Nuclear medicine imaging in the evaluation of functional gastrointestinal disorders

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Introduction
The functional gastrointestinal disorders (FGIDs) are an enigmatic group of maladies of the GI system which, until recently, were poorly understood and often neglected by clinicians. These disorders present with a constellation of GI tract systems, such as nausea, vomiting, abdominal bloating and diarrhoea. Following detailed clinical and imaging evaluation in the search for organic disease, if no such cause is found, the diagnostic and therapeutic process in these patients can often diminish in clinical priority and importance.

Over the last three decades, however, the Rome Foundation has focused academic and clinical attention on the FGIDs by bringing together expert opinion and evidence in a consensus process that has been instrumental in improving the understanding of the complex, multifactorial pathogenesis of the FGIDs as important causes of GI morbidity.1-2

Established functional nuclear medicine (NM) techniques have an important role in the evaluation of some of these disorders, notably in functional gastroduodenal disorders ([99mTc]-labelled gastric emptying scintigraphy – GES), functional bowel disorders (23-[35S]-25-tauroselcholic acid – SeHCAT) and functional gallbladder disorders (131I-technetium-hepatobiliary iminodiacetic acid – HIDA scintigraphy). These three NM techniques, and their clinical relevance to the FGIDs, will be discussed in more detail in this article, with particular emphasis on the importance of standardisation of the technique and evaluation of clinical outcomes based on the results of these tests.

The functional GI disorders
The FGIDs are a complex group of disorders that present with a constellation of gastrointestinal symptoms that affect activities of daily living. Until recently, there was poor clinical understanding of these conditions. For instance, a survey of 376 members of the American Gastroenterological Association (AGA) showed that more than half of them felt that these conditions were best labelled as a ‘stress disorder’.3 More recently, the Rome Foundation, in its third iteration of classification of the FGIDs, has established clear clinical criteria for the diagnosis and classification of these conditions.4 Through an extensive consensus process matured over five years and involving 87 experts from 18 countries, the Rome III criteria provide diagnostic measures and investigative algorithms for 28 adult and 17 paediatric functional GI conditions. This has led to improved clinical understanding of the FGIDs, raising the profile and clinical importance of these conditions and facilitating a more holistic, and less dismissive, approach to these patients. The key features of all of these conditions are:
(a) certain diagnostic criteria have to be met, often including the exclusion of organic disease that could mimic the same or similar symptoms, and
(b) symptoms must have begun six months before diagnosis and have continued for a minimum of three months in an active phase.

Gastric emptying scintigraphy and gastroparesis
Clinical background
Before diagnosing a functional gastroduodenal disorder, especially those that present with troublesome or intractable nausea and vomiting, a pathological delay in gastric emptying (ie gastroparesis) often has to be excluded as a potential cause of the patient’s symptoms. Gastroparesis is defined as a “symptomatic chronic disorder of the stomach that is characterised by delayed gastric emptying in the absence of mechanical obstruction”. The cardinal clinical symptoms of the condition are nausea, vomiting, abdominal bloating and early satiety. It is recognised that up to 80% of these patients are female and that between 25-55% of diabetic patients will develop the condition at some stage.5-6

Recent data from the National Inpatient Sample (NIS) in the United States has shown that between 1994-2009 annual hospitalisation rates for gastroparesis as a primary diagnosis increased from 918 to 16,736, which is a remarkable observation that highlights the increasing recognition by physicians of this important condition.7 There have also been recent developments in the therapeutic options available for patients with refractory gastroparesis, beyond conventional drug therapy with prokinetics and anti-emetics, to include novel invasive (and relatively costly) treatments such as gastric neuromodulation with the Enterra device (Medtronic, Minneapolis, USA).8 This has placed further emphasis on the use of gastric emptying scintigraphy (GES) in patients with suspected gastroparesis, as the test provides the current ‘gold standard’ for the diagnosis of this increasingly important condition.

Technique and interpretation of GES
It is well recognised that there is a lack of standardisation of GES in NM departments in the UK and elsewhere. Performing the technique in a standardised and reproducible manner is of paramount importance, and procedure guidelines and consensus statements produced by the Society of Nuclear Medicine (SNM) and the American Neurogastroenterology and Motility Society are extremely helpful in this regard.9-10 An initial assessment listing the patient’s current medications is essential, as it is well known that certain pharmacological agents can affect the rate of gastric emptying. For instance, gastric emptying is retarded
by opioid analgesics, calcium channel blockers, anticholinergic drugs and proton pump inhibitors, and is accelerated by metoclopramide, domperidone, erythromycin and beta-blockers.

