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 system 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, 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, and these were used to test associations with fatigue and Mn levels. The raw MTR data were used for the primary comparison between PBC patients and healthy volunteers. We chose two rather than one internal control ROI because, contrary to the assertions in the editorial, there is evidence for Mn accumulation in brain structures, other than the GP, in patients with cirrhosis. Rose et al reported significantly elevated Mn concentrations in the frontal and occipital cortex, pallidum, putamen, and caudate while Maeda et al showed elevated Mn concentrations in the GP, putamen, and frontal white matter. Both series, the highest Mn concentration was in the GP. Our choice of two standard ROIs was made to maximise the interpretation of the raw data although we accept that the a priori assumption that pathology is absent from these regions in this and all relevant magnetic resonance studies to date, which have used internal controls, may be false. This may explain the unexpected trend towards a positive association between blood Mn and the putaminal index.

Drs Milkiewicz and Heathcote have expressed concern about an apparent autocorrelation 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 stages 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. 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 further ‘take the steps in the right direction’.

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Conflict of interest: None declared.

References

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

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 (>5×10^10 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. Fatigue was present and interferon therapy was planned to be 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 prednisone and mesalazine (5-ASA) was initiated. Steroids were tapered over four weeks, which had been ongoing treatment with prednisone and mesalazine 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 >6×10^10 IU/ml) and an 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 antiviral treatment with interferon-
ribavirin rather than a concomitant disease. Similar observations have been made by
others.1,4 To our knowledge, the present case is the fourth reported in the literature. Interferon has immune stimulating properties1 and may trigger autoimmune diseases and 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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Conflict of interest: None declared.

The toll-like receptor 4 (TLR4) Aasp299Gly polymorphism is associated with colonic localisation of Crohn’s disease without a major role for the Saccharomyces cerevisiae mannann-LBP-CD14-TLR4 pathway

It is with great interest that we read the paper by Fachinotto 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 colleagues1 have recently reported that the S cerevisiae mannann-LBP complex is recognised by CD14 on myeloid cells and triggers a similar response through TLR4 leading 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). ASCA IgA and IgG ELISAs were performed as described previously.1 Genotyping for the CD14-260 C>T and TLR4+896 A>G single nucleotide polymorphisms (SNPs) was performed as described previously by our group.2 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) were 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 (+896 G) 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. Carriage of TLR4 +896 G significantly increased the risk of colonic localisation of CD compared with non-colonic localisation (43% vs 12%; p = 0.0017; OR 5.5 (95% CI 1.9–15.4)). There was a clear trend (test for trend: z2 = 16; p < 0.0001) when we compared the increasing frequency of the G allele of TLR4 +896 in controls (10%) to CD patients (19%) and to CD patients with colonic localisation (43%).

We also assessed if ASCA status was correlated with carriage of the TLR4 G allele. However, there was no difference between

Author’s reply

As interferon alpha (IFN alpha) suppresses the proinflammatory cytokines and induces various anti-inflammatory cytokines, it may show efficacy in chronic inflammatory disorders of the gut. In Crohn’s disease, lamina propria cells manifest increased expression of IFN-g whereas in ulcerative colitis lamina propria cells and natural killer T cells demonstrate increased secretion of the Th2 cytokines interleukin 5 (IL-5) and IL-13.

IFN alpha has been demonstrated to potently suppress synthesis of both IL-5 and IL-13 in human leukocytes, making it an attractive agent for the treatment of ulcerative colitis. IFN alpha therapy showed no benefit in patients with Crohn’s disease. This may be explained by the fact that Crohn’s disease is thought to be a Th1 linked disease. IFN alpha therapy seems to be more successful in chronic active ulcerative colitis, a more Th2 linked disorder. Sumer and Palabiyikoglu reported that more than 80% of patients with active ulcerative colitis responded to high dose IFN alpha therapy within two weeks of treatment and were in complete clinical and endoscopic remission after six months of therapy.1 Madsen et al recently presented a study comparing systemic IFN alpha therapy and prednisolone enemas in the treatment of left sided ulcerative colitis.2 Ulcerative colitis is accompanied by high levels of IL-5 in colonic tissue and IFN alpha effectively suppresses IL-5 synthesis in leukocytes. IFN beta has been used in a pilot study investigating its role in patients with steroid refractory active UC.3 In this study, a high responder rate was observed with a mean time to response of three weeks.

