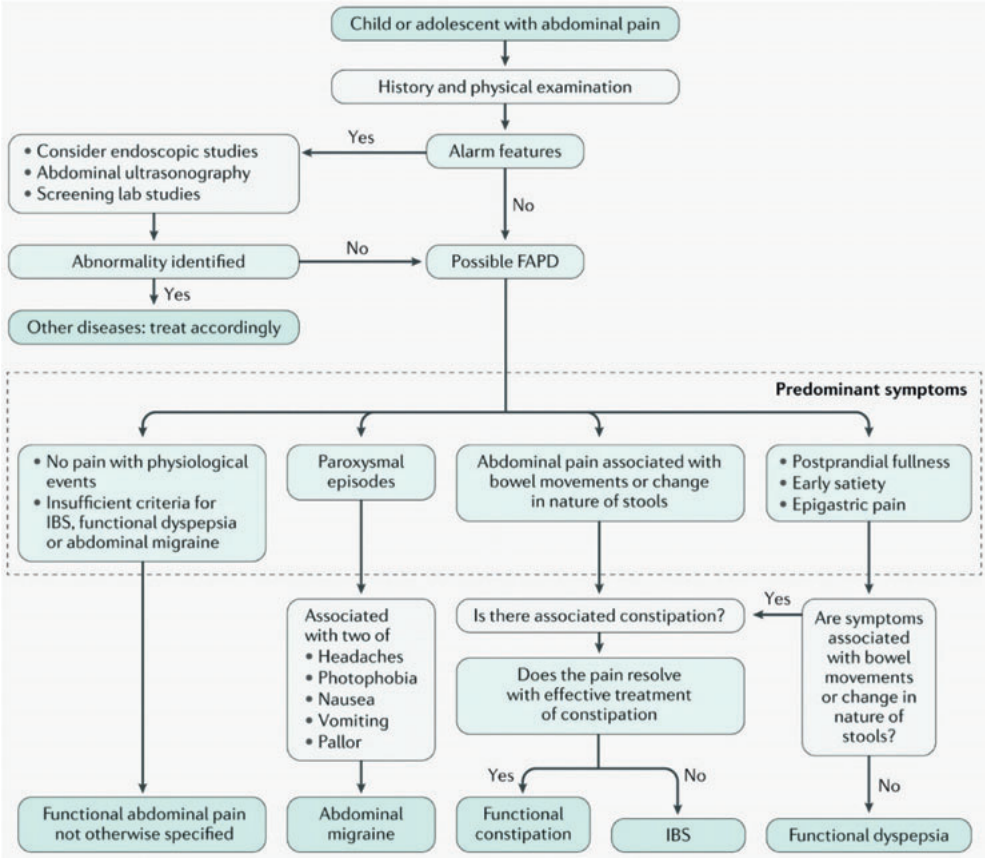

Figure 3. *Rome IV diagnostic workflow of pediatric FAPDs.*
Adapted with permission from Rome Foundation. GI genius interactive clinical decision toolkit. Rome Foundation https://romeonline.org/product/rome-iv-interactive-clinical-decision-toolkit-logicnets (2020). Copyright 2016 Rome Foundation, Inc. All Rights Reserved. FAPD, functional abdominal pain disorder; IBS, irritable bowel syndrome.

MANAGEMENT

In pediatric FAPDs, no evidence-based international management guidelines are available. The heterogeneity of these disorders, even within single subtypes, makes it challenging to design a treatment algorithm to fit all children. Especially since up to 40% of children continue to experience symptoms despite treatment.[11,12,134] Treatment often includes one or more of these strategies: (1) first-line management consisting of validation, explanation and a positive diagnosis, (2) non-pharmacological treatment, and (3) pharmacological treatment. Although the number of treatment options has grown recently, managing these disorders can still be challenging and unsatisfactory. In particular since there is a lack of high-quality intervention studies in these patient groups, which are necessary to guide adequate clinical management. Intervention studies are also difficult to compare, as there is no uniform definition and various outcome measures are used to describe treatment outcomes.[135–139] The solution for this problem may be the development of a core outcome set (COS): a standardized set of outcome measures that should minimally be measured and reported in all intervention trials in a disease-specific domain.[135,140,141] **Chapter 8** describes the development of a COS for therapeutic trials in pediatric FAPDs.