Following a six-hour fast, the patient is given a standardised solid meal (eg scrambled egg, single slice of toast, 120ml water) admixed with 12.14MBq of a technetium (Tc)-labelled colloidal compound. Gamma camera imaging with two-minute anterior and posterior planar views are obtained at standard time points (30 minutes, one hour, two hours, three hours and four hours), and a time-activity curve is generated based on the percentage retention values at each of these time points (figure 1). Comparison with standard reference points for upper and lower limits of the normal range allows evaluation for an abnormal delay in gastric emptying (table 1, figure 2). It should be noted that neither routine evaluation of liquid emptying nor relying on 'emptving half-times' are recommended.

The retention value at the four-hour time point can also provide an objective measurement of the degree of severity in delay in gastric emptying (mild = 10-20%, moderate = 20-35%, severe >35%). The definition of abnormally rapid gastric emptying is less precise, with data from Tougas et al suggesting that <30% retention at one hour would provide the 95% confidence interval for correctly identifying rapid emptying, although it remains unclear whether the 30-minute time-point may be able to more reliably identify such patients, and more work is needed in this area. SeHCAT scan for bile acid malabsorption

Clinical background

It is estimated that between 2-9% of the general population suffers with symptoms of chronic diarrhoea, and these patients will not infrequently seek medical attention. Bile acids are essential for the dispersion, digestion and absorption of dietary fat, and after secretion into the gut from the gallbladder (where they are stored in bile), bile acids are reabsorbed by specialised mucosa in the terminal ileum in order to complete what is known as the ‘enterohepatic circulation’ of bile acids. The failure of this mechanism can result in bile acid malabsorption (BAM) with bile acids reaching the colon, which in turn can lead to chronic diarrheal symptoms. BAM is treatable with bile acid sequestrants. A recent retrospective study at the biliary centre in the UK, 10-minute patient and background counts are taken at three hours and at seven days, and the seven-day percentage retention value is calculated from the above. As this is a low-dose and low-activity technique, attention to detail is especially important, as extraneous sources of radiation in the vicinity of the patient when the counts are obtained may adversely affect the accuracy of the test. Moreover, the procedure is considered most reliable and efficient using a ‘no collimator’ technique, although a minority of centres perform the technique using collimators. Although originally it had been advocated that seven-day retention values <10% should be considered abnormal, with increasing recognition that patients with retention values <15% will benefit symptomatically from bile acid sequestrants, the latter is now taken as the threshold for an abnormal value, with further classification based on the severity of BAM as follows: 10-14.9% (mild), 5-9.9% (moderate) and 0-4.9% (severe).

Technique and interpretation of SeHCAT scanning

The technique for SeHCAT scanning is well documented and relatively straightforward. Following the ingestion of a 370kBq capsule of SeHCAT (GE Healthcare, Chalfont St Giles, UK), 10-minute patient and background counts are taken at three hours and at seven days, and the seven-day percentage retention value is calculated from the above. As this is a low-dose and low-activity technique, attention to detail is especially important, as extraneous sources of radiation in the vicinity of the patient when the counts are obtained may adversely affect the accuracy of the test. Moreover, the procedure is considered most reliable and efficient using a ‘no collimator’ technique, although a minority of centres perform the technique using collimators. Although originally it had been advocated that seven-day retention values <10% should be considered abnormal, with increasing recognition that patients with retention values <15% will benefit symptomatically from bile acid sequestrants, the latter is now taken as the threshold for an abnormal value, with further classification based on the severity of BAM as follows: 10-14.9% (mild), 5-9.9% (moderate) and 0-4.9% (severe).

Functional gallbladder disorders and HIDA scintigraphy

Clinical background

Functional gallbladder (GB) disorder or gallbladder dyskinesia is defined as “a motility disorder of the gallbladder that manifests with typical biliary pain in the absence of gallstones and with normal liver function tests”.

