REVIEW

The future developments in neurogastroenterology: the 'new black'

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Received 14 March 2012

Accepted 23 March 2012

Despite the fact that functional bowel disorders (FBDs) are the most common gastrointestinal conditions, neurogastroenterology has for years been the Cinderella subspecialty in gastroenterology, and one of the least popular specialties among trainees in gastrointestinal (GI) surgery. Is this all about to change?

Lagging behind

Approximately 25% of the adult population suffers from FBDs, and yet the specialty is poorly developed, and research funding is relatively limited compared with subspecialties such as inflammatory bowel disease or hepatology. The cause of this indifference relates, largely, to the lack of effective treatments, this in turn being ultimately due to the lack of understanding of pathophysiology. While advances in molecular biology, imaging and endoscopy have revolutionised the characterisation and treatment of many GI disorders, it can be argued that there has been little progress in understanding the dysmotile gut. The causes of this are understandable. Full thickness biopsy of the gut to allow study of the myenteric neuromusculature is rarely possible. Functional studies of the gut have been inadequate due to the tortuous and extensive nature of the organ and the need to study it over prolonged periods of time (since visualisation of gut function over minutes or even hours is inadequate to understand abnormal physiology). The inability to understand the molecular, biochemical and neuromuscular dysfunction in these conditions has led to treatments that are ineffective. There is, of course, little job satisfaction trying to manage conditions where there are inadequate treatments.

New developments: the next 5 years

Invasive diagnostic procedures are less than ideal in the assessment of gut dysmotility,

as they usually alter normal function and cannot be used for prolonged measurement. Technological refinements will provide an increased ability to study motility non-invasively. Improvements in dynamic MRI scanning will allow detailed analysis of gastric, small bowel and colonic activity in an unprepared state (though only for short periods of time). Ingested capsule devices will continue to develop, with magnetic tracking and assessment of visual, pH and pressure measurements in various combinations. High-resolution manometry has revolutionised oesophageal diagnostics, and has already been developed for colonic assessment. More extensive studies with this modality will provide some valuable insights. On the histopathological front, the recent development of consensus criteria for defining abnormalities of the myenteric plexus and gut muscle will lead to a better appreciation of the importance of these features in producing symptoms, although the relatively small number of samples will limit major conclusions. Despite all these developments, the next 5 years will see only modest insights into disease pathogenesis, and it will be a decade from now before technological advances lead to major breakthroughs in our understanding of FBDs.

The advances which will have the greatest impact on the specialty over the next 5 years will be the licensing of new drugs. We have already seen in the last few years the release, with variable success, of drugs such as alosetron, tegaserod and prucalopride. The next few years will see late-stage clinical trials completed in a small but significant number of other drugs, including both agonists and antagonists of 5HT and opioid receptors. Drugs that affect gut hormone function, such as those that affect motilin and ghrelin, are also in late-stage trials; and compounds that affect

gut secretion (such as linaclotide and lubiprostone) are already licensed in the USA. The addition of new probiotic preparations will complete the growing armoury of treatments for neurogastroenterologists who will, at last, feel they have a range of treatments to offer patients, with a choice of compounds in each group allowing for tailored and combination therapies.

The impact of these drug developments will go much farther than the direct effect on patient care. The increasing involvement of the pharma industry in the field, where previously most treatments have been over the counter, will lead to a considerable increase in sponsored meetings and publicity about these conditions, raising their profile and increasing clinician interest. Large-scale commercial trials inject funding into neurogastroenterology research infrastructure and speed up the rate of progress, leading to a virtuous cycle. Media interest in IBS has always been high, but has previously been inhibited by lack of 'good news' stories, so the increasing therapeutic potential is likely to be widely publicised. Increasingly, patients are asking for specialist referrals as a result of reading about a new treatment (usually prucalopride, at the current time) on patient-initiated websites or social networking sites. This is only likely to increase as more treatments become available, and in view of the prevalence of FBDs in the population the profile of these conditions is likely to rise rapidly.