1. First-line Management

The cornerstone of helping a child with FAPDs is first to validate the symptoms followed by a proper explanation of the diagnosis according to the biopsychosocial model.[1] An evidence-based, multidisciplinary treatment plan is essential to improve recovery and long-term prognosis.[142]

- **Validation, explanation and a positive diagnosis.** One of the first steps is to acknowledge that the pain is real even though no severe organ damage is present. It can be helpful to explain that the pain is caused by hypersensitive nerves, using metaphors like a fire alarm that keeps on alarming although there is no fire.[142] Enough time must be allocated to make a positive diagnosis by discussing all the evidence that supports your diagnosis of FAPDs. Education on the interplay of different biopsychosocial factors that generate and maintain chronic abdominal complaints is also helpful. Finally, one needs to elicit expectations and elucidate that the long-term prognosis is favorable. The primary treatment goal should not

be the complete eradication of pain but optimization of daily functioning, including school participation, a normal sleep pattern, and participation in extracurricular activities.[40,143] The practitioner should remain connected with patients and parents through email and/or phone contact and follow-up visits tailored to each case every 4-12 weeks to increase treatment adherence and reduce the feeling that patients and families are discharged and left without support.

- **The parental response to their child's abdominal pain**. A multidisciplinary family approach is an essential part of the treatment strategy. An randomized controlled trial (RCT) studied the effects of parental attention versus distraction versus no instruction in children with chronic FAP.[144] Abdominal complaints were reduced by half in the distraction group and nearly doubled in the attention group. The study suggests that parental distraction is a powerful coping strategy. Moreover, Lindley et al showed that healthcare consumerism in families lacking insight into their child's problem can be harmful to the child with FAP.[145] Prognostic indicators of 'healthcare consumerism' were refusal to engage with psychological services, involvement of more than three consultants, lodging of a manipulative complaint with hospital management by the child's family, and lack of development of insight into psychosocial influences on symptoms.[145]

- **Identify psychological and physical stressors** that may play a crucial role in a child's abdominal pain experience and, possibly, help reverse them. Parental acceptance of the biopsychosocial model of illness has shown to be an important factor for symptom relief in children with FAPDs.[146]

- **Additional analgesic therapy,** such as non-steroidal anti-inflammatory drugs, acetaminophen, and aspirin is sometimes used by HCPs to treat pain. However, the efficacy of these drugs in treating pediatric chronic abdominal pain is not supported in any clinical trial, and should be used with caution in clinical practice.[147-149]

2. Non-pharmacological Treatment

Non-pharmacological treatment consists of dietary interventions and psychosocial interventions.

Dietary Interventions

In the last decade, there has been a great interest in the role of diet in the pathogenesis and management of FAPDs.[150,151] Almost all children with a FAPD report that at least one food is associated with deterioration of their gastrointestinal symptoms, and as a result, children frequently avoid foods, such as gluten and implement diet strategies.[87,88,95] However, it is likely that these food-associated symptoms are more the result of the gastrocolic reflex than that they are caused by food intolerances.[57,152,153] Indeed, research has shown little evidence that dietary interventions are helpful for this population.[40,154,155] It is in clinical practice however difficult to differentiate which specific food components initiate FAPD symptoms. This leads to an abundance of diagnostic testing, and, consequently, a variety of recommended dietary interventions, mostly based on expert opinion.[156] Therefore, **chapter 5** provides an up-to-date overview regarding the efficacy and safety of dietary interventions in pediatric FAPDs, to guide HCPs, children and their families, in evidence-based treatment decisions in clinical practice.

