Assessing Gastrointestinal Symptoms and Perception, Quality of Life, Motility, and Autonomic Neuropathy in Clinical Studies

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Abstract

Imprecise characterization of complaints of the upper and lower gastrointestinal (GI) tract puts patients at risks of either a delayed diagnosis or misdiagnosis and contributes to an increase in the overall direct and indirect costs of the health system. The current scenario in the case of functional GI diseases originates from at least two conditions: frequency of diseases and bothersome symptoms with an impact on the quality of life (QoL). To make a correct diagnosis is therefore almost mandatory.

Once a positive diagnosis of functional involvement of the GI tract is made, the correct diagnosis assessment includes the study of symptom characteristics, entity and perception, detection of abnormal patterns of GI motor-function (gallblader and gastric emptying, oro-cecal and colonic transit, etc.), potential involvement of the autonomic nervous system (sympathetic, parasympathetic), and overall impact of such abnormalities on the QoL and psychological profiles. Results of these tests can be variable, depending on the type and intensity of the illness. In the present review, the state-of-the-art methods for correct assessment of several factors regarding the onset, perpetuation and outcome of functional GI diseases are discussed.

Key words

Gastrointestinal symptoms – motility – quality of life – irritable bowel syndrome – autonomic neuropathy.

Introduction

Gastrointestinal (GI) complaints of the upper and lower tract are a frequent cause of consultation and hospital admission at any age. Imprecise characterization of the causes underlying the symptoms may cause delayed diagnosis, misdiagnosis and contribute to the overall direct and indirect costs of the health system.

A major task is therefore to try to dissect organic (namely, GI neoplasia and inflammation) from functional disturbances. Once a positive diagnosis of functional involvement of the GI tract is made, the correct diagnostic assessment involves the study of symptom distribution, entity and perception, investigation of abnormal patterns of GI motor function, potential involvement of the autonomic nervous system, and overall impact of such abnormalities on QoL and psychological profiles. To which extent such studies should be performed either at a peripheral level or exclusively in a third-referral center is a matter of debate. In the present review, the possibility that the above-mentioned studies are variably combined in the workup of patients with functional involvement of the GI tract, is discussed. Our group has reported this approach in several clinical studies (Table I).

Assessment of symptoms

To identify exactly types of symptoms and their intensity is essential when studying either the upper or the lower GI tract, or both. This aspect has been emphasized also in the recent consensus of Rome III on functional GI diseases [1]. As correctly stated by the experts, interpretation of dyspeptic symptoms in functional GI diseases should rule out the presence of alarm symptoms (e.g. weight loss, anemia, positive occult fecal blood etc.), use of NSAIDs and aspirin (which can cause misleading symptoms), a clear role for H. Pylori infection, positive findings at the upper GI endoscopy [2]. Gastro-esophageal reflux syndrome (GERD) should be diagnosed if noncardiac chestpain and retrosternal burning and/or regurgitation are present. Most important symptoms for dyspepsia include epigastric pain, burning, postprandial fullness and early satiation (Table II). A validated semi-quantitative scoring system can be employed to assess a subset of four symptoms (epigastric pain, burning, belching/burning, postprandial fullness),

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Table I. Some clinical conditions in which gastrointestinal symptoms and perception, quality of life, motility, and autonomic neuropathy have been variably investigated

Disease	Measurements
Gallstone disease	GB emptying, stomach emptying, oro-cecal transit, GERD
Irritable bowel syndrome	Symptoms, psychological aspects, QoL, GB emptying, stomach emptying, oro-cecal transit
Thalassemia major	Symptoms, QoL, GB emptying, stomach emptying, oro-cecal transit, ANS neuropathy
Chronic constipation (colonic inertia)	Symptoms, QoL, esophageal motility, GB emptying, stomach emptying, oro-cecal transit, ANS neuropathy
Systemic scleroderma	Symptoms, QoL, esophageal motility, GB emptying, stomach emptying, oro-cecal transit, ANS neuropathy
Gastrectomized patients	Symptoms, GB emptying, response to erythromycin (prokinetic agent)
Hepatitis A	Symptoms, GB emptying, gastric emptying

