How should we classify and treat patients with functional gastrointestinal disorders?

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Understanding risk factors and heterogeneity and moving towards a mechanistic understanding of symptom genesis

Major everyday challenges face clinicians handling functional gastrointestinal (GI) consultations. The symptoms reported by this largest group of GI patients can be extremely difficult to treat: this therapeutic deficit fundamentally reflects our limited understanding of their biological basis. Consequently, but problematically, currently applied classifications of functional GI disorders (FGIDs) are almost entirely symptom based. Indeed leading authorities have by consensus stated that the 'functional bowel disorders are identified *only by symptoms*', with treatment therefore based on explanation and reassurance, and drugs targeting the predominant symptoms [Longstreth *et al*. 2006]. Is such a nonmechanistic approach to medicine and therapeutics acceptable in the 21st century? Or is it simply inescapable at this time?

FGID diagnosis generally requires that conventional investigation reveals no identifiable abnormality, structural or other. Indeed, definitive findings on endoscopy, histology or imaging will probably move the patient into other domains such as motility or inflammatory bowel disorders. Yet there is blatantly disordered gut function in these patients. Altered bowel habit or stool form, defaecatory dysfunction, abdominal distension/bloating, nausea, early satiety and visceral pain represent the most common symptoms. These can have a devastating impact on the quality of life of affected individuals at the severe end of the spectrum, and here explanation and reassurance is only of limited utility as an acceptable therapeutic approach. Nonetheless, it is important to note that the key physiological functions of the gut are clearly quite intact since nutrition is generally maintained perfectly well unless eating is restricted. This fundamentally distinguishes the FGIDs from more profound motility disorders.

Are the FGIDs diseases of the GI tract?

The field is further complicated by the reality that symptom reporting is highly heterogeneous, and by the extremely high frequency of extra-GI symptoms (e.g., fatigue, muscle pain, urogenital dysfunction). Therefore, it is essential that investigators and clinicians are mindful that the gut may only be an affected organ in a systemic problem, and not necessarily the site of the primary pathology.

Since the biological basis of these symptoms is unknown, how can a logical and targeted pharmacological strategy be developed? Currently prescribed agents simply and crudely attempt to swing the pendulum of altered gut function (e.g., reported bowel habit or the measured rate of gastric emptying) in the opposite direction, to treat gut spasm which probably does not exist, and to nonspecifically interfere with neurotransmission in the gut-brain axis. In all the other branches of GI medicine however, recent and major

therapeutic advances have all occurred by targeting key biomolecular targets: the proton pump, tumour necrosis factor alpha (TNFα), *Helicobacter pylori* and the hepatitis viruses, and the growth factors associated with GI neoplasms, to list key successes. To date, no agent has been applied to FGIDs with such precision, and never can be across such a heterogeneous population.

The underlying pathophysiology is almost certainly multifactorial in the majority of patients. Although most therapeutic reviews in this field optimistically cite long wish-lists of potential targets, the lack of truly promising singular targets doubtless underpins the increasingly cold feet of the pharmaceutical industry in sustaining target discovery research in FGIDs. The only truly specific approaches launched to date targeted serotonin receptors, with some modest efficacy evident but also with apparent risk that the regulators could not accept for common and non life-threatening illness.

The pathobiological heterogeneity of patients recruited merely on the basis of similar symptoms is probably the reason for small therapeutic effects in clinical trials, and also a problem the industry helped to create by supporting the drive to classify FGIDs on a tangible but entirely non-mechanistic basis.

On the other hand, it is important to remember that an effective novel drug target does not need to be implicated directly in the disease process, but may be a key component in the physiological circuitry underpinning the symptoms. A key borrowed example here is the targeting of β-adrenoreceptors in ischaemic heart disease (IHD) or asthma. There are no genetic or molecular disorders of these targets in these common diseases. Therefore, animal models or population genomic studies of these diseases could never identify these receptors as the highly effective drug targets that they plainly are. Truly integrative physiology must be maintained as an essential component of clinical and biological research. Moreover, this integration must include abnormal function in central neural systems, which are modulated by current stress or even prior experience, and certainly drive abnormal gut function. Indeed the CNS is arguably proving the most highly tractable FGID target to date, whether pharmacological or psychological in approach.

