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 potential central neurological causes. 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 hypermanganesaemia 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 system variability, to be removed. We therefore wholeheartedly concur with the suggestion that cerebral MRS would have been useful in supporting the histological diagnoses as cerebrospinal 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 take further “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 (>5×10¹⁰ IU/ml). There was no history of gastrointestinal disease or morbidities.

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. However, at week 14, the patient reported a sudden onset of watery and sometimes bloody diarrhoea, Colonoscopy showed continuous pancolitis with basal plasmocytosis, 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 and interferon/ribavirin was continued with complete clinical and endoscopic remission. Histology showed a mild residual increase in mononuclear inflammatory cells. PCR revealed a virological relapse of HCV (high viraemia >6×10¹⁰ 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. 

To our knowledge, the present case is the fourth reported in the literature. Interferon has immune stimulating properties and may trigger autoimmune diseases and autoantibody reactions.

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.

References


Author’s reply

As interferon alpha (IFN alpha) suppresses the ontogeny of 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 secretion of IFN-y whereas in ulcerative colitis lamina propria cells and natural killer T cells demonstrate increased secretion of IFN gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. J Immunol 1996; 157: 1261-70.


4. Sumer N, Palabiyikoglu M. Induction of remission by interferon-alpha in patients with active ulcerative colitis. Clin Trials 1995; 2: 16, p = 0.049; odds ratio (OR) 2.1 (95% confidence interval (CI) 1.0-4.1). Disease phenotype was assessed as described previously by our group. The CD14-264 TLR4 +G allele. Significant association of the TLR4 +G allele with both CD and UC patients was observed. A total of 112 CD patients and 170 UC patients were categorised using the Vienna classification (general patient characteristics are described elsewhere). ASCA IgA and IgG ELISAs were performed as described previously. Genotyping for the CD14-264 TLR4 +G single nucleotide polymorphisms (SNPs) was performed as described previously by our group. The CD14-264 TLR4 +G 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 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 as described previously by our group. The CD14-264 TLR4 +G 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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Table 1 CD14 – 260 and TLR4-896 genotype distribution in Crohn’s disease (CD) patients and healthy controls (HC).

<table>
<thead>
<tr>
<th>Group</th>
<th>CD14 A + G (%)</th>
<th>CD14 A- G (%)</th>
<th>TLR4 A + G (%)</th>
<th>TLR4 A- G (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>HC</td>
<td>170/88</td>
<td>28/42</td>
<td>40/24</td>
<td>12/28</td>
</tr>
<tr>
<td>CD</td>
<td>112/88</td>
<td>35/54</td>
<td>48/24</td>
<td>18/22</td>
</tr>
<tr>
<td>A1</td>
<td>97/59</td>
<td>29/51</td>
<td>48/24</td>
<td>17/22</td>
</tr>
<tr>
<td>A2</td>
<td>12/51</td>
<td>6/54</td>
<td>47/24</td>
<td>7/22</td>
</tr>
<tr>
<td>B1</td>
<td>43/50</td>
<td>23/57</td>
<td>67/43</td>
<td>27/33</td>
</tr>
<tr>
<td>B2</td>
<td>45/52</td>
<td>12/58</td>
<td>20/40</td>
<td>37/33</td>
</tr>
<tr>
<td>B3</td>
<td>24/59</td>
<td>3/57</td>
<td>18/42</td>
<td>6/28</td>
</tr>
<tr>
<td>L1</td>
<td>41/59</td>
<td>14/41</td>
<td>24/40</td>
<td>17/23</td>
</tr>
<tr>
<td>L2</td>
<td>3/23</td>
<td>26/77</td>
<td>15/43</td>
<td>31/29</td>
</tr>
<tr>
<td>L3</td>
<td>17/47</td>
<td>3/43</td>
<td>24/43</td>
<td>19/21</td>
</tr>
<tr>
<td>L4</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
</tbody>
</table>

*TLR4/G was more frequent in CD patients compared with HC (19% v 10%; p = 0.0489; odds ratio (OR) 2.076 (95% confidence interval (CI) 1.041–4.142)).

TLR4 G allele carriage in ASCA positive and ASCA negative patients (23% v 14%; p = 0.033) (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 identical to that of CD patients with colonic localisation (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 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, Amott 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, LPSs) and endogenous (for example, human HSPs) agonists, and as heterozygous carriehers 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 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 the 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 critically 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 at 5 years is 32%, yet on the Kaplan-Meier survival curves, but critically 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 at 5 years is 32%, yet on the Kaplan-Meier survival curves, but critically 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 at 5 years is 32%, yet on the Kaplan-Meier survival curves, but critically 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 at 5 years is 32%, yet on the Kaplan-Meier survival curves, but critically the discrepancy is only for the neoadjuvant arm. In all cases the survival data for the surgery alone arm matches up precisely.
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;53:923–30). 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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Conflict of interest: None declared.

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.1 In clinical settings, local anesthetics such as lidocaine and ropivacaine were used, administered per rectum, for the treatment of distal ulcerative colitis with no side effects.7–9 However, systemic lidocaine has been shown to suppress only spontaneous ectopic discharges without blocking nerve conduction,2 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. Björck 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.10 In experimental models, plasma concentrations of 1.2–2.1 mg/l of lidocaine has been shown to be effective for neuropathic pain.11 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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doi: 10.1136/gut.2004.055525
Conflict of interest: None declared.

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 may be a pragmatic alternative, colestevelam hydrochloride (WelChol, Sankyo Pharmaceuticals Inc., Japan).

A 30 year old man presented with steatorrhoea, progressive weight loss, marked abdominal bloating, and lethargy following 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 colestevelam 2.5 g/3.75 g on alternate days. This was well tolerated, with complete cessation of his steatorrhoea 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 colestevelam (table 1). In all of these cases colestevelam was well tolerated with no side effects.

Colestevelam 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.7 Colestevelam 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.8 This allows 7-hydroxylase, the rate limiting enzyme in bile acid synthesis, to increase the conversion of 7-hydroxy bile acids, to 7-β-hydroxy bile acids, and allow the bile acids to enter the biliary system and be excreted. It is reported to be 4–6 times as potent as traditional bile salt sequestrants, possibly due to its greater binding affinity for glycocholic acid.8 It is administered in tablet form, and in one study the rate of compliance with colestevelam was 93.9 The unique hydrogel polymeric
Table 1 Characteristics of four patients with markedly symptomatic bile salt malabsorption resistant to anti-diarrhoeal agents and intolerant of cholestyramine given colesevelam

<table>
<thead>
<tr>
<th>Age</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>


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: +44 (0)20 8200 6688 ext. 7767 (Wednesday to Friday) or ext. 7906 (Monday to Friday); fax: +44 (0)20 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 tel: +1 800 558 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 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.

For study proposals to take part in the register, the Steering Group wishes to see the proposal for validation by a steering group, and any data that is released to researchers wishing to analyse and publish the register data.

Additional information is available in the register fact sheet. Completed proposals should be sent before 10th March 2005 and should be submitted to register.co-ordinator@phc.dh.gov.uk.

References


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

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