MÆDICA - a Journal of Clinical Medicine

EDITORIALS

Rome III: an ongoing journey for better diagnosis and treatment of functional gastrointestinal disorders

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ABSTRACT

This article has no intention to be an exhaustive presentation of a process that encompasses thirty years of shaping concepts, designing studies, interpreting and integrating data in the field of functional gastrointestinal disorders. It is merely a revue of this huge team effort, trying to emphasize its achievements and its benefits in terms of better clinical care and advancing scientific knowledge.

Since more then half of gut disorders encountered by gastroenterologists and primary care physicians are functional, meaning without identifiable pathophysiological defects, diagnosing them requires a substantial change in thinking for doctors trained for basic science and solid evidence. Even if fruitless searching for an anatomical cause in these widespread conditions may generate needless tests and consultations, the necessity of excluding an organic disease is still valid. Yet again some of the newest methods of investigation can identify anomalies even in these conditions, making the distinction between organic and functional even more difficult. Thus there are sufficient reasons to offer this brief insight in functional disorders of the gastrointestinal tract.

Key words: functional gastrointestinal disorders, Rome III

BACKGROUND

It is only 3 decades ago that the reductionistic model of disease which pursued the identification of a single biological etiology was replaced by the more complex, biopsychosocial model of illness (1). The concept moved away from defining pathology only by abnormal morphology to linking mind and body as part of a system which when deregulated produces illness and disease. This model allows symptoms to be physiologically multidetermined as well as influenced by socio-cultural and psychosocial factors. Accordingly, psychosocial development in early life is affected not only by environmental factors such as family influences, abuse, major losses or infections, but also by genetics, determining the later susceptibility to life stress or emotion and the development of coping strategies as well as susceptibility to gut malfunction, with abnormal motility, visceral hypersensitivity and modified mucosal immunity. Functional gastrointestinal disorders (FGIDs) are the clinical result of these interactions of psychosocial factors and altered gut physiology through the brain-gut axis (2). A further advance in our understanding of FGIDs was brought about by the development of investigative methods which allowed the quantification of these alterations and their relative significance in symptom generation. Motility assessment by manometry, hypersensitivity testing with the barostat and the investigation of peptides, mucosal inflammation and immunity and alteration in intestinal flora, are now the mainstay of scientific research in this domain. Brain imaging using positron emission tomography

and functional magnetic resonance imaging offers reproducible information about the central modulation of gastrointestinal function and its relationship to emotional and cognitive areas (3). There are also standardized psychological tests which permit the quantification of emotions, stress, cognition and quality of life, invaluable as research tools.

The Rome process was meant to deal with this rapidly growing knowledge, imposing the recognition of FGIDs as distinct clinical entities. It began some 20 years ago, generated by the need of the academic environment for a classification system that could be used equally for research and clinical care. Afterwards this initiative was continued and served to continuously modify and update information on these disorders. On the other hand, better standardization brought about more solid clinical data, advances in basic science of the gut and therapies directed to identifiable abnormalities. ❑

ROME III

The Rome III classification system, like the other two before it, relies on symptom based criteria and the exclusion of pathologically defined disorders. However there is a tendency to emphasize the FGIDs motor and sensory physiology and their CNS relationships. The adult FGIDs are classified in six categories, labeled A through F, from which five are defined by anatomical location (esophageal, gastroduodenal, bowel, biliary, anorectal), functional abdominal pain syndrome (FAPS) being considered somewhat apart in category D. Pediatric conditions are classified first by age range, in categories G (neonate/toddler) and H (child/adolescent). Each category contains several disorder each defined by relatively specific clinical features (Table 1). However, symptoms generally overlap so emphasis is put on the dominant or more specific one, such as pain associated with changes in bowel habit, which distinguishes irritable bowel syndrome (IBS) from functional diarrhea, when there is no pain, or functional bloating, when there is no change in bowel habit. There are different diagnostic and treatment options for each disorder. ❑

