LETTERS

Fatigue in primary biliary cirrhosis

We would like to take the opportunity to clarify some of the points in response to the recent leading article (Gut 2004;53:475–7) which accompanied our report of reduced globus pallidus (GP) magnetisation ratios (MTRs) in patients with fatigue and primary biliary cirrhosis (PBC).

As we stated in the paper, fatigue in PBC is a subjective multidimensional symptom with many potential determinants, including sleep disturbance, depression, and personality, in addition to a potential central neurological cause. We therefore wholeheartedly concur with Drs Milkiewicz and Heathcote when they state that brain manganese (Mn) deposition is certainly not the cause of fatigue in all patients with PBC. We certainly do not believe that we drew this conclusion. However, we do believe that our findings of reduced GP MTRs in patients with stage I–II disease, which were associated with hypermanganeseaemia and measured fatigue, do open up a novel avenue of research into a poorly understood symptom in patients with PBC.

In order to control for inter-examination systematic variability, it is necessary to normalise the raw MTRs against an internal region of interest (ROI). Although it might initially appear easier to analyse the raw MTR data, normalisation to an internal standard allows external sources of variation to be removed. We followed previously published protocols to calculate GP indices, normalised to the putamen and to the frontal white matter, 1 and these were used to test associations with fatigue. Additionally, while external sources of variation, unrelated to the patient, to be removed. We followed previously published protocols to calculate GP indices, normalised to the putamen and to the frontal white matter, 1 and these were used to test associations with fatigue, while Milkiewicz and Heathcote have expressed concern about an apparent auto-correlation in our data that did not equal 1. Table 2 in our paper shows the correlation coefficients between individual MTR indices and blood Mn level. We did not compare the normalised putamen index against the normalised putamen index.

We are grateful to the two commentators for extending our interpretations and naturally agree that bile duct loss, rather than liver fibrosis, governs the severity of cholestasis and that there may be dissociation between these features in PBC. For the purposes of this study, we chose to examine patients with stage I–II disease to remove the possibility of hepatic encephalopathy or cirrhosis as a cause for the MTR findings. We believe that both this patient selection and the demonstration of normal cerebral magnetic resonance spectroscopy (MRS) in these patients, compared with healthy volunteers, does indeed achieve this. We found reduced GP MTRs in patients with stage I–II disease, which were associated with hypermanganeseaemia and measured fatigue, but we also studied four patients with stage III–IV disease and, as a group, there were no significant differences in GP MTR indices compared with stage I–II patients. Although this may be due to the small number of individuals studied, the lack of clear distinction between stage I–II and stage III–IV disease may also reflect a process that adversely affects the brain long before the development of cirrhosis, owing to early bile duct loss.

The commentators point out that the value of liver biopsy staging of PBC is limited owing to sampling error and that there may not have been a true distinction between the stage I–II and III–IV groups. We accept the possibility of sampling error but, in our view, liver biopsy still remains the gold standard for diagnosing cirrhosis. We disagree with the suggestion that cerebral MRS would have been useful in supporting the histological diagnoses as cerebral MRS abnormalities are only seen in a minority of patients with Child-Pugh A cirrhosis. 2 We did not assume that MRS would be abnormal in stage III–IV patients; in fact, there were no significant differences between these patients and stage I–II patients.

Fatigue in PBC merits further research. We hope that we will be able to take further “steps in the right direction”.

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References


Acute ulcerative colitis during successful interferon/ribavirin treatment for chronic hepatitis

A 54 year old man was treated with pegylated interferon alpha 2a 180 µg weekly and ribavirin 1000 mg daily for chronic hepatitis C genotype 3a (>5×10^5 IU/ml). There was no history of gastrointestinal disease or morbidity.

At week 12, hepatitis C virus-polymerase chain reaction (HCV-PCR) was negative and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels remained elevated at 2–3 times above the upper limit of normal. Treatment with pegylated interferon and ribavirin was planned until week 24. However, at week 14, the patient reported a sudden onset of watery and sometimes bloody diarrhoea. Colonoscopy showed continuous pancolitis, macroscopically suggestive of inflammatory bowel disease (IBD). Histology revealed a severe highly active pancolitis with basal plasmacytosis, crypt abscesses, and crypt distortion, as seen in ulcerative colitis.