Abbreviations: ANS, autonomic nervous system; GB, gallbladder; GERD, gastroesophageal reflux disease; QoL, quality of life

Table II. Dyspeptic symptoms and their definitions according to Rome III criteria [2]

Symptom	Definition
Epigastric pain	Epigastric refers to the region between the umbilicus and lower end of the sternum, and marked by the midclavicular lines. Pain refers to a subjective, unpleasant sensation; some patients may feel that tissue damage is occurring. Other symptoms may be extremely bothersome without being interpreted by the patient as pain
Epigastric burning	Burning refers to an unpleasant subjective sensation of heat.
Postprandial fullness	An unpleasant sensation like the prolonged persistence of food in the stomach
Early satiation	A feeling that the stomach is overfilled soon after starting to eat, out of proportion to the size of the meal being eaten, so that the meal cannot be finished. Previously, the term "early satiety" was used, but satiation is the correct term for the disappearance of the sensation of appetite during food ingestion.

resulting in a maximal score equal to 48 [3]. In our series, the upper normal limit estimated from the mean ± 2SDs of healthy controls was equal to 8 [4, 5]. Additional information for the lower GI tract in irritable bowel syndrome (IBS) or constipated patients or patients with malabsorption include the frequency and quality of bowel habits by using objective evaluations, bloating, flatulence, and abdominal pain. The so-called "Bristol stool scale" measures the weekly frequency of bowel movements from a daily diary over a time span of one month. The scale assesses the quality of stools based on a semi-quantitative scale, as a marker of colonic transit, and is a reliable method to estimate colonic transit time [6]. The Bristol score is abnormal in IBS patients (above upper normal limits in about 50% of the patients) [5] and clearly abnormal in scleroderma patients [4]. Gallstone patients also can have delayed colonic transit [7, 8]. Beside a semi-quantitative score for each symptom, we found a very informative and powerful method of the visual-analogue-scale (VAS) to monitor each symptom at different time points. In this case, VAS consists of a 100mm-horizontal line (extreme left = "no symptom at all"; right ends = "maximum feeling of…") which patients have to mark along its length [9]. Scores at baseline (i.e. time 0) can be the mean of 3 measurements over 3 days in the fasting state at the same time in the morning. The last baseline measurement is taken immediately before the test is started and then at subsequent time-points if a test meal is used (i.e. every 15 min during 2 or 4 hrs in the case of liquid and mixed meal, respectively). VAS time-related curves of score for each symptom as well as Area Under Curve (AUC) for each VAS can be constructed and compared. Additional information can be provided by measuring appetite as a type of "internal validation score" when compared with satiation. We found that the two measurements are inversely correlated between healthy and ill subjects [4, 5]. As expected, the feelings of satiety and appetite at time 0 are inversely correlated on the two study days (placebo: r=-0.85; P=0.0001; erythromycin: r=-0.81; P=0.001) [10].

The visceral hypersensitivity is another topic of research. The term enhanced visceral sensitivity or visceral hyperalgesia refers to a lowered threshold for induction of pain by gastric distension when gastric compliance is normal. Patients with functional dyspepsia have been shown to have visceral hypersensitivity [11]. By using an electronic barostat to monitor the gastric tone responses and a 0 to 10 perception score to monitor the sensorial to either gastric accommodation or to cold stress, it was clear that patients with functional dyspepsia had similar mechanical accommodation of the stomach to gastric distention (compliance) compared to controls [12]. By contrast, isobaric gastric distention elicited more upper abdominal discomfort in the patients with dyspepsia. Similar results were reported in a study measuring perceptual thresholds or altered pain referral in functional dyspepsia patients compared to patients with organic causes of dyspepsia [11]. Of note, patients with dyspepsia are also more sensitive to acid infusion into the duodenal bulb compared to controls [13]. Visceral hypersensitivity, but not somatic sensitivity, appears to be abnormal and independent of delayed gastric emptying in IBS [14]. The pathophysiology of visceral hypersensitivity might be due to both peripheral (mechanoreceptor dysfunction) or central mechanisms (aberrant processing of afferent input in the spinal cord or brain) [15]. Others have combined the study of gastric distension/relaxation and symptom perception in response to a standard volume of liquid test meal (e.g. 200 mL and 500 mL) using the gastric barostat and real-time ultrasonography in healthy subjects [16] or ultrasonography alone in diabetic [17] and in dyspeptic patients [18, 19].