CHANGES MADE IN ROME III

The utility of the framework offered by Rome classification system is reflected also by the

A. Functional esophageal disorders
- A1. Functional heartburn
- A2. Functional chest pain of presumed esophageal origin
- A3. Functional dysphagia
- A4. Globus

B. Functional gastroduodenal disorders
- B1. Functional dyspepsia
  - B1a. Postprandial distress syndrome
  - B1b. Epigastric pain syndrome
- B2. Belching disorders
  - B2a. Aerophagia
  - B2b. Unspecified excessive belching
- B3. Nausea and vomiting disorders
  - B3a. Chronic idiopathic nausea
  - B3b. Functional vomiting
  - B3c. Cyclic vomiting syndrome
- B4. Rumination syndrome in adults

C. Functional bowel disorders
- C1. Irritable bowel syndrome
- C2. Functional bloating
- C3. Functional constipation
- C4. Functional diarrhea
- C5. Unspecified functional bowel disorder

D. Functional abdominal pain syndrome

E. Functional gallbladder and Sphincter of Oddi (SO) disorders
- E1. Functional gallbladder disorder
- E2. Functional biliary SO disorder
- E3. Functional pancreatic SO disorder

F. Functional anorectal disorders
- F1. Functional fecal incontinence
- F2. Functional anorectal pain
  - F2a. Chronic proctalgia
    - F2a1. Levator ani syndrome
    - F2a2. Unspecified functional anorectal pain
  - F2b. Proctalgia fugax
- F3. Functional defecation disorders
  - F3a. Dyssynergic defecation
  - F3b. Inadequate defecatory propulsion

G. Functional disorders: neonates and toddlers
- G1. Infant regurgitation
- G2. Infant rumination syndrome
- G3. Cyclic vomiting syndrome
- G4. Infant colic
- G5. Functional diarrhea
- G6. Infant dyschezia
- G7. Functional constipation

H. Functional disorders: children and adolescents
- H1. Vomiting and aerophagia
  - H1a. Adolescent rumination syndrome
  - H1b. Cyclic vomiting syndrome
  - H1c. Aerophagia
- H2. Abdominal pain-related functional gastrointestinal disorders
  - H2a. Functional dyspepsia
  - H2b. Irritable bowel syndrome
  - H2c. Abdominal migraine
  - H2d. Childhood functional abdominal pain
    - H2d1. Childhood functional abdominal pain syndrome
- H3. Constipation and incontinence
  - H3a. Functional constipation

TABLE 1. Rome III Functional Gastrointestinal Disorders

changes it suffered in time, concordantly with new data in the literature. Compared to Rome II there is a time frame change, with symptoms originating 6 month before diagnosis, with a period of activity of 3 months, this criteria being less restrictive than the previous ones. Also, there are changes in classification categories, rumination syndrome being moved from functional esophageal to functional gastroduodenal disorders, because of new evidence that links it to disturbances localized to this latter segment of GI tract. FAPS was included into a new category (D) because it relates more to CNS amplification of normal visceral signals rather than abnormalities within the GI tract. The category of Childhood functional GI disorders was split in two age-related categories, because there are different clinical conditions specific to the growth and development of the child. The functional dyspepsia syndrome includes now two conditions, postprandial distress syndrome and epigastric pain syndrome, defined by a complex of symptoms with physiological support rater than by pain or epigastric discomfort, like previously. More restrictive criteria are operative for functional disorders of the gallbladder and sphincter of Oddi, reducing the needless demand for invasive procedures such as retrograde cholangiopancreatography or manometry, sometimes used to confirm the diagnosis. It is also recommended that IBS subtyping should be simply based on stool consistency (4).