Psychosocial Interventions

Psychosocial interventions include cognitive behavioral therapy (CBT), hypnotherapy (HT), yoga, neurostimulation, guided imagery, and others.[157] The most commonly used psychosocial interventions in clinical practice are CBT and HT. CBT aims to alter the behaviors, cognitions, and emotions, that may contribute to IBS symptom escalation or maintenance.[157–159] Children and parents are taught to implement different coping and distraction strategies, and often also relaxation techniques, to decrease symptoms. CBT can be provided in various settings, such as face-to-face therapy,[160–162] to parents via the telephone,[163] or targeted to children via the internet.[164–166]

In HT, a patient is induced into a hypnotic state. During this state, a therapist guides the patient to respond to suggestions to alter its subjective experiences, perception, emotion, sensation, and thoughts or behavior.[167,168] HT can be provided individually by a therapist, and even in the long-term, there is a continued benefit of HT at five years follow-up.[169–171] One of the disadvantages of HT is the lack of enough well-trained hypnotherapists, its time investment, and the lack of coverage by healthcare insurances. Home-based HT using standardized scripts is an attractive alternative treatment option and was originally developed to make hypnosis for children with IBS and FAP-NOS more widely available.[172,173] Especially

in countries or areas with a low number of licensed hypnotherapists or with high costs for therapist. Previously we have shown that standardized home-based gut-directed hypnosis exercises with compact disc (CD) is non-inferior to individual hypnotherapy (iHT) by a therapist in the treatment of children with FAPDs.[172] However, if the effect of home-based treatment with standardized hypnosis recordings is still present after five years is unknown. Therefore, in **chapter 3** we conducted a follow-up study to investigate the long-term effects of standardized-hypnosis-recordings at home.

CBT and HT have proven to be successful in the management of pediatric FAPDs in earlier research.[40,157] However, the quality of the evidence was low. Since then, the results of new RCTs have become available. To give an up-to-date overview, we performed a systematic review on psychosocial interventions in children with FAPDs in **chapter 4**.

3. Pharmacological Treatment

Different elements of the gut-brain axis, including the CNS, the gastrointestinal tract, or both, can be targeted by pharmacological agents. The primary goal of treatment is to decrease abdominal pain and to improve adequate relief of concomitant symptoms. In the case of IBS, treatment may also focus on improving defecation consistency and frequency. In adults with FAPDs, antispasmodic agents, peppermint oil and tricyclic antidepressants (TCAs) are significantly more effective than placebo.[174,175] In 2015, a systematic review on pharmacological interventions in pediatric FAPDs was performed, including six studies with 275 children. This study reported a lack of high-quality, placebo-controlled pharmacological trials and no evidence to support the use of any pharmacologic compound in clinical practice.[176] However, new pharmacological agents which may alter future treatment recommendations have been published since then. Therefore, in **chapter 6**, we systematically reviewed the efficacy and safety of pharmacological interventions available for pediatric FAPDs.

SHARED DECISION MAKING

When more than one medical acceptable option is available for a patient, the process by which the optimal decision for diagnosis, intervention or follow-up may be accomplished is shared decision making (SDM).[177,178] The main purpose of

SDM is to include patients in decision making, thereby improving quality of care and patient satisfaction, as well as reducing costs.[179–185] SDM can also be applied in pediatrics. Children (4–18 years) are nowadays supported and encouraged to participate in decisions about their healthcare.[186,187] To promote SDM in daily medical practice, the *'3 Good Questions'* (*3GQ*) program was developed and implemented in the Dutch adult population.[188] These questions have been adapted to children's language level and understanding, to ease children's involvement within pediatric care and enhance the quality of information provided during children–physician consultations. The feasibility of this *3GQ* program for SDM in pediatric medicine was determined in **chapter 7**.

This thesis ends with a **summary and discussion** of the results of the preceding chapters. The **discussion** will focus on recommendations for diagnostic and management strategies, on challenges in research, and future perspectives.

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