Assessment of QoL and psychological profiles

The health survey SF-36 is a short form of the questionnaires assessing health-related quality of life (HRQOL) [5, 20]. The SF36 includes 36 items which measure eight multi-item variables: general health, physical function, role physical, role emotional, social function, mental health, body pain, and vitality. Healthy subjects in this setting had a HRQOL profile remarkably similar to that derived from subjects across different cultures in USA and UK [20-22]. Abnormal scores were reported in our studies in 100 patients with IBS compared with 100 healthy subjects [5]. In another study assessing GI motility, a lower health perception was found in adult patients with beta thalassemia recruited from a third referral center [4].

Another set of information includes psychological profiles: persistent somatization, demoralization, irritable mood, type A behavior and alexithymia. By using specific questionnaires, psychosomatic specialists may bring together a large number of seemingly unrelated disorders under the headings of the various anatomical systems and pave the way for multidisciplinary work in clinical medicine. Criteria for persistent somatization are functional medical disorders (e.g. fibromyalgia, fatigue, esophageal motility disorders, nonulcer dyspepsia, IBS, neurocirculatory asthenia, urethral syndromes), with a duration exceeding 6 months causing distress, or repeated medical care, or resulting in impaired QoL. There are some characteristics of somatization in patients suffering from various functional disorders. The most important psychometric instruments which may both rapidly and reliably identify possible cases of somatization, especially in primary care setting are: Symptom Checklist-90 Revised, the Othmer and DeSouza test, the Somatic Symptom Index, the Screening for Somatoform Symptoms, the Patient Health Questionnaire-15 and the WHO screening scales. According to evidence, cognitive-behavioral strategies represent the preferred psychological treatment for somatization. Demoralization represents the common reason why subjects seek psychotherapeutic treatment and results from the consciousness of being unable to cope with a pressing problem, or of having failed one's own expectations or those of others. This syndrome is found to frequently occur before the onset of medical disorders and can be exacerbated or triggered by a physical illness, especially if life-threatening or disabling, or by painful and prolonged treatments such as chemotherapy or mastectomy. The most relevant questionnaires are the Demoralization (general distress) scale of the MMPI-2, the Demoralization scale of the Psychiatric Epidemiology Research Interview and the Beck Hopelessness Scale. Irritable mood is a feeling state characterized by reduced control over temper which usually results in irascible verbal or behavioral outbursts, although the mood may be present without observed manifestation. The assessment of irritable mood has been almost exclusively based on self-report instruments, such as the Buss-Durkee Hostility Inventory, the Irritability, Depression and Anxiety Scale and the Cook-Medley Hostility Sale. Both the Symptom Questionnaire and the Illness Behavior Questionnaire contain a scale dealing with irritability as well. The most relevant features of type A behavior encompass excessive involvement in work and activities subjected to deadlines, time urgency, rapid speech and movements, hostility, high competitiveness, desire for achievement, tendency to speed up physical and mental activities and irritable mood. DCPR criteria allow the identification of type A behavior also in non-cardiological settings, as in consultation-liaison psychiatry patients (11%), patients with skin diseases (12%), functional GI disorders (8%) and cancer (8%).

Another psychological factor involved in functional gastrointestinal disorders is alexithymia. This is a cognitive and emotional disorder including: difficulties in identifying, describing, and verbalizing one's own feelings; restricted imagination and few dreams; trend to focus on somatic perceptions and to amplify them. It is investigated with the Toronto Alexythimia Scale (TAS) [23-25]. Alexithymia is significantly more represented in our group of patients with IBS than healthy subjects [5]. Some other aspects can be assessed by the Middlesex Hospital Questionnaire (MHQ): anxiety, phobic behavior, obsessive-compulsive behavior, somatization, depression, and hysteria [26]. Scores are also greater in IBS patients than controls [5].