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It is very important to realise that these symptoms have considerable overlap with more common clinical conditions, both organic and functional, such as gastro-oesophageal reflux disease, irritable bowel syndrome, functional dyspepsia and, of course, gallstone disease. Therefore, the initial clinical assessment of these patients has to include evaluation of routine biochemical parameters, such as liver function tests, and conventional investigations, such as abdominal ultrasound and oesophago-gastro-duodenoscopy (OGD). If the initial evaluation does not provide a diagnosis, the current ‘gold standard’ test for diagnosis of biliary dyskinesia is considered to be a HIDA scan with provocation with a cholecystokinin (CCK) analogue, which can assess gallbladder emptying and provide a gallbladder ejection fraction (GBEF). If this is abnormal (often accepted as a GBEF <40%), the patient should be offered laparoscopic cholecystectomy (LC).

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If this is abnormal (often accepted as a GBEF <40%), the patient should be offered laparoscopic cholecystectomy (LC). If the GBEF is normal, the patient should be reassessed. It has been shown in selected series of patients evaluated by this methodology that the technique can help in the prediction of patients with biliary symptoms and normal conventional imaging who will derive symptomatic benefit from GB surgery. For instance, in a 35-case series from the author’s institution, it was shown that in 100% of patients who underwent LC following an abnormal provocation HIDA scan, the histopathology of the resected GB showed chronic cholecystitis and 75% of these patients were symptomatically better following surgery. The technique of provocation HIDA and interpretation of the resulting findings is described in more detail below.
Technique and interpretation of provocation HIDA scintigraphy

The most widely used HIDA derivative in clinical practice is 99mTc-Mebrofenin (Bracco diagnostics, Princeton, NJ) due to its high hepatic extraction efficiency. The patient should be fasted for six hours. After injection of a standard dose of 150MBq, dynamic imaging is performed for approximately 45 minutes. Activity is rapidly taken up by the liver, which is visualised by five minutes, with peak liver activity $T_{peak}$ achieved by ten minutes. In normal subjects, hepatic duct visualisation is followed by GB filling, which usually occurs by 15-30 minutes, and bile drainage into the small bowel is then seen by 30-60 minutes. When peak GB activity is detected, the provocation stimulus for GB emptying is administered, and a further 45-60 minute dynamic acquisition is performed. The ‘gold standard’ provocation test is considered to be a 60-minute intravenous infusion of a synthetic cholecystokinin (CCK) analogue (Sincalide for injection, Kinevac, Bracco Diagnostics, Princeton, NJ). A variation in technique with regards to the duration of infusion of CCK analogue is common, ranging from 5-30 minutes (figure 3).  

The alternative to CCK analogue is a standard fatty meal or the oral ingestion of a proprietary preparation of a high-calorific triglyceride emulsion, such as Calogen 200 ml (Nutricia, Co Dublin, Ireland). The latter has the advantages of being a relatively cheap and physiological stimulus for GB emptying, and clinical validation for this method is also available, so this is now favoured in some centres as the provocation method of choice. The precise threshold for an abnormal GBEF varies between $<33-40\%$, depending on the provocation method used, with the lower of these values applying to techniques using a physiological stimulus for GB emptying, such as a standard fatty meal or oral Calogen.

Conclusion

FGIDs are increasingly being recognised as important causes of long-term morbidity. Some nuclear medicine techniques have a very useful, and potentially expanding, role in the management of some of these conditions. Standardisation of protocols and assessment of patient outcomes is highly desirable to ensure both the quality and clinical relevance of these functional techniques.

References


<table>
<thead>
<tr>
<th>Time point</th>
<th>Lower normal limit for gastric retention (ie a lower value suggests rapid gastric emptying)</th>
<th>Upper normal limit for gastric retention (ie a greater value suggests delayed gastric emptying)</th>
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<td>0.5 h</td>
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TABLE 1 Normal limits for gastric retention on solid-meal gastric emptying scintigraphy. (Adapted from references 10-11).
Figure 1
Solid meal gastric emptying scintigraphy shows a normal rate and pattern of gastric emptying (processed on Xeleris workstation, GE Healthcare Limited).

Figure 2
Solid meal gastric emptying scintigraphy shows a severe delay in gastric emptying or gastroparesis (processed on Xeleris workstation).
Figure 3
HIDA scintigraphy with Sincalide (synthetic CCK analogue) provocation shows an abnormal gallbladder ejection fraction of 24% (processed on Xeleris workstation).