Behavioural therapy techniques, such as biofeedback, are used widely in the UK to treat constipation, but currently lack clear guidelines for indications, methods of therapy and training. Large-scale multicentre trials will deal with these issues, and we will also see techniques developing to improve function in faecal incontinence, urgency of defecation and rectal pain syndromes. However, these developments will be modest compared with those of device-based therapies. In the last 5 years, we have seen the rapidly expanding use of sacral nerve stimulation for faecal incontinence, and latterly also for constipation. Gastric neuromodulation is now also available in specialist centres for the treatment of gastroparesis. These techniques will be further refined, but also added to. For sacral nerve stimulation, studies identifying optimum stimulation parameters and adjustment procedures to deal with reductions in efficacy will report findings, as well as further work on optimising therapy in constipation and understanding mechanisms of action. For gastric neuromodulation, we will see the advent of gastric pacemaker mapping, individualising lead placement for each individual and improving therapeutic outcome.

New methods of gut stimulation are being developed and may become available. One of these is vagal stimulation, either using external magnetic induction, or by direct stimulation using implantable devices. Direct magnetic stimulation of the gut has also been shown to be effective, both in animal models and in some human studies, and a CE marked device will become available in the next few years.

Into the future

The 5 years leading up to 2022 will be the most exciting in the history of neurogastroenterology. Disease processes will be characterised with the potential for better diagnostics and new therapies that target the cause of the disease rather than the symptoms.

Fast-acquisition MRI scanning and software development will allow non-invasive assessment of gut function with considerable clarity, and research scanners will allow some prolonged studies. Provocation tests during scanning (such as ingestion of food or administration of drugs such as neostigmine) will provide diagnostic tests far more predictive than our current crude transit studies. The 'holy grail' of gut physiology however, is the study of function in a continuous ambulatory setting and this can never be achieved through an MRI scanner. Ambulatory studies will become feasible with the use of gut mucosal microprobes, attached endoscopically, and functioning over several days to monitor three-dimensional conformation, pressure and wall tension in the local vicinity of the probe. A small number of probes within a defined area (such as the stomach or recto-sigmoid) would yield invaluable insights into normal and abnormal functions. Another way of facilitating continuous ambulatory visualisation is with high-resolution ultrasound. The use of two or three such scanners (each only a centimetre across) simultaneously fixed to the abdominal wall, and the development of software which would produce three-dimensional reconstructions, would allow large portions of gut to be studied in a continuous ambulatory setting. Thus, we will gain insights into gut movements in health and disease that we have not come close to in the past. However, this is only halfway to understanding disease, with neuromuscular, molecular and biochemical characterisation needed to develop new treatments. Genetic studies are still in their infancy in the field of FBDs, but in another 10 years many genetic susceptibility loci will have been identified, and genetic mutations will reveal key biochemical triggers of disease. A new method of suction biopsy, rather like the Crosby capsule, but with an internal stapling device, will allow safe and minimally invasive full-thickness biopsy in patients with severe FBD. The ability to take biopsy specimens from significant numbers of patients, and even to assess changes over time, will provide further major steps forward. Developments in histopathological, ultrastructural and biochemical assessment of these biopsies will provide many insights into the disease processes. Thus, the combination of continuous non-invasive, sometimes ambulatory, imaging of function, the ultrastructural and pathological characterisation and genetic studies, will lead to a new era where FBDs are redefined and understood. Diagnostics will be revolutionised by the development of blood tests for confirmation of diagnosis and biopsy tests for subtyping the disease.