Assessment of GI motility

Although the study of GI motility is best performed in referral centers, most of the tests yield significant information with relatively simple equipments. A position paper has been issued by our group on this topic [27]. The study of esophageal function might require manometry, ambulatory pH-metry, and esophageal scintigraphy [28]. We showed that abnormal esophageal motility is present in patients with "functional" colonic inertia [29] but also in a subgroup of patients with gallstone disease who show simultaneous abnormalities of gall bladder (GB) and gastric motor function after a standard meal [30]. The study of GB fasting and postprandial motor function is of interest too and is currently obtained by functional ultrasonography (see also [31]). By this noninvasive technique, the GB image is taken in the fasting state and after ingestion of the standard test meal [32]. Oblique and sagittal scans are obtained in the right hypocondrium employing a 3.5 MHz probe. The GB content appears as anechoic with a pear-shaped image on the longitudinal scan and as a circular image (right panel) on transversal scan. Mathematical algorithms are used for the measurement of GB volume, according to the ellipsoid formula [4, 5, 10, 27, 30, 33-44]. Fasting GB volume in healthy subjects is approximately 25 mL in adults with max cutoff value of up to 45 mL [36, 45]. Overall, indices of GB motility are as follows: fasting volume (mean of 3 measurements at -15, -5 and 0 minute before test meal, expressed in mL); residual volume (minimal volume measured postprandially, expressed in mL and as percent of

fasting volume); T1/2 (a time to achieve 50% decrease of fasting volume). With a liquid test meal of 200 mL with 13 g (39%) fat, 10 g (13%) protein and 35 g (48%) carbohydrates for a total of 300 kcal, 1270 kJ, 365 mOsm/L (Nutridrink®, Nutricia, Milano, Italy), the GB should contract by 50% in about 20-25 min and reaching a maximum contraction of 75% in about 40-45 min [36, 38]. Contraction can be slower but more complete with a mixed (liquid-solid meal) [46-49] or in the presence of prokinetic agents [10, 37, 38, 50, 51]. Contraction can be impaired (delayed and less complete with increased fasting GB volume) in gallstone patients but also in other illnesses (Table III). The study of gastric emptying might require from time to time radionuclide scanning with 99Tc-HIDA and 131I for simultaneous solid-liquid emptying [28]. This technique is invasive and costly and has been replaced by the ultrasonographic assessment of gastric emptying to both liquid [52] and solid meals [53, 54]. Gastric emptying is assessed looking at time-related changes of antral areas at the same time points as for the GB [9, 54]. The equipment and the test meal can be the same as for the GB [52]. Our group found impaired gastric emptying in a number of conditions including patients with gallstone disease (Table I).

The study of oro-cecal transit time (OCTT) can also provide additional information in patients referred for GI symptoms. According to general guidelines, the day before the breath test, subjects undergo a 12-hour carbohydrate-free diet [55, 56], followed by a 12-hour fasting period. Before starting the test, subjects undergo a thorough mouth wash with 50 mL of a 1% chlorexidine solution to prevent oro-pharyngeal fermentation of sugars by local microflora. Smoking and physical exercise are not allowed 2h before and during breath samplings [57, 58], as well as eating. Subjects collect alveolar air, avoiding deep inspiration or hyperventilation before exhalation. Breath samples following the ingestion of each substrate are analyzed at baseline in duplicate and at each time point. Both static and more practical portable, validated devices can be used (LactoFAN®, Lans Medical BV, NL or Bedfont EC60, USA). OCTT requires the ingestion of a substrate with 10g lactulose in 100 ml tap water. Breath samples are collected every 10 minutes up to a maximum of 360 min, hydrogen concentrations are analyzed and OCTT is established as previously described [4, 5, 59]. A rise of 10 p.p.m. above baseline on two consecutive measurements is considered as oro-cecal transit time and expressed in minutes [29]. Although the interpretation of either normal (up to 130 min) [5] or delayed OCTT still remains to be elucidated, several groups of patients with GI symptoms have delayed OCTT (Table I). We found that lactose malabsorbers have slower OCTT than patients who are lactose intolerant [60].