The antiviral treatment was stopped and treatment with prednisolone and mesalazine (5-ASA) was initiated. Steroids were tapered over four weeks, which was associated with clinical and endoscopic remission. 5-ASA was continued at a dose of 3 g daily for eight weeks followed by 2 g daily.

Three months later (receiving 5-ASA 2 g daily) there was complete clinical and endoscopic remission. Histology showed a mild residual increase in mononuclear inflammatory cells. PCR revealed a virological relapse of HCV (high viraemia >6×10^5 IU/ml) and AST which was unchanged twofold elevation in ALT and AST.

We suspect that the ulcerative colitis-like severe pancolitis in this patient with no
history of IBD was probably an adverse effect of the anti-viral treatment with interferon-
rhavirin rather than a concomitant disease. Similar observations have been made by others. 16,17 To our knowledge, the present case is the fourth reported in the literature. Interferon has immune stimulating properties 18 and may trigger autoimmune diseases and/or transplant rejections. Hence, in light of this, the report on interferon treatment in active ulcerative colitis (Gut 2003; 52:1728–33) seems interesting and warrants further research.

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The toll-like receptor 4 (TLR4) Asp299Gly polymorphism is associated with colonic localisation of Crohn’s disease without a major role for the Saccharomyces cerevisiae mannan-LBP-CD14-TLR4 pathway

It is with great interest that we read the paper by Frishmuth and colleagues (Gut 2004; 53:987–92) in which they described a novel association of the toll-like receptor 4 (TLR4) +896 A>G polymorphism with both Crohn’s disease (CD) and ulcerative colitis (UC), supporting the genetic influence of pattern recognition receptors (PRRs) in triggering inflammatory bowel disease (IBD). PRRs are sensors of pattern associated molecular patterns of microorganisms in the intestinal flora. Independently, we performed a similar study. However, special attention to the presence of anti-Saccharomyces cerevisiae antibody (ASCA) was taken, as Tada and colleagues 19 have recently reported that the S cerevisiae mannan-LBP complex is recognised by CD14 on monocytes and signaling through TLR4 leads to the production of proinflammatory cytokines in a manner similar to that induced by lipopolysaccharide (LPS). Patients and controls were recruited from the Outpatient Department of Gastroenterology, VU University Medical Centre, Amsterdam, the Netherlands. The group consisted of 112 CD patients and 170 unrelated Dutch Caucasian controls. Diagnosis of disease was based on clinical, histopathological, and endoscopic findings. CD patients were categorised using the Vienna classification (general patient characteristics are described elsewhere). 20 ASCA IgA and IgG ELISAs were performed as described previously. 21 Genotyping for the CD14-260 C>T and TLR4+896 A>G single nucleotide polymorphisms (SNPs) was performed as described previously by our group. 22 The CD14-260 and TLR4+896 genotypes, allele, and carrier frequencies were compared between the different clinical patient groups and controls. In addition, synergism between CD14 and TLR4 genotypes and alleles (carrier trait analyses) was studied. Vienna classification and ASCA status were included in the statistical modelling.

The results are shown in table 1. The frequency of the G allele of TLR4 was significantly increased in CD patients compared with controls (19% vs 10%; p = 0.049; odds ratio (OR) 2.1 (95% confidence interval (CI) 1.0–4.1)). Disease phenotype was assessed in patients using the Vienna classification. Genotype of the CD14-260 C>T and TLR4+896 A>G single nucleotide polymorphisms (SNPs) was performed as described previously by our group. 23 The CD14-260 and TLR4+896 genotypes, allele, and carrier frequencies were compared between the different clinical patient groups and controls. In addition, synergism between CD14 and TLR4 genotypes and alleles (carrier trait analyses) was studied. Vienna classification and ASCA status were included in the statistical modelling.

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TLR4 G allele carriage in ASCA positive and ASCA negative patients (23% vs 14%; p = 0.33) (data not shown) and there was no difference between TLR4 G allele carriage in ASCA positive and negative CD patients with colonic localisation (40% vs 46%; p = 1.00) while the frequency of G allele carriage was identical to that of CD patients with colonic localized disease (43%) without correcting for ASCA status.

