

## TULBURĂRILE INTERACȚIUNII INTESTIN-CREIER: O PREZENTARE TAXONOMICĂ

### THE DISORDERS OF THE GUT-BRAIN INTERACTION: A TAXONOMIC UPDATE

Andrei V. Pop, Dan L. Dumitrașcu  
UMF Iuliu Hațieganu, Cluj Napoca

Autor corespondent: **Dan L. Dumitrașcu**, e-mail: [ddumitrascu@umfcluj.ro](mailto:ddumitrascu@umfcluj.ro)

#### Abstract:

The functional gastrointestinal disorders recently received a better name, given by the Rome IV working committees. They are called now disorders of the gut-brain interaction. The new name reflects the progress in the knowledge of these disorders. They are no more perceived as idiopathic conditions, but rather as self-standing pathological entities. Therefore, they are no more diagnosed after ruling out any other pathology but benefit of criteria for positive diagnosis. The taxonomy remains however based on the topographic area to which symptoms are attributed. This paper reviews the disorders of the gut-brain interaction following the Rome IV taxonomy. The main clinical and pathogenetic features of each of them are presented

#### Rezumat:

Tulburările funcționale digestive au primit recent un nou nume, mai bun, dat de comitetele de lucru Roma IV. Ele sunt denumit acum tulburări ale interacțiunii intestin-creier. Noul nume reflectă progresele în cunoașterea acestor suferințe. Ele nu mai sunt considerate acum condiții patologice idiopatice, ci mai degrabă ca tulburări de sine stătătoare. Totodată diagnosticul nu se mai bazează pe excluderea altei patologii, ci pe criterii bine definite de diagnostic pozitiv. Taxonomia rămâne însă aceeași, bazată pe segmentul topografic căruia îi sunt atribuite simptomele. Prezentul articol trece în revistă tulburările de interacțiune creier intestin urmând taxonomia Roma IV și prezentând elementele clinice și patogenetice definitorii fiecăreia.

**Key-words:** *Disorders of the gut-brain interaction, Functional gastrointestinal disorders, Rome criteria*

**Cuvinte cheie:** *Tulburări ale interacțiunii intestin-creier, Tulburări gastro-intestinale funcționale, criterii Roma*

#### Introduction

Gut-brain axis describes a bidirectional association between the gut and the brain; playing an important role in the understanding of the gastrointestinal disorders. (*Mukhtar et al., 2019*) It has been described as an interconnection between the gut functions and the emotional part of the brain. (*Khlevner et al., 2018*) For the gut-brain axis to function properly it must have a good activity of the intestine as well as a normal behavior of the brain, these being translated by signals received from the brain, the intestine or from both. (*De Palma et al., 2014*) Any disturbance in one of these systems can cause a malfunction of the both of them. (*Khlevner et al., 2018*) It is already known that microbiota plays an important role in the gut-brain axis, this synergy being also referred as microbiota-gut-brain axis. Beside the

nervous system (through vagus nerve and autonomic nervous system) in the interaction between gut microbiota and the brain, a key role is also played by the gut production of metabolites, hormones and immune factors. (*Wang and Wang, 2016*) For example gamma-amino butyrate can be produced by *Lactobacillus* species and *Bifidobacterium* species, serotonin can be produced by *Escherichia* species, *Streptococcus* species and *Enterococcus* species, dopamine can be produced by *Bacillus* species and norepinephrine can be produced by *Bacillus*, *Proteobacteria* and *Escherichia coli*. (*Galland, 2014*)

Nowadays, the Functional Gastrointestinal Diseases (FGID) are also known as Disorders of Gut-Brain Interaction, that involve mechanisms which are described as an association between microbial dysbiosis, altered mucosal function and

motility abnormalities, correlated with abnormal central sensitization, visceral hypersensitivity and autonomic regulation (*Schmulson, 2018*).

Functional Gastrointestinal Diseases are classified according Rome IV, based mainly on symptoms and anatomic regions (*Drossman, 2016*).

### Esophageal Disorders

Functional chest pain More than a third of the cases with noncardiac chest pain related to the esophagus are caused by functional chest pain (FCP), being the second most common cause of noncardiac chest pain (*Fass et al., 2019*). FCP can be described as an unexplained chest pain or discomfort located in the midline of the chest, without heartburn or dysphagia, without gastroesophageal reflux or eosinophilic esophagitis and a major motility disorder. The symptoms must be present at least once per week, which appeared in the last 6 months before diagnosis with the criteria fulfilled for the last 3 months (*Schmulson, 2018, Galimiche et al., 2006*).