Assessment of autonomic neuropathy

The role of autonomic neuropathy in the genesis of GI symptoms and impaired GI motor function needs to be fully investigated. Symptoms and signs of autonomic dysfunction can be evaluated by taking the clinical history according to Rangari et al [61]. The questionnaire looks for the presence and extent of orthostatic hypotension, gastric symptoms, bowel disorders, sweating disorders, bladder dysfunction and, in males, impotence. This approach, however, might be inaccurate and more objective methods are required. Early studies have used the acetylcholine "sweat spot test" (SST) [62] as a quantitative measure of autonomic nervous system function to better characterize patients undergoing lumbar sympathectomy [63]. The SST in particular is used to investigate the involvement of cholinergic sympathetic fibers by analyzing sweat abnormalities on the dorsum of the foot in response to both termic stimulus and intradermic

Table III. Conditions potentially associated with impaired gallbladder motility [31].

Condition	Principal mechanism(s)
5-Hydroxytryptamine - inhibitors	Inhibition of 5-hydroxytryptamine re-uptake
Acute hepatitis A	Delayed gastric emptying, viraemia
Celiac disease	Decreased release of endogenous CCK
Chronic pancreatitis	Increased fasting and residual GB volumes; decreased release of endogenous CCK
Crohn's disease	Increased endogenous CCK release, decreased fasting GB volume
Diabetes mellitus*	Autonomic neuropathy, GB stasis
Down syndrome	Decreased fasting and emptying GB volumes
Growth hormone deficiency	Partial decrease of endogenous CCK release
Hypertriglyceridaemia*	Impaired gall bladder motility due to decreased sensitivity to CCK
Irritable bowel syndrome	Decreased GB emptying; impaired response to endogenous CCK
Insulin resistance*	Decreased GB emptying
Liver cirrhosis	Decreased GB emptying: lack of coordination with gastric emptying
Obesity*/rapid weight loss	Enlarged fasting / residual GB volume; decreased postprandial emptying
Octreotide therapy (e.g. acromegaly)	Inhibition of endogenous CCK release; GB stasis
Oral bile acid therapy	Increased fasting and residual GB volume
Pregnancy	Progesterone-induced GB stasis
Primary sclerosing cholangitis	Increased fasting and residual GB volume
Somatostatinoma	Inhibition of endogenous CCK release; GB stasis
Spinal cord injury	GB stasis
β-thalassemia major	Decreased GB emptying and autonomic neuropathy
Total parenteral nutrition	GB stasis (lack of enteral nutrition, decreased release of endogenous CCK)
Total/partial gastric resection	Vagotomy, increased fasting GB volume and decreased GB emptying

Abbreviations: CCK, cholecystokinin; *Can be components of the metabolic syndrome [66, 67]

injection of acetylcholine. Additional information can be gained by using cardiorespiratory reflex tests, as sensitive methods to assess the presence of autonomic neuropathy [64]. In our clinic, a portable device is used to measure the "beat-to-beat" modifications of the R-R interval using skin electrodes connected to Cardionomic® (Lifescan, Italy). Lying-to-standing and standing-to-lying tests are used for sympathetic involvement. Valsalva manoeuver, deep-breathing, cough test, and postural hypotension test are used for parasympathetic involvement. The results of each test are scored as normal, borderline or abnormal, according to age-controlled values. The overall results for autonomic neuropathy are therefore normal (all tests normal), indicate early involvement (one abnormal test or two borderline abnormal), or definite involvement (two or more abnormal tests) [61]. More recently, the heart-rate-variability test has been employed as an accurate overall estimation of sympathetic, parasympathetic balance in the body [61]. We found abnormal autonomic nervous system function in a subgroup of patients with constipation [65], in patients with severe colonic inertia [29], scleroderma [59], and thalassemia major [4].

Conclusions

The complexity of pathological conditions affecting the GI tract requires an accurate approach to dissect organic from functional conditions. Because functional GI disorders have a great impact on both QoL and health resources, the precise characterization of GI complaints of the upper and lower tract needs attention and correct diagnosis.

In referral centers, the workup of most patients with chronic functional diseases will need quantitative assessment of symptom distribution and perception, detection of abnormal patterns of GI motor function, involvement of the autonomic nervous system, and the study of the overall impact of such abnormalities on QoL and psychological profiles. It should be emphasized that this approach requires careful interaction between internists, specialists, pharmacologists and psychiatrists-psychologists, to pave the way for multidisciplinary work in clinical medicine.

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