These insights will act as major sources of inspiration for new treatments, but even without these developments, there are likely to be two areas of

pharmacological therapy which will mature at this time and which have the potential to revolutionise management. The first is the development of visceral analgesics, which will emerge following the recent characterisation of receptors important to pain pathways in these conditions. Pain is often the most debilitating symptom experienced by patients with FBD, and the availability of specific and effective visceral analgesics will have far-reaching benefits. Probiotic therapy is another area that will blossom around this time. The use of probiotics, to date, has been inevitably simplistic, and the results, not surprisingly, have been modest. The principle of supplementing 'good bacteria' is, in some ways, like releasing a captive-bred endangered animal species into a jungle from which it is disappearing without understanding the ecological pressures that have led to the diminution of that species. Studies that detail the ecological determinants of gut flora fluctuations will allow more informed therapy which may involve provision of probiotics together with other factors that influence the prosperity of those species that are beneficial. Indeed, the latter are likely to be more important than administration of the bacterial supplements. The ability to treat visceral pain and manipulate gut flora will augment the growing number of drugs affecting motility and secretion, resulting in a substantial pharmacologic arsenal. New therapies, based on characterisation of pathological and genetic processes will expand this area even further.

Perhaps, with such capacity for drug therapy, there will be less need for device-based therapy. However, there will always be refractory and intractable cases, and for these there will be a new generation of devices. These will be 'clever devices', with responsive capability. The device, be it a sacral nerve, vagal or gastric stimulator, will be wirelessly linked to a sensing device, most likely a microprobe securely attached to the gut wall. In its simplest form, a probe in the stomach or rectum will detect whether the organ is full or empty and will provide continuous feedback to the stimulation device so that stimulation parameters can be adjusted according to prevailing physiological need. No bodily system works well without variable controls, and it is not difficult to understand that today's stimulation devices, devoid of such control, are significantly handicapped.

Organisation of services will be radically changed 10 years from now. One aspect of this will be the use of integrated multi-modality therapy. It is clear that FBDs are complex conditions that may be caused by a combination of aberrant gut physiology, behavioural issues and psychological factors. It is common that all these may be active in a single patient so that, for example, a patient with constipation may have poor colonic motility due to neuromuscular dysfunction, together with anismus, a poor diet and exacerbation of symptoms due to work-related stress. Currently, treatments are offered in series, with the easiest and most acceptable to patients (prescription of tablets) offered first. Thus, a pro-motility drug given in this situation may

fail and be withdrawn, with the patient then going on to biofeedback and finally psychological therapies. This process will fail if all the factors are not dealt with, so correct sequencing or co-administration of therapies is necessary. Programmes of multi-modality therapy will be developed, but the complexity of studying these will mean that refinement and standardisation will take 5–10 years. Probably the most significant development in health service organisation will be the widespread uptake of telehealth and telemedicine services. These are likely to have a greater impact in conditions with a more progressive natural history and where multiple professionals are involved, disorders such as cancer, dementia and palliative care. However, the wide-reaching effects of these services will be felt in all fields of medicine. Face-to-face outpatient contacts will be reduced, and electronic communication through email and Skype will become the norm. Patients will have greater access to online algorithmic self-help advice, some of it using interactive 'manage my bowel' programmes, and patients will learn from each other through monitored online forums and social networking sites.

However, for both clinicians and patients alike, the most remarkable change of this new era will be that irritable bowel syndrome will be transformed from a 'functional' or medically unexplained disorder to a series of interlinked diseases and, for the first time, clinicians will have an array of possible therapies.

Endnote

The development of specialisation in the NHS started after the Second World War. In the early 1950s, chest diseases were the main cause of death and morbidity in the UK, yet chest medicine was an unpopular and underdeveloped specialty. Streptomycin was discovered in 1952, providing the potential to treat tuberculosis. Although the drug had problems and was superseded by others, it was a sentinel event, marking the beginning of a new era, and 10 years later, chest medicine was the most popular specialty in the NHS. Alosetron and tegaserod were the sentinel events in irritable bowel syndrome (IBS). They have had problems, and have been surpassed by new drugs such as prucalopride, but they mark the beginning of a new epoch where pharmacological therapy of irritable bowel syndrome will become widespread, where clinicians feel empowered, patients more satisfied, and the profile of these conditions rises. The dam has been breached and we await a flood of interest and new developments that will make neurogastroenterology an exciting area to work in, and the fastest growing subspecialty in gastroenterology.

Competing interests YY has received speaker fees from Shire and Almirall. Research support received from Medtronic.

Provenance and peer review Commissioned; internally peer reviewed.