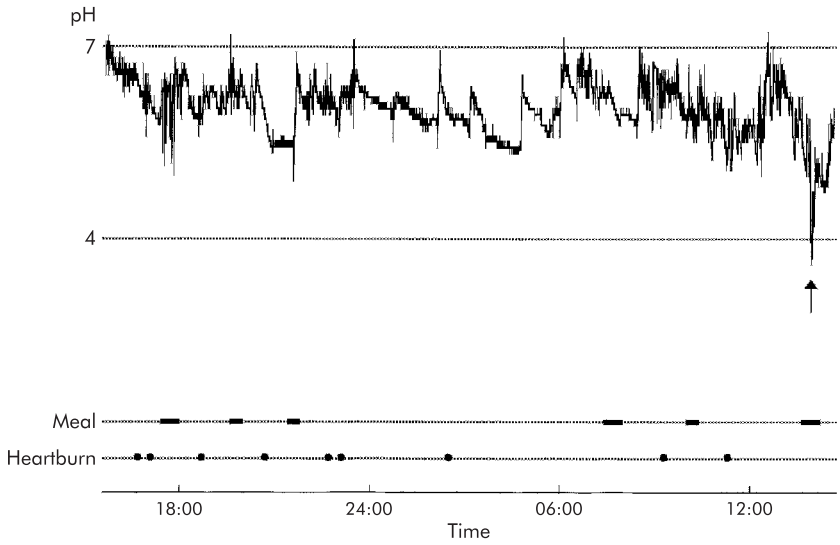

Figure 1 Tracing of 24 hour pH monitoring. No acid reflux episodes occurred. The drop in pH indicated by the arrow was caused by ingestion of (acidic) food.

a patient with pernicious anaemia which they felt was most likely induced by bile reflux.[4] Their patient's heartburn resolved on treatment with cholestyramine, a resin that binds bile salts. Our patient underwent a cholecystectomy a few years previously, a condition which may facilitate entry of bile into the stomach.[5] Bile may have been responsible for symptom generation in our patient. Although the study of Orlando and Bozymski suggests a relationship between reflux and symptoms, it does not prove such a relationship as confidently as can be done using symptom association analysis.

In conclusion, combined impedance-pH monitoring can be used to evaluate symptoms in patients with achlorhydria. The relationship between symptoms and weakly acidic and weakly alkaline reflux episodes can be investigated with this technique, which may have consequences for patient management.

Acknowledgements

AJ Bredenoord is supported by a grant from Janssen-Cilag, Tilburg, the Netherlands.

A J Bredenoord
Department of Gastroenterology, Sint Antonius Hospital, Nieuwegein, the Netherlands

A Baron, A J P M Smout
Gastrointestinal Research Unit, Department of Gastroenterology, University Medical Centre, Utrecht, the Netherlands

Correspondence to: Dr A J Bredenoord, Department of Gastroenterology, St Antonius Hospital, PO Box 2500, 3430 EM Nieuwegein, the Netherlands; a.bredenoord@antonius.net

doi: 10.1136/gut.2006.092650

Conflict of interest: None declared.

References

1 **Silny J**. Intraluminal multiple electric impedance procedure for measurement of gastrointestinal motility. *J Gastrointest Motil* 1991;**3**:151–62.
2 **Bredenoord AJ**, Weusten BL, Curvers WL, *et al*. Determinants of perception of heartburn and regurgitation. *Gut* 2005;**55**:313–18.
3 **Palmer ED**. Subacute erosive (''peptic'') esophagitis associated with achlorhydria. *N Engl J Med* 1960;**262**:927–9.
4 **Orlando RC**, Bozymski EM. Heartburn in pernicious anemia—a consequence of bile reflux. *N Engl J Med* 1973;**289**:522–3.
5 **Mearin F**, De RX, Balboa A, *et al*. Duodenogastric bile reflux and gastrointestinal motility in pathogenesis of functional dyspepsia. Role of cholecystectomy. *Dig Dis Sci* 1995;**40**:1703–9.

Liver fibrosis assessment by transient elastography in hepatitis C patients with normal alanine aminotransferase

We read with interest the paper by Foucher *et al* (*Gut* 2006;**55**: 403–8) where the authors assessed the accuracy of transient elastography for the detection of cirrhosis. Its use in assessing the severity of chronic liver disease in other clinical scenarios warrants further evaluation. According to large population studies, the prevalence of chronic hepatitis C virus (HCV) infected patients who have persistently normal serum alanine aminotransferase (PN-ALT) levels is most likely 30–50%.[1] A major problem is defining whether or not these patients will suffer a progressive disease; additionally, although no consensus exists regarding who must be treated and when antiviral therapy should be initiated, positive decisions have been reinforced by recent results of a large clinical trial indicating that pegylated interferon plus ribavirin combination therapy is effective and safe in these patients with PN-ALT.[2]

In a recent review, the schedule of antiviral combination treatment of patients with chronic hepatitis C and normal aminotransferases was described, and indications for antiviral therapy in some cases was decided on the basis of histological findings[1]; hence liver biopsy seems to be key in this decision and a patient must be treated if there is significant fibrosis (≥OR = F2). However, although liver biopsy remains the ''gold standard'' for assessment of hepatic fibrosis, it represents an invasive procedure with some risks and limitations, as noted by Foucher *et al*, and is not well accepted by all patients. Non-invasive methods such as Fibrotest, Forns' index (FI), and APRI have been designed to assess liver fibrosis.[3]

Fibroscan (FS), a new transient elastography technique to measure liver stiffness or elasticity,[4 5] has provided some optimism as an alternative method for staging liver disease. Stiffness non-significantly correlates with fibrosis stage and is a promising and reproducible method for the detection of cirrhosis, independent of the operator.[5] Our aim was to use FS to assess hepatic fibrosis in patients infected by HCV with PN-ALT, comparing the accuracy of FS to that previously described for biomarkers.