Recent progress in FGID biomedicine

Despite the inescapable issues and difficulties outlined above, recent significant progress has been made in several key domains.

Arguably the single most important advance has been the recognition that persistent low-grade inflammation exists in the gut in certain FGID scenarios. The clearest example is the chronic inflammation reproducibly demonstrated in patients with postinfectious irritable bowel syndrome (PI-IBS), with no significant prior gut symptoms and in whom gut function was assumed to be normal before a defined episode of bacterial gastroenteritis [Spiller, 2003; Spiller *et al.* 2000]. Crucially, this low-grade but diffuse inflammation would not be noticed by a routine pathological assessment of gut histology, yet careful analysis reveals significant increases in inflammatory cells (T-lymphocytes, macrophages and mast cells) and also enteroendocrine cells. Increased mucosal permeability and abnormal 5-HT metabolism are also demonstrable. These studies now need to move from the descriptive to the mechanistic, in order to understand and identify the molecular processes that are preventing the return to normality in a predisposed subset of individuals who develop chronic inflammation. Translational research is also needed to understand the relevance to the broader FGID population. Care must be taken to unravel cause from consequence, and other disciplines concerned with psychoneuroimmunology will have lessons to teach the GI community.

The model is of further pivotal potential importance since it epidemiologically links PI-IBS risk to two key risk factors: female gender and psychological stress. The stress response at the time of gut injury, including cytokine and hypothalamic-pituitary-adrenal axis dysregulation may therefore also begin to unify the extra-GI symptom components and suggest broader therapeutic targets. These injury/repair mechanisms may also be pertinent to FGIDs that not uncommonly develop following GI or gynaecological surgery.

A further and linked area of ongoing advance is the recognition that the gut microbiota play a fundamental role in normal physiology and the response to injury or infection, and the growing evidence that intestinal dysbiosis exists in at least a subset of patients. This is more likely to be a subtle alteration than gross bacterial overgrowth [Quigley, 2007]. There is also a growing

realisation that antibiotic usage can trigger, or potentially treat, FGID symptoms, and dysbiosis is an attractive potential mechanism by which this may occur. Therefore, strategies to manipulate the gut flora present an exciting novel approach to research and possibly therapy. Yet much remains to be discovered about normal gut ecology in the first instance.

Additional organic abnormalities identified or suggested in subsets of patients include atopy, disturbed intestinal gas handling, autonomic nervous system dysfunction and ion channelopathies, each of which may lead to specific and targeted strategies. Clear and specific dietary intolerances may also exist, but the management of these is self evident. However, the symptoms of FGIDs are often triggered more nonspecifically simply by eating, so the activation of postprandial activity may be a key driver. The GI response to food and the cellular mechanisms of nutrient sensing and signalling are therefore of considerable current interest. The role of nutrient-sensing enteroendocrine cells, their secreted peptide and amine signals (including 5-HT) and gut-to-brain signalling via the vagus nerve may be pivotal in postprandial symptom genesis, and the implication of these entities in the low-grade inflammatory state of PI-IBS may be biologically informative.

The continually advocated concept of visceral hypersensitivity in FGIDs cannot be ignored. It remains frustratingly unclear whether or where an abnormality that amplifies nonpainful stimuli in the gut to an experience of pain exists: this may occur at the level of the gut, en route to the brain (e.g., spinal cord) or in the brain itself, or throughout this matrix [Anand *et al.* 2007]. There is clearly an urgent need to develop useful and valid clinical research and diagnostic tools to dissect central from peripheral mechanisms before these key question can be truly resolved. Centrally based and psychological disorders fundamentally have a neurochemically encoded basis and are no less amenable to experimental dissection – indeed, they may be more so.