New insights on the pathophysiology of functional gastrointestinal disorders

As already stated the symptoms of the FGIDs have several known physiological determinants, such as increased motor reactivity, enhanced visceral sensitivity, altered immune reactivity and inflammation, and abnormal CNS-ENS (enteral nervous system) regulation. Some disorders, such as fecal incontinence, are based mostly on motor dysfunction, while others, such as FAPS, are primarily considered as a consequence of amplified central perception of a normal visceral input. However others, like IBS, have a more complex substrate, which combines all these factors in different proportions. ❑

GENETICS

Blurring further away the distinction between functional and organic, there is consistent proof of the existence of a genetic predisposition to the development of FGIDs. Some patients with IBS have lower levels of IL-10, an anti-inflammatory cytokine, which can affect intestinal neural sensitivity. Other polymorphism identified in these patients involve the serotonin reuptake transporter, influencing the levels serotonin and the therapeutic response to 5-HT blocking agents (5), the protein which have an effect on both CNS and gut-related actions, and α2-adrenoreceptor with impact on gastrointestinal motility. Interestingly, serotonin reuptake polymorphisms are encountered in mood disturbances, providing a possible link of IBS with psychiatric co-morbidities.

Familial aggregation of FGIDs is not only genetic but also education related, the health care seeking behavior being learned from parents. ❑

PSYCHOSOCIAL FACTORS

Even if psychosocial factors are the first recognized to exacerbate GI symptoms and to modify the experience of illness and illness behavior, they are still not required for the diagnosis. That is because patients with FGIDs show greater psychological disturbance only in referral centers, being associated with a health seeking behavior. Also, functional GI disorder may by itself generate psychosocial consequences, influencing what is known as one's health-related quality of life. ❑

MOTILITY

Strong emotions or environmental stressors determine an increased motility of the gastrointestinal tract. This normal motility response is even higher in FGIDs (6). It correlates partially with symptoms like vomiting, diarrhea and constipation, but offers no explanation to chronic or recurrent abdominal pain. ❑

VISCERAL HYPERSENSITIVITY

Visceral hypersensitivity is another cardinal physiologic modification that explains in part the lack of correlation with motility abnormalities that some FGIDs show. Some patients demonstrate a lower pain threshold with balloon bowel distention (visceral hyperalgesia), or even an increased sensitivity to normal intestinal function (allodynia). There may be also an increase area of somatic referral of visceral

pain. This hypersensitivity may still be amplified by sensitization, exemplified by the progressive increase in pain intensity induced by repetitive balloon inflation, a normal process exacerbated in FGIDs (7). Hypersensitivity and sensitization can be explained either by increased peripheral receptors sensitivity, increased by mucosal inflammation, mast cell degranulation or increased serotonin activity, either by amplifying transmission in the spinal cord dorsal horn through neuron growth induced by repetitive stimulation. Other mechanisms are increased central perception or altered central downregulation of visceral afferent transmission. ❑

INFLAMMATION

Only a few years ago it was recognized that nearly one half of IBS patients demonstrates an increased number of activated mucosal inflammatory cells (8). About one third of patients with IBS or dyspepsia recall an acute enteric infection preceding the development of symptoms and conversely up to a quarter of patients with acute enteric infection will eventually develop IBS or dyspeptic symptoms, demonstrating the same increase in inflammatory cells number and inflammatory cytokine expression in the mucosa (9). This ongoing inflammation generates probably visceral hypersensitivity and sensitization. ❑

CNS-ENS INTERACTIONS

The brain-gut axis works bidirectionally linking emotional and cognitive centers in CNS with peripheral functioning of GI tract. Extrinsic or enteroceptive information (emotion, thought) can therefore influence on GI sensation, motility, secretion and inflammation. Visceral afferent input can reciprocally affect central pain perception, mood and behavior. Post-infectious IBS (PI-IBS) is an illustrative model of brain-gut interactions. By comparing the patients who develop PI-IBS to those who recover uneventfully from infection and to an asymptomatic control group, the distinguishing features consist in increased mucosal inflammation and higher levels of psychological distress at the onset of infection. There are no differences in visceral sensation thresholds or motility between those who recover and those who develop IBS, implying that CNS increased amplification of peripheral signals in psychologically distressed individuals leads them to conscious awareness and perpetuation of symptoms (10). CNS could also increase inflammation through altered hypothalamic-pituitary-adrenal axis reactivity to stress. So, PI-IBS occurrence depends on brain-gut dysfunction, visceral sensitization and high level of psychological distress.

