



## Functional Abdominal Pain Syndrome

### The Clinical Problem

Functional abdominal pain syndrome (FAPS) is a state of chronic recurrent abdominal pain that is not due to structural, organic, or metabolic diseases, as far as can be detected by current routine clinical examinations [7]. Abdominal pain in FAPS is unrelated to provocation, exaggeration, or relief by everyday physiological stimuli such as eating, exercise, defecation, or menstruation [7]. FAPS is one of the functional gastrointestinal disorders (FGIDs) and is distinct from other categories of FGIDs such as irritable bowel syndrome (IBS), unspecified functional bowel disorder, epigastric pain syndrome in functional dyspepsia, functional chest pain of presumed esophageal origin, functional gallbladder and sphincter of Oddi disorders, and functional anorectal pain in adults [10]. Infant colic in neonates and toddlers, as well as IBS, abdominal migraine, functional dyspepsia, and FAPS in children and adolescents, can also be related to pain [10]. For instance, IBS is characterized by abdominal pain or discomfort that is perceived as a weak sensation of abdominal pain and is characterized by more than two of the following three conditions: relief by defecation, onset associated with changes in stool frequency, and onset associated with changes in stool form [19]. Epigastric pain syndrome in functional dyspepsia is defined by chronic pain or burning localized to the epigastrium of at least moderate severity, at least once per week, and by intermittent pain, not generalized or localized to other abdominal or chest regions, that is not relieved by defecation or passage of flatus and does not fulfill the criteria for gallbladder or sphincter of Oddi disorders [25]. The gastrointestinal symptoms of these pain-related FGIDs have different features. However, the basic mechanisms of pain may not be mutually exclusive among these disorders.

### Epidemiology and Social and Economic Impact

The reported prevalence of FAPS in North America ranges from 0.5% to 2% [9] and does not differ from rates reported in other countries [8,15]. In contrast, the prevalence of IBS is approximately 10–20%, that of functional dyspepsia is 20–30% [6], and that of functional gallbladder and sphincter of Oddi disorders is 7.6–20.7% [3]. Therefore, FAPS is a less common FGID than IBS, functional dyspepsia, or functional gallbladder and sphincter of Oddi disorders [7]. However, the prevalence of FAPS is still greater than that of ulcerative colitis (0.0076%) [18] or chronic pancreatitis (0.0041%) [27], which represent nonmalignant organic diseases that usually cause chronic abdominal pain. FAPS is more common in women, with a female : male ratio of 3:2, with prevalence peaking in the fourth decade of life [4,11]. Patients with FAPS have high work absenteeism and health care utilization, and thus the syndrome imposes a significant economic burden [11,22].

### Clinical Characteristics

The primary feature of FAPS is abdominal pain. However, many diseases can cause chronic abdominal pain. Therefore, any structural, organic, or chemical disease should be excluded. Patients with FAPS often have pain-related behaviors [7]. First, they often deny a role for psychosocial stressors. However, pain may diminish when patients are engaged in distracting activities but increase when they are discussing a psychologically distressing issue. Second, they express pain through verbal and nonverbal methods. They urgently report intense symptoms disproportionate to the available clinical and laboratory data. Third, they seek health care frequently. They often visit the emergency room and request opioid analgesics. Fourth, they request diagnostic studies or even exploratory surgery to determine the organic origin of their condition. Fifth, they focus attention on complete relief of pain rather than on adapting to having a disease. Sixth, they take on limited personal responsibility for self-management. In addition to these features, distinct psychopathologies are usually found in patients with FAPS, including depressive disorders, anxiety disorders, and somatoform disorders (axis-I disorders in the *Diagnostic and Statistical Manual of Mental Disorders* [1]). Some forms of personality disorders categorized as axis-II disorders may also be identified. As is the case for other chronic pain conditions, some patients with FAPS may have catastrophizing thoughts [7] or a history of early life trauma, including physical or sexual abuse [24].

## Pathophysiology

The precise etiology and pathophysiology of FAPS are poorly understood. However, brain-gut interactions play a crucial role in most of the pain-related FGIDs, especially IBS [14,20,21]. Among IBS patients, a subgroup with severe symptoms have a pathophysiological similarity to patients with FAPS [24]. Physiologically, signals originating from the gastrointestinal tract are conducted to the brain via visceral afferent pathways, which are mainly classified into parasympathetic afferent and sympathetic afferent fibers [14,21]. Parasympathetic afferent fibers within the vagus nerve end at the nucleus of the solitary tract, which also sends signals to the various corticolimbic structures [20]. Sympathetic afferent fibers converge into the dorsal root ganglia and are connected to secondary sensory neurons in lamina I of the dorsal horn of the spinal cord. This visceral afferent signal ascends to the spinothalamic tract and relays the stimuli to the thalamus. The signal then spreads to the insula, cingulate cortex, and the other structures of the pain neuromatrix. The lamina I neurons also send signals to the limbic system and paralimbic sensorimotor cortex (including the amygdala and hypothalamus) via the parabrachial nucleus [14]. Therefore, visceral pain signals are directly related to homeostatic regulation, which is mediated by corticotropin-releasing hormone (CRH) [13]. For instance, activation of the CRH-expressing neurons in the paraventricular nucleus of the hypothalamus stimulates colonic motility via sacral parasympathetic outflow [13]. Unlike in IBS, there are no brain-imaging studies of FAPS. However, the fact that abdominal pain in FAPS is unrelated to physiological events strongly suggests sensitization or associative learning of the pain-related area of the brain rather than peripheral sensitization. In fact, FAPS patients have hyposensitivity to non-noxious physiological rectal distension by barostat [23]. Descending pain modulation systems (opioidergic and noradrenergic pathways) originate in distinct brainstem regions and are activated automatically in a reflex-like fashion in response to a noxious stimulus [7]. Tonic descending pain modulation systems originate from serotonergic nuclei in the brainstem and play a role in the central control of baseline spinal cord excitability [7]. Together with descending pain modulation systems of the periaqueductal gray, cortical networks on pain modulation circuits (including the insula, amygdala, anterior cingulate cortex, orbitofrontal cortex, medial and dorsolateral prefrontal cortex, and parietal cortex) are suggested to be involved in the pathophysiology of FAPS. In patients with chronic back pain, a decreased volume of gray matter of the whole brain was related to pain duration, and the decrease was prominent in the bilateral dorsolateral prefrontal cortex [2]. A strong negative correlation was identified between the thickness of the right dorsolateral prefrontal cortex and ratings on a pain catastrophizing scale in IBS patients [5]. Thus, functional and structural changes in the brain may underlie the pathophysiology of FAPS.