Several studies have described both TLR4+896 A→G and CD14-260 C→T in CD. Klein et al have described a German population and found an increased incidence of CD14-260 heterozygous and homozygous mutants in CD patients compared with healthy controls. This association could not be confirmed in our population. Preliminary data by Brant et al demonstrated an increased risk of suffering from CD in a Dutch population carrying the TLR4 +896 SNP, confirming our results. Franchimont and colleagues (Gut 2004;53:987–92) corraborated the results of Brant et al. However, we found an association between the G allele of TLR4+896 and disease phenotype (colon localization). In contrast with the aforementioned studies and results, Arnot et al were unable to demonstrate an association between susceptibility to CD and the CD14 and CD14 SNPs in a Scottish and Irish population.

The association between TLR4 and CD underscores the role of impaired innate immunity in CD. TLR4 signalling is based on both exogenous (for example, LPS) and endogenous (for example, human HSPs) agonists, and as heterozygous carriage of the TLR4 +896 A→G does not seem to impair LPS signalling,* further agonist identification to elucidate the microorganisms involved in CD and especially in colonic localisation is essential to obtain insight into both the pathophysiological and immunogenetic aspects of CD. This insight may be helpful in developing strategies for the prevention and treatment of CD.

The association we demonstrated between TLR4 and CD is most likely not strongly based on the S. cerevisiae mannan-LBP-CD14-TLR4 pathway but, as we have demonstrated, on the ASCA data in our group. It would be interesting to know whether Franchimont et al tested for ASCA in their CD patients and whether or not an association between ASCA and TLR4 was observed.

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References


Reoperative chemoradiotherapy for oesophageal cancer: a systematic review and meta-analysis

Just as the weakest link in a chain determines how much weight the chain will hold, the weakest link in the data used by Fiorica et al will determine how much weight we as readers should give to their findings and conclusions regarding neoadjuvant chemoradiotherapy for oesophageal adenocarcinoma (Gut 2004;53:925–30). Clearly, the weakest link in their data is the material by Walsh et al, and prior to placing any confidence in the conclusions by Fiorica et al, a careful assessment of the reliability of the Walsh data is imperative. Well known criticisms of the Walsh trial include the lack of routine staging with computed tomography scanning that led to five patients undergoing surgery alone for stage 4 disease, the exclusion of a number of patients in the neoadjuvant arm for “protocol violations” when in fact several had evidence of progressive disease and should have been considered treatment failures, and the lack of a uniform surgical technique that led to five different types of operations performed and what are arguably the worst surgical results for oesophageal adenocarcinoma reported in the literature. However, these criticisms are overshadowed by a greater problem in the Walsh trial related to internal inconsistencies in the survival data. Careful review of the Walsh manuscript reveals that the survival data in the text of the report does not match the data in the Kaplan-Meier survival curves, but surprisingly the discrepancy is only for the neoadjuvant arm. In all cases the survival data for the surgery alone arm matches up precisely. For example, in the text of the manuscript, survival by intention to treat at three years in the neoadjuvant arm is reported as 32%, yet on the Kaplan-Meier graph survival by intention to treat in the neoadjuvant arm is approximately 48%. Similar discrepancies occur at essentially every data point for both the intention to treat and the treatment actually received graphs, but only for the neoadjuvant arm, with survival on the Kaplan-Meier graph improving beyond the data in the text. Importantly, the statistics for survival are calculated from the Kaplan-Meier curves, raising concern that the data in the text of the report does not match the data in the Kaplan-Meier survival curves, but surprisingly the discrepancy is only for the neoadjuvant arm.
The response by Walsh was that the graphs were mislabelled, but even with a different label the data points continue to be incongruent.

In light of this, I would like to know how Fiorica et al handled the data from the Walsh trial. Did they use data from the Kaplan-Meier survival curves or from the text and tables in the manuscript? Were they aware of the discrepancy and if so why did they not comment on it in their manuscript and specify how they dealt with it in their meta-analysis? In light of these concerns, as well as other issues regarding this trial, is it appropriate to even include it in a meta-analysis unless the raw data are independently reviewed and the statistics validated? This is an especially important issue as the Walsh study is the only trial that included just patients with adenocarcinoma, and as stated in the manuscript by Fiorica et al, robust analysis showed that exclusion of the Walsh trial would lead to loss of statistical significance for overall mortality (Gut 2004;53:925–30). This would leave us where we started, lacking any significant evidence that neoadjuvant therapy improves survival for patients with oesophageal adenocarcinoma.