Globus is a nonpainful, persistent or intermittent symptom that appears between meals and usually improves with eating. It is described as tightness in the throat, a retained food bolus, or in the most of cases a sense of a lump, without dysphagia or odynophagia and cannot be materialized with a structural lesion, motor disorder or gastroesophageal reflux. It affects almost 46% of the healthy persons, with the highest incidence at middle age. The symptoms must be present at least once per week and appeared in the last 6 months before diagnosis with the criteria fulfilled for the last 3 months (*Schmulson, 2018, Galimiche et al., 2006, Fass et al., 2019*).

Functional dysphagia is described as an abnormal sense of passing, lodging or sticking through esophagus for solid and/or liquid foods, without any structural, mucosal or motor changes, gastroesophageal reflux or eosinophilic esophagitis (EoE) (*Suzuki, 2017, Aziz et al., 2016*).

Functional heartburn appears as a retrosternal burning pain or discomfort which cannot be defined as a motor disorder, without structural explanation or histopathologic mucosal abnormalities and without any response to antisecretory therapy without evidence for

GERD. The symptoms must be present at least twice per week, and appeared in the last 6 months before diagnosis with the criteria fulfilled for the last 3 months (*Aziz et al., 2016*).

Reflux hypersensitivity is a new introduced in Rome IV and characterized by heartburn and chest pain, with histological modification of esophageal mucosa, like basal cell thickness, papillary elongation and dilated intercellular spaces, but with a normal acid reflux. The symptoms must be present at least twice per week, and appeared in the last 6 months before diagnosis with the criteria fulfilled for the last 3 months, the endoscopy must be normal, without any signs of EoE, without any motor disorders and a normal acid exposure on PH monitoring (*Suzuki, 2017, Aziz et al., 2016*).

### Gastroduodenal Disorders

Functional dyspepsia is a common condition, affecting up to 20% of general population, being epidemiologically divided in two clinically different syndromes. (*Tomita et al., 2018*) The first one, postprandial distress syndrome (PDS) occurs mostly postprandial, is always related to meals and it is described as postprandial fullness or early satiety. The second one, epigastric pain syndrome (EPS), sometimes overlapping the first one, is less common, and it is described as a recurrent epigastric pain or burning, not necessarily related to meal. Even though no apparent organic diseases involved, FD is frequently associated with symptoms like bloating, nausea and heartburn (*Talley, 2017, Talley et al., 2016*).

Belching disorders is a common condition and it can only be considered pathological when is too frequent or disturbing. It is described as an audible air escape, come into the pharynx from the stomach, known as gastric belch, or from esophagus, known as supra gastric belching (*Stanghellini et al., 2016*).

Nausea and Vomiting Disorders Nausea can be described as a subjective unpleasant sensation experienced on the throat or epigastrium with an impending requirement to vomit. Vomiting is the act of expulsion of gastrointestinal content performed with the help of the chest wall and abdominal muscles. The prevalence of unexplained vomiting is up to 2%

of women and 3% of men. Chronic nausea vomiting syndrome (CNVS) is a disease that affects the usual activities, being described as nausea and vomiting at least one time per week, without any evidence of metabolic, systemic, or organic disease. Cyclic vomiting syndrome (CVS) affects both genders, being described at young adults, usually after 5- or 6-years onset. It can be associated with diabetes mellitus, menses, or pregnancy. Cannabinoid hyperemesis syndrome (CHS) is related to marijuana use in one third of patients. It can be stopped by cutting of marijuana stopping (*Stanghellini et al., 2016, Tack et al., 2006*).

Rumination syndrome initially described at children, it is now observed also at adults at all ages, women being mostly affected. It is defined as effortless regurgitation into the mouth, manifested repetitively at lately swallowed food, and succeeded by re-swallowing, rechewing or expulsion (*Tack et al., 2006*).

### **Bowel Disorders**

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders. It is a chronic functional disorder who has the main symptom abdominal pain or discomfort, associated with abnormal stool frequency (diarrhea or constipation or association between them) and/or abdominal bloating (*Mearin et al., 2016b, Sultan and Malhotra, 2017*). IBS affects the lower gastrointestinal tract, and the symptomatology does not have any structural or biochemical known explanation (*Ford et al., 2017*).