Finally, the evidence that true or significant disorders of GI motility exist in FGIDs is not compelling, and intrusive investigations employed to dissect all these processes are inescapably likely to have an effect on the variables studied. This is especially so when results from naïve and anxious patients (very consciously intubated to induce discomfort in part of their gut or incarcerated in a claustrophobic MR scanner) are compared to control data from relaxed and experienced healthy volunteers. Moreover, key measured functions such as gastric emptying rates are highly variable if repeatedly measured even in healthy subjects and consequently are of limited investigational or clinical utility.

Towards a new physiological and biological classification of FGIDs?

Given recent advances, and a clear recognition that real biological abnormalities exist below the radar of standard investigations, a purely symptom-based approach to diagnosis and classification is no longer justifiable. If true therapeutic advances are to be made then these need to be fully characterised and form the basis for rationally targeted therapies. It is difficult to imagine a multicentre pharmacological trial initiated for a set of patients who shared an isolated symptom of, for example, unexplained breathlessness, with participants recruited purely on the grounds that they had the same symptom and normal cardiorespiratory investigations, and could therefore be placed in the same diagnostic category and recruited to the same study. Yet at one level, this is precisely what happens with FGIDs, and probably explains the marginal benefits above placebo generally observed in trials. Since it is likely that multiple different abnormalities culminate in similar reported symptoms (breathlessness is again a good example), it is now essential to biologically deconstruct the patient group in order to construct rational therapeutic hypotheses.

Risk factors rather than causes? Deconstructing the FGIDs

It is fundamentally important to appreciate that multiple pathobiological factors for development of any chronic illness overlap, and may be additive or multiplicative. In developing IHD for example, risk is a composite outcome of multiple genes, and of smoking, diabetes, diet, blood pressure and plasma lipids. A search for 'the cause' or 'the treatment' in IHD is patently pointless. The same caveat applies for any multifactorial disorder, and the consequent polypharmacy is far less likely to be appropriate or acceptable for FGIDs.

Although empirical treatment of symptoms therefore remains necessary in clinical routine *pro tem*,

if true progress is to be made it is now timely for the research community to construct a systematic and scientific approach to fully phenotype FGID patients in a large cohort. A panel of rational investigation, including development of new tools where necessary, should be geared to identify the risk components outlined above and performed meticulously in a large cohort of subjects. Symptoms should be considered as variables to be recorded rather than underpinning diagnostic labels. Synthesising the available and resultant data, and open to new discoveries, this multidisciplinary approach might include a comprehensive analysis of the following:

- central versus peripheral sensitivity/processing abnormality
- biomarkers of chronic mucosal inflammation: cell types and cytokines
- high throughput 'omic technologies and systems biology to identify dysregulated pathways in low-grade chronic inflammation
- microbiota and dysbiosis
- epithelial barrier and tight junction function
- systemic inflammatory biomarkers
- autonomic nervous system integrity
- psychological state and HPA activation.

This list is self-evidently not exhaustive.

In parallel, large population-based epidemiological studies are equally essential, in the first instance using the most tractable model of new onset postinfectious FGIDs in order to better define the biopsychosocial and microbiological factors that increase individual risk of developing chronic symptoms, an outcome seen in the minority of individuals.

Clearly this approach will never lead to a 'magic bullet' and probably never deliver a 'blockbuster' drug, so it is at first glance unlikely to be attractive to the pharmaceutical industry.

Given the size of the problem, however, the assignment of individual patients to a new classification based on their underlying abnormality can only lead to a better understanding of symptoms and how to treat them than the current approach, which is simply labelling.

Beside the status quo, is there any alternative?

Conflict of interest statement

The author states no conflict of interest in compiling this editorial.

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