New modalities of brain imaging, such as positron emission tomography or functional magnetic resonance imaging are capable of assessing brain function in response to visceral stimulation (11). They are helpful not only in defining what regions of the brain are implicated in the modulation of visceral pain and motility, like the anterior cingulated cortex (ACC), but also in visualizing CNS responses to various treatments, like psychological therapies an antidepressants, permitting more accurate prediction of efficacy. ❑

TREATMENT

The implication of psychosocial factors in FGIDs may be used as a therapeutic advantage, an effective treatment being critically dependent of the establishment of an effective physician-patient relationship. Thereafter, treatment is based on the severity and the nature of symptoms. In mild cases therapy is directed toward education of the patient, reassurance and avoidance of unneeded medications and offending dietary substances (lactose, caffeine, fat, alcohol). Moderate cases may benefit from symptom monitoring, with a patient diary which can help identify possible dietary, lifestyle or behavioral influences, with pharmacotherapy directed at specific symptoms and psychological treatment for motivated patients. Severe cases may need antidepressants or even referral to specialized pain treatment centers for a multidisciplinary team approach.

The concept of a brain-gut axis led to a novel treatment approach based on neuropeptides and receptors present in the ENS and CNS. Among possible therapeutic agents are serotonin, enkephalins and opioid agonists, substance P, calcitonin gene-related polypeptide and cholecystokinin, neurokinin receptor, and corticotrophin-releasing hormone antagonists. ❑

Conclusion

Hopefully this brief revue of the new state of knowledge in FGIDs will help to a better understanding of these true clinical entities and, by drawing attention to the published Rome III documents, will improve diagnosis and care of our patients.

REFERENCES

1. **Engel GL** – The clinical application of the biopsychosocial model. *Am J Psychiatry* 1980; 137:535-544
2. **Jones MP, Dilley JB, Drossman D, Crowell MD** – Brain-gut connections in functional GI disorders: anatomic and physiologic relationships. Neurogastroent Motil 2006; 18:91-103
3. **Drossman DA** – Brain imaging and its implications for studying centrally targeted treatments in IBS: a primer for gastroenterologists. *Gut* 2005; 54:569-573
4. **Drossmann DA** – The Functional Gastrointestinal Disorders and the Rome III Process. *Gastroenterology* 2006; 130:1377-1390
5. **Camilleri M, Atanasova E, Carlson PJ, Ahmad U, Kim HJ, Viramontes BE, et al** – Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2002; 123:425-432
6. **Pandolfino JE, Kahrilas PJ** – AGA technical review on the clinical use of esophageal manometry. *Gastroenterology* 2004; 128:209-224
7. **Munakata J, Naliboff B, Harraf F, Kodner A, Lembo T, Chang L, et al** – Repetitive sigmoid stimulation induces rectal hyperalgesia in patients with irritable bowel syndrome. *Gastroenterology* 1997; 112:55-63
8. **Chadwick VS, Chen W, Shu D, Paulus B, Bethwaite P, Tie A, et al** – Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology* 2002; 122:1778-1783
9. **McKendrick W, Read NW – Irritable bowel syndrome** – post-salmonella infection. *J Infection* 1994; 29:1-3
10. **Drossman DA** – Mind over matter in the postinfective irritable bowel. *Gut* 1999; 44:306-307
11. **Hobson AR, Aziz Q** – Brain imaging and functional gastrointestinal disorders: has it helped our understanding? *Gut* 2004; 53:1198-11206

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