Nowadays the diagnosis of IBS is not a diagnosis of exclusion, is based on symptom Rome IV criteria: recurrent abdominal pain at least one day per week, associated with at least two of the following symptoms: related with defecation, change in frequency of stool or change in form of stool. The symptoms must have been appeared in the last 6 months before diagnosis with the criteria fulfilled for the last 3 months. In patients with IBS, and without any alarm features, is not recommended to use other diagnostic tests (*Schmulson and Drossman, 2017, Grad and Dumitrascu, 2020*). Related stool frequency, Rome IV describes four subtypes of IBS: IBS-C (more than 25% of stool with Type 1-2 of Bristol Stool Scale, but less than 25% of stool Type 6-7 of Bristol Stool

Scale), IBS-D (more than 25% of stool with Type 6-7 of Bristol Stool Scale, but less than 25% of stool Type 1-2 of Bristol Stool Scale), IBS-M (more than 25% of stool with Type 1-2 of Bristol Stool Scale, and more than 25% of stool Type 6-7 of Bristol Stool Scale) and IBS-U (Patients who fulfil IBS diagnostic criteria, but cannot be included in any other of the three subtypes) (*Schmulson and Drossman, 2017, Drossman and Hasler, 2016*).

Functional constipation (FC) Is defined according to Rome IV criteria, and is described as a sensation of incomplete evacuation or is manifested as a difficulty in passing stools on inadequate bowel movements followed often by straining during defecation. Symptomatology must be present 3 months before and have appeared for at least 6 months diagnosis. It must fulfill 2 or more of the following criteria: defecatory straining ( $\geq 25\%$  bowel movements); hard or lumpy stools ( $\geq 25\%$  bowel movements); a feeling of incomplete evacuation ( $\geq 25\%$  bowel movements); defecatory obstruction ( $\geq 25\%$  bowel movements); manual maneuvers to facilitate defecation ( $\geq 25\%$  bowel movements); or fewer than 3 spontaneous complete bowel movements per week. Also, another criteria for diagnosis is the absence of diarrhea, excepting the situation when the patient is taking laxatives; and no IBS criteria should be fulfilled (*Mearin et al., 2016a*).

Functional diarrhea (FDr) is described as a watery stool or repeated passage of loose, with bloating or abdominal pain in some cases, but not as dominant symptoms. The symptoms must also fulfill the time criteria for the diagnosis of FDr, which the onset of symptoms are 6 months before diagnosis, with the presence of them during the last 3 months. Reported prevalence of FDr is around 2-3% (*Porter et al., 2011, Schmulson et al., 2006, Roshandel et al., 2006*). Is extremely important to make differential diagnosis with IBS-D, where abdominal pain and/or bloating are dominant criteria. The importance of differential diagnosis with IBS-D is that both are cases with various pathogenesis (*Carrasco-Labra et al., 2019*).

Functional abdominal bloating/distension (FABD) is characterized by a subjective

perception of captured gas or a sensation of pressure, but without objective expansion. (Lacy *et al.*, 2020) It can be present in any part of the abdomen or even throughout the abdomen. Is different of abdominal distension and is described as an expansion of the abdominal circumference. FABD is defined according to the Rome IV criteria; the symptoms are both subjective once those regarding bloating or repeated abdominal fullness or pressure or objective once regarding abdominal distension. It should be mention that FABD should not be confused or overlapped with IBS, FGID, or FC. Although some symptoms like mild abdominal pain or minor bowel movement abnormalities can be present. (Mari *et al.*, 2019)

Unspecified functional bowel disorder it considered a diagnosis when a patient has symptoms for functional bowel disorders (FBDs), but the symptoms do not fulfill none of the 4 specific FBDs categories (Lacy *et al.*, 2016).

Opioid-induced constipation is a disorder induced by the action of opioids on the central nervous system and gastrointestinal tract; sometimes it can even overlap with other disorders of FGID. OIC is characterized by a change, after initiating opioid therapy, in the defecation pattern or habit, with a feeling of incomplete evacuation, decreased bowel frequency or worsening of straining. Sometimes the patients may confront with overflow incontinence or with fecal impaction or may overlap OIBD, when the patients can experience nausea, reflux or bloating (Lacy *et al.*, 2016).