## Diagnostic Evaluation

The present diagnosis of FAPS is based on the Rome III criteria [10]. Diagnostic criteria for FAPS must include all of the following: (a) continuous or nearly continuous abdominal pain, (b) no or only an occasional relationship of pain with physiological events (e.g., eating, defecation, or menses), (c) some loss of daily functioning, (d) an indication that the pain is not feigned (e.g., malingering), (e) insufficient symptoms to meet criteria for another FGID that would explain the pain, and (f) criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis [7]. Moreover, any structural, organic, or chemical diseases should be excluded. Differential diagnosis should include malignant neoplasm of the gastrointestinal tract, biliary tract, pancreas, and liver; ulcerative colitis; Crohn's disease; peptic ulcer; ulcer of the small intestine; stenosis of the gastrointestinal tract; colonic diverticulitis; ischemic colitis; cholelithiasis; cholangitis; cholecystitis; pancreatitis; chronic intestinal pseudo-obstruction; megacolon; colonic inertia; food allergy; allergic or eosinophilic gastroenteritis; parasites; arteriosclerosis in the abdomen; aortic aneurysm; peritonitis; Fitz-Hugh-Curtis syndrome; Henoch-Schoenlein purpura; porphyria; endocrine, metabolic, or hematological diseases; collagen diseases; abdominal wall pain; gynecological and urological diseases; and so on. A precise medical interview and careful physical examination can greatly contribute to an accurate diagnosis, but urinalysis, fecal examination, complete blood count, blood chemistry, abdominal ultrasonography, and plain X-ray film of the abdomen are routinely examined. Upper-gastrointestinal endoscopy, an upper-gastrointestinal series, colonoscopy, barium enema, capsule endoscopy, small-intestinal endoscopy, barium fluoroscopy of the small intestine, abdominal computed tomography, abdominal magnetic resonance imaging, endoscopic retrograde cholangiopancreatography, abdominal angiography, and gastrointestinal manometry and/or barostat may also be examined, depending on the clinical situation.

## Treatment

A cure is not possible, so in caring for patients with FAPS, the aims of treatment are to reduce suffering and improve the quality of life [24]. Treatment relies on a biopsychosocial approach with a therapeutic patient-physician partnership at its base [10]. Pharmacotherapy for FAPS is centered on antidepressants [7,24]. Tricyclic antidepressants (amitriptyline, imipramine, or desipramine), tetracyclic antidepressants (mianserin), selective serotonin reuptake inhibitors (fluoxetine, paroxetine, fluvoxamine, sertraline, or escitalopram), serotonin-norepinephrine reuptake inhibitors (duloxetine, milnacipran, or venlafaxine), and a noradrenergic and specific serotonergic antidepressant (mirtazapine) are used on the basis of our understanding of the neurotransmission of visceral pain [7,24]. Antipsychotics (e.g., quetiapine) are sometimes prescribed [24]. Antidepressants suppress the activities of the pain matrix, facilitate descending pain modulation systems, and possibly help neurogenesis via brain-derived neurotrophic factor [7,24]. In a systematic review in children and adolescents with pain-related FGIDs, however, 59% of participants reported feeling better in the amitriptyline group compared with 53% in the placebo group (relative risk: 1.12; 95% confidence interval: 0.77 to 1.63), which was not a significant difference [17]. Psychotherapy is a reasonable approach for FAPS patients [7,24]. Especially in children with

IBS or FAPS, hypnotherapy has proven to be highly superior, with a greater reduction in pain scores compared with standard medical treatment [26]. Moreover, a 1-year follow-up found that treatment was successful in 85% of the hypnotherapy group and only 25% of the standard medical treatment group. A systematic review also supports evidence that cognitive-behavioral therapy may be a useful intervention for children with recurrent abdominal pain [16]. Finally, if patients with FAPS have narcotic bowel syndrome due to a paradoxical increase in abdominal pain associated with continued or escalating dosages of opioids, detoxification treatment is beneficial for patients [12].

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