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References

Systemic lidocaine and mexiletine for the treatment of a patient with total ulcerative colitis

In basic research, neural modulation in ulcerative colitis has been shown. In clinical settings, local anaesthetics such as lidocaine and ropivacaine were used, administered per rectum, for the treatment of distal ulcerative colitis with a response rate of 83% after long treatment periods (6–34 weeks) for proctosigmoiditis (n = 49). We report a patient with total ulcerative colitis that was ameliorated by continuous intravenous administration of lidocaine followed by oral administration of mexiletine (a congener of lidocaine). A 24 year old man suffering from exacerbation of ulcerative colitis was admitted to our hospital. Total ulcerative colitis had been initially diagnosed one year previously. Disease extent was re-examined by barium study to reveal a total type of colitis. Conventional medical therapies, including steroids (prednisolone, and steroid pulse therapy), 5-aminosalicylate, and leucocytepheresis were not effective. Abdominal pain with bleeding per rectum was very severe at night. We administered continuous systemic lidocaine (1 mg/min on the first day and 1.3 mg/min on subsequent days) only at night, resulting in complete disappearance of abdominal pain and bloody diarrhoea on the first day of treatment. This therapy was given for one week followed by oral mexiletine (300 mg/day on the first two days and 200 mg/day thereafter) administration. Prednisolone was tapered without exacerbation of colitis during this treatment, and the patient left our hospital.

Clinical reports by Kemler and colleagues, who reported on a patient with ulcerative colitis exacerbated by spinal cord stimulation, and by Peck and Wood, who obtained complete remission of a patient with ulcerative colitis after spinal cord injury, support the involvement of neural control in ulcerative colitis. Systemic lidocaine, which has been shown to suppress only spontaneous ectopic discharges without blocking nerve conduction, and mexiletine may modulate central and/or peripheral nerve function. Thus, in this case, the effectiveness of these drugs could be attributed to modulation of nerve function. Bjorck et al found that when using a 2% gel (400 mg lidocaine), maximum plasma levels were 0.5–1.9 mg/l in patients with proctitis two hours after application of the gel. In experimental models, plasma concentrations of 1.2–2.1 mg/l of lidocaine has been shown to be effective for neuro- pathic pain. Therefore, it is possible that in ulcerative colitis, lidocaine administered per rectum could exert its pharmacological effects after being absorbed into blood and has an effect on central and/or peripheral nerves. Another possibility is direct anti-inflammatory effects of these drugs on immune cells. However, it is not known whether systemic administration of lidocaine can achieve adequate concentrations in colonic tissue to have a direct anti-inflammatory effect on immune cells. A prominent feature of this case was the close association between pain and other symptoms such as bloody diarrhoea. Systemic lidocaine caused prompt symptomatic relief followed by amelioration of ulcerative colitis which was assessed by sigmoidoscopy and blood inflammatory parameters (data not shown), suggesting that pain or pain inducing substances could be a cause of exacerbation of ulcerative colitis as well as a result of the disease.

Lidocaine and mexiletine therapy could be useful for the treatment of the subgroup of patients with ulcerative colitis that are refractory to conventional medical treatments. While we do not know how to select responders to this treatment, pain could be one of the indicators.