### **Centrally Mediated Disorders of Gastrointestinal Pain**

Centrally mediated abdominal pain syndrome (CAPS) is defined as a continuous or intermittent repeated abdominal pain, that affects several life fields (family life, intimacy, work, social). It has no evidence of being caused by the gut function, or any other structural or metabolic disorders that can be diagnosed up to this point. It must be underlined that before CAPS diagnosis is established, any other organic cause of abdominal pain must be excluded. It is thought that "adhesions" are a cause for the pain, but there is no evidence to sustain this fact. CAPS I not a common disease, it has a prevalence of 0.5-2.1% and women are

up to 2 times more affected, having a peak in the 40's. (Keefer *et al.*, 2016).

Narcotic bowel syndrome (NBS)/Opioid-induced GI hyperalgesia is characterized by a central hyperalgesia, localized to the gastrointestinal tract, produced by the treatment of the opioids. It is defined as a paradoxical pain that increases at growing doses of narcotics, which are initially administered to treat the pain (Szigethy *et al.*, 2014, Drossman and Szigethy, 2014). As a particularity of the disease is the progression of intensity, duration and frequency of the pain episodes. (Keefer *et al.*, 2016)

### **Gallbladder and Sphincter of Oddi (SO) Disorders**

Biliary pain, is characterized by a disorder of the gallbladder (GB) or Sphincter of Oddi (SO), manifested by pain that appears at some intervals, affects several life fields, is alleviated by acid suppression or postural change, radiated to the back and/or right infra-scapular region, and sometimes associated with nausea and vomiting. The symptoms are apparently cured after ablation of the SO or GB removal. Functional Gallbladder Disorder (FGD) describes an entity with the same symptomatology as the biliary pain, but without having an organic or structural change like stones or sludge of GB. Functional Biliary Sphincter Disorder is characterized at patients with biliary pain after cholecystectomy; that may have liver enzymes elevated or dilated bile duct, but not both, and without bile duct stones or other structural abnormalities (Cotton *et al.*, 2016).

Functional pancreatic SO disorder is described as a pancreatic pain, caused by the sphincter hypertension, with negative endoscopic ultrasound. A cause for this is the obstruction of the sphincter. It can have several causes, including opioids, tumors of the papilla or duct stones. Many of the unexplainable cases of pancreatitis had elevated sphincter pressure (Cotton *et al.*, 2016).

### **Anorectal Disorders**

Fecal incontinence is a disabling condition affecting up to 9% of individuals of both sexes, characterized by uncontrolled passage of fecal through anus with different stages of severity

that can vary from flatulence with an involuntary passage to complete evacuation of fecal (*Shah and Villanueva Herrero, 2020, Grossi et al., 2019*).

Functional anorectal pain has 3 forms of presentation, which differ by the duration of the pain, and the presence or absence of anorectal tenderness (*Bharucha and Lee, 2016, Rao et al., 2016*). The first one Levator Ani Syndrome is described as a pain or a pressure feeling that increases with standing and is objectivated at clinical examination with a spasm of levator ani muscles, or tenderness at palpation. The second one, Unspecified Functional Anorectal Pain has the same symptoms as the previous one, but without tenderness during the posterior traction of the puborectalis muscle. The last one, Proctalgia Fugax, is characterized by a rectal acute severe pain, cramping, aching, or stabbing, that lasts from seconds up to half an hour, and disappear suddenly. Affects the normal activity and can awake the patient. In 90% of cases is limited to the rectum (*Rao et al., 2016*).

Functional defecation disorder (FDD) is a disorder characterized by a disturbance in the act of defecation that happens because of an inadequate relaxation of the pelvic floor muscles and/or the inadequate actions of propulsive forces during the attempt. It is often associated with the sensation of incomplete evacuation, extreme straining, and digital assistance of bowel movements. The diagnosis of FDD must take into consideration both symptoms and physiological testing. FDD can be classified into two different disorders, inadequate defecatory propulsion and Dyssynergic defecation, with distinct pathophysiology and symptomatology. Dyssynergia patterns is described in the literature as an association between constipation and paradoxical anal contraction. Inadequate defecatory propulsion is defined inappropriate contraction of the anal sphincter and/or pelvic floor muscles during attempted defecation. (*Rao et al., 2016*)

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