Another IFN beta study in ulcerative colitis has been presented recently.4 In this small, placebo controlled, randomised, dose escalating study, clinical remission was observed in 50% of IFN beta treated patients compared with 14% in the placebo group. We recently presented data on the first placebo controlled use of IFN alpha in the treatment of active UC in patients with or without corticosteroid and/or immunosuppressive treatment.5 We observed no significant advantage of any IFN group over placebo but did not observe worsening of disease in any IFN treated patient. The mechanisms of action of IFN alpha are probably multiple but the possible interactions of IFN alpha with the cytokine cascade and immune system are usually not considered. Favouring Th1 responses and suppressing Th2 type immune responses could imply that type 1 IFNs may be therapeutic in diseases such as ulcerative colitis or allergic disorders. We agree with the authors that IFN alpha might have the potential to enhance inflammatory reactions and alloreactivity in certain situations but are also convinced that it has strong immunomodulatory and anti-inflammatory properties. Larger controlled trials with IFN alpha in ulcerative colitis are eagerly awaited.

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Conflict of interest: None declared.

References


References


TLR4 G allele carriage in ASCA positive and ASCA negative patients (23% v 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% v 46%; p = 1.00) while the frequency of G allele carriage was positive and negative CD patients with ASCA positive and ASCA negative (43% v 46%; p = 1.00) 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 Braat 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) corroborated the results of Braat et al. In contrast with Franchimont et al, we found a clear association between the G allele of TLR4+896 and disease phenotype (colonic localisation). In contrast with the aforementioned studies and results, Arnott et al were unable to demonstrate an association between susceptibility to CD and the TLR4 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 carriers 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 demonstrated between TLR4 and CD is most likely not strongly based on the S cerevisiae mannann-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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Conflict of interest: None declared.

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 strongest link in their data is the materiality 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 being performed and what are arguably the worst surgical results for oesophageal adenocarcinoma reported in the literature. However, these clonometric oversights are 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 only the Kaplan-Meier curves. Importantly 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 based on 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 graphs not matching the data in the text. Importantly, the statistics for survival are calculated from the Kaplan-Meier curves, raising concern that the difference in survival between groups is in fact not significant. This alarming discrepancy has never been adequately addressed despite a letter to the New England Journal of Medicine and a subsequent reply by Dr Walsh.

www.gutjnl.com
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.

S R DeMeester

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-term treatment periods (6–34 weeks) for procto-colitis (n = 49). This would leave us where we started, lacking any significant evidence that neoadjuvant therapy improves survival for patients with oesophageal adenocarcinoma.

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 a viable alternative, colesevelam hydrochloride (WelChol, Sankyo Pharmaceuticals Inc., Japan). A 30 year old man presented with steatorrhea, progressive weight loss, marked abdominal bloating and abdominal pain. He underwent 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 colesevelam 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 colesevelam (table 1). In all of these cases colesevelam was well tolerated with no side effects.

Colesevelam is a non-absorbed water insoluble polymer which sequesters bile. It has not been approved for usage by the US FDA, and has been received as a valuable alternative for lowering cholesterol. Colesevelam has high affinity for dihydroxy and trihydroxy bile acids in the intestine which causes increased faecal bile acid secretion, reducing the enterohepatic circulation of bile acids. This allows 7-hydroxylase, the rate limiting enzyme in bile acid synthesis, to increase the conversion of hepatic cholesterol to bile acids. It has notyet been approved for use in the UK. One abstract suggests that colesevelam may be beneficial for patients with diarrhoea who have undergone small bowel resection for Crohn’s disease. The abstract published data to support its role in bile salt induced diarrhoea. Colesevelam is reported to be 4–6 times as potent as traditional bile salt sequestrants, possibly due to its greater binding affinity for glycochenodeoxycholic acid. It is administered in tablet form, and in one study the rate of compliance with colesevelam was 93%.