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References

New treatment for bile salt malabsorption

Currently available binding resins used for symptomatic bile salt malabsorption are generally poorly tolerated because of unpalatability and associated gastrointestinal side effects. We suggest that there is now a viable alternative, colesvelam hydrochloride (WelChol, Sankyo Pharmaceuticals Inc., Japan). A 30 year old man presented with steatorrhea, progressive weight loss, marked abdominal bloating and lethargy. A right hemicolectomy following a road traffic accident in 1966. Physical examination, relevant blood tests, barium follow through, colonoscopy, and microscopic examination of colonic biopsies were normal. A trial of cholestyramine in preference to a SeCHAT scan caused cessation of diarrhoea on one sachet per day. However, his abdominal bloating continued unabated and he found the treatment unpalatable. Cholestyramine was therefore changed to colesvelam 2.5 g/3.75 g on alternate days. This was well tolerated, with complete cessation of his steatorrhea and lethargy, and no side effects. In addition, he rapidly gained weight. A further four patients with markedly symptomatic bile salt malabsorption resistant to anti diarrhoeal agents and intolerant of cholestyramine were subsequently commenced on colesvelam (table 1). In all of these cases colesvelam was well tolerated with no side effects.

Colesvelam is a non-absorbed water insoluble polymer which sequesters bile. It has been approved for usage by the US FDA, and has been received as a valuable alternative for lowering cholesterol. Colesvelam has high affinity for dihydroxy and trihydroxy bile acids in the intestine which causes increased faecal bile acid secretion, reducing the enterohpatic circulation of bile acids. This allows 7-hydroxylase, the rate limiting enzyme in biliary cholesterol to bile acids, which has not yet been approved for use in the UK. One abstract suggests that colesvelam may be beneficial for patients with diarrhoea who have undergone small bowel resection for Crohn's disease. The published data to support its role in bile salt induced diarrhoea. Colesvelam is reported to be 4–6 times as potent as traditional bile salt sequestrants, possibly due to its greater binding affinity for glycocholic acid. It is administered in tablet form, and in one study the rate of compliance with colesvelam was 93%. The unique hydrogel polymeric
structure enables greater tolerability with less potential drug interactions than with resins. Repeated adverse events from the largest clinical trial to date include flatulence, dyspepsia, and diarrhea although the incidence of adverse events does differ significantly from that observed with placebo, and is lower than with cholestyramine. It is rarely associated with constipation, unlike cholestyramine. Colesevelam is non-absorbed and is excreted entirely via the gastrointestinal tract, preventing systemic side effects. Furthermore, there is little evidence for clinically significant interactions involving colesevelam. Pharmacokinetic studies with colesevelam have not shown clinically significant effects of absorption of six other coadministered drugs.

There is a theoretical risk of fat soluble vitamin deficiency following such efficient bile acid sequestration. None of our patients developed any significant change in fasting triglycerides or fat soluble vitamin levels to date.

Each film coated tablet contains colesevelam 625 mg (active ingredient). The recommended starting dose for monotherapy for hypercholesterolaemia is 3.75 g once a day or 1.25 g in adults. The optimal dose for bile salt malabsorption is not clear but an effective dose has varied between two and six tablets/day in our series. Colesevelam was obtained from IDIS Ltd.

This colesevelam is a novel bile acid binding resin in tablet form that maintains the benefits of cholestyramine, yet is palatable, associated with decreased adverse effects, and has greater potency. It provides a very attractive alternative therapy for patients with bile salt malabsorption and further study is warranted.

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References


6th International Symposium on Functional Gastrointestinal Disorders

This symposium is co-sponsored by the Office of Continuing Medical Education, University of Wisconsin Medical School, and the International Foundation for Functional Gastrointestinal Disorders (IFFGD). It will take place on 7–10 April 2005 in Milwaukee, Wisconsin, USA, at The Pfister Hotel, 424 E. Wisconsin Avenue, Milwaukee, Wisconsin 53202 (tel: +1 414 273 8222; toll free tel: +1 800 558 8222; fax: +1 414 273 5025; email: info@thepfisterhotel.com; web: http://www.iffgd.org/symposium2005.html).

In reference 38 of the paper by C Gasche and P Grundtner, published in the January issue (Genotypes and phenotypes in Crohn’s disease: do they help in clinical management? Gut 2005;54:162–7), the page span is incorrect, it should read 1658–64.

In the paper by Sheu et al in the July 2003 issue of Gut (B-S Sheu, S-M Sheu, H-B Yang, A-H Huang, and J-J Wu. Host gastric Lewis expression determines the bacterial density of Helicobacter pylori in babA2 genopositive infection. Gut 2003;52:927–932), the B and C slides of figure 1 have been transposed and the arrow on D should be labelled Le then Le.