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Reference


structure enables greater tolerability with less potential drug interactions than with resins.1

Reported 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.1 It is rarely associated with constipation, unlike cholestyramine.4 Colesevelam is non-absorbed and is excreted entirely via the gastrointestinal tract, preventing systemic side effects.5 Furthermore, there is little evidence for clinically significant interactions involving colesevelam.6 Pharmacokinetic studies with colesevelam have not shown clinically significant effects of absorption of six other coadministered drugs.7

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).1 The recommended starting dose for monotherapy for hypercholesterolaemia is 3.75 g/day or 1.25 g/day, depending on treatment with colesevelam and cholestyramine.4 Colesevelam is a novel bile acid-binding resin in tablet form that maintains bile acid sequestration. None of our patients suffered intractable vomiting side effects.2

The optimal dose of colesevelam is 4.375 g in adults.3

Clinical trial to date include flatulence, associated with decreased adverse side effects.6

Table 1 Characteristics of four patients with markedly symptomatic bile salt malabsorption resistant to antidiarrhoeal agents and intolerant of cholestyramine given colesevelam

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>Reason for bile salt malabsorption</th>
<th>Outcome with cholestyramine</th>
<th>Outcome with colesevelam</th>
<th>Duration of colesevelam treatment (months)</th>
<th>Current dose of colesevelam</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>M</td>
<td>Idiopathic</td>
<td>Diarrhoea improved but not tolerated because it induced severe dyspepsia</td>
<td>Diarrhoea resolved, no side effects</td>
<td>7</td>
<td>3.75 g/day</td>
</tr>
<tr>
<td>59</td>
<td>F</td>
<td>Right hemicolectomy</td>
<td>Diarrhoea improved but not tolerated due to unpalatability</td>
<td>Diarrhoea resolved, no side effects</td>
<td>3</td>
<td>3.75 g/day</td>
</tr>
<tr>
<td>68</td>
<td>F</td>
<td>Radiation enteritis and right hemicolectomy</td>
<td>Diarrhoea improved although suffered intractable vomiting</td>
<td>Diarrhoea resolved, no side effects</td>
<td>2</td>
<td>2.5 g/day</td>
</tr>
<tr>
<td>40</td>
<td>F</td>
<td>Radiation enteritis</td>
<td>Diarrhoea improved although suffered intractable nausea</td>
<td>Diarrhoea resolved, no side effects</td>
<td>2</td>
<td>1.25 g/day</td>
</tr>
</tbody>
</table>

4 Steinmetz RL. Colesevelam hydrochloride. Am J Health Syst Pharm 2002;59:932–9

Any researchers interested in applying for access to information held within the national register should contact Dr Helen Harris (Register Co-ordinator) or Ms Shirley Cole (Research Assistant), Immunisation Department, CDSC, Centre for Infections, Health Protection Agency, 61 Colindale Avenue, London NW9 6EQ, UK (tel: (020) 8200 6868 ext. 7767 (Wednesday to Friday) or ext. 7906 (Monday to Friday); fax: (020) 8200 7868; email: helen.harris@hpa.org.uk or shirley.cole@hpa.org.uk).

No data will be released that could identify individual patients directly or via linkage to other data. Any study proposals should then be submitted to the register co-ordinator for consideration by the steering group by Thursday 31 March 2005 (deadline).

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: +1 800 538 8222; fax: +1 414 273 5025; email: info@thepfisterhotel.com; web: http://www.iffgd.org/symposium2005.html).

The national register of hepatitis C infections with a known date of acquisition
A new call for study proposals.
In 1998, a national register of hepatitis C virus (HCV) infections with a known date of acquisition was established. The register was set up to help inform the natural history of HCV related disease in the UK and now contains anonymous data for one of the largest cohorts of individuals with known date HCV infections, with over 1120 registered patients. The majority of infections in the register are those that were acquired following transfusion of HCV infected blood that was issued before the introduction of routine screening of the blood supply for HCV, but other routes of acquisition are represented.

In order to get maximum benefit from this national resource, the register steering group would like to invite clinical and epidemiological researchers to submit proposals to access data held in the register. It is envisaged that a variety of studies might benefit from linkage with or access to the register, and proposals from all specialties and institutions are welcomed. Such studies are urgently needed to help determine the current and future burden of HCV related disease on healthcare services, and to assess the impact of currently available treatments as well as those that may become available in the future.

doi: 10.1136/gut.2003.035660corr1


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 genepositive infection. Gut 2003;52:927–32), the B and C slides of figure 1 have been transposed and the arrow on D should be labelled Le6 not Le5.

NOTICES

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