We analysed prospectively 28 chronically infected HCV patients (18 females) with PN-ALT (at least three determinations yearly), assessing hepatic fibrosis by FS. Concordance and correlation between FS, FI, and APRI were also evaluated. Almost all consecutive patients were asymptomatic and none had the well known complications of advanced liver disease or cirrhosis.[6] Patient characteristics (mean (SD)) were as follow: age 44.3 (10) years, body mass index 24.1 (2.8) kg/m^2, platelets count 249.6 (58)/mm^3, serum cholesterol 190.5 (26) mg/dl, serum aspartate aminotransferase 25 (5) IU/l, serum ALT 27.7 (6.7) IU/l, and serum gamma glutamyl transferase 23.2 (21) IU/l. Results of the study were as follow: 26 (92.8%) patients had HCV genotype 1. Mean value for FS was 6.35 (3.3) kPa, indicating absence or mild stage fibrosis (<8.5 kPa); as expected, mean values for FI (3.35 (1.4)) and APRI (0.27 (0.09)) also reflected minimal or no fibrosis (<4.5 and <0.5, respectively). These provocative findings show that this cohort of PN-ALT chronically infected HCV patients had a low stage of fibrosis, based on three non-invasive methods. A previous study has compared and validated these methods in chronic hepatitis C patients with elevated ALT.[7]

Liver biopsy has been used as the ''gold standard'' for assessment of hepatic fibrosis. It has been used for staging liver damage in chronic viral hepatitis and for decision analysis as to the need for treatment in patients with chronic hepatitis C. The limitations of biopsy, such as patient acceptability, sampling error, or diagnostic inaccuracy, and the remote risk of complications, have led clinical investigators to study alternative methods of staging chronic viral hepatitis.[4 8] Measurement of serum biological markers is the most widely used procedure for estimation of liver fibrosis[8]; combining serum biomarkers with FS may increase the accuracy of these non-invasive methods, suggesting that it may be valid to circumvent the limitations of hepatic histology.[7 8] FS is an objective and safe technique, enthusiastically accepted by patients. Hence periodic examinations can be performed as a follow up protocol for assessment of hepatic fibrosis progression or improvement. Moreover, it is a precise method for detection of cirrhosis and is a promising method of predicting complications of cirrhosis.

Accordingly, our data suggest that therapeutic management of PN-ALT patients could be established according to fibrosis stage detected by successive FS examinations. Those PN-ALT patients with evidence of fibrosis by FS would need to start early antiviral treatment. Although less effective in obese subjects, transient elastography may be very useful for the diagnosis and therapeutic management of PN-ALT chronically HCV infected patients, questioning the need for biopsy.[7 8] Further studies are warranted to evaluate the diagnostic accuracy for staging hepatic fibrosis, the natural history of disease, and the optimum response to combination antiviral therapy. Additionally, it has been demonstrated that combining FS

measurements with biomarkers may increase the diagnostic accuracy of both tests.[7 8]

In conclusion, repeated stiffness assessment appears to be a good and safe alternative method of indicating antiviral combination therapy in PN-ALT patients reluctant to undergo liver biopsy.

R Moreno-Otero, M Trapero-Marugan, J Mendoza

Gastroenterology and Hepatology Service, Hospital Universitario de La Princesa, Autonomous University of Madrid, Madrid, Spain

Correspondence to: Professor R Moreno-Otero, Gastroenterology and Hepatology Service, Hospital Universitario de La Princesa, Autonomous University of Madrid, Diego de León, 62, Planta 3, Madrid 28006, Spain; rmoreno.hlpr@salud.madrid.org

Supported by grant ISC III 03/02.

Conflict of interest: None declared.

References

1 **Alberti A**. Towards more individualised management of hepatitis C virus patients with initially or persistently normal alanineaminotransferase levels. *J Hepatol* 2005;**42**:266–74.
2 **Zeuzem S**, Diago M, Gane E, *et al*. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. *Gastroenterology* 2004;**127**:1724–32.
3 **Wai CT**, Greenson JK, Fontana RJ, *et al*. A simple non-invasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003;**38**:518–26.
4 **Sandrin L**, Fourquet B, Hasquenoph JM, *et al*. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol* 2003;**29**:1705–13.
5 **Ziol M**, Handra-Luca A, Kettaneh A, *et al*. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. *Hepatology* 2005;**41**:48–54.
6 **Benvegnù L**, Gios M, Bocato S, *et al*. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut* 2004;**53**:744–9.
7 **Castera L**, Vergniol J, Foucher J, *et al*. Prospective comparison of transient elastography, fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005;**128**:343–50.
8 **Afdhal NH**, Nunes D. Evaluation of liver fibrosis: a concise review. *Am J Gastroenterol* 2004;**99**:1160–74.

Fatal aseptic meningoencephalitis following infliximab treatment for inflammatory bowel disease

Tumour necrosis factor α (TNF-α) plays a pivotal role in the pathogenesis of Crohn's disease. Infliximab, a chimeric monoclonal antibody against TNF-α, has been shown to be highly effective in the treatment of Crohn's disease.[1] However, treatment with infliximab may give rise to serious adverse events, including autoimmune disorders.[2] We report a case of fatal aseptic meningitis associated with infliximab therapy.

A 53 year old Caucasian man was admitted to a regional hospital with progressive bloody diarrhoea. His medical history revealed a myocardial infarction in 1993. Endoscopy and histology established a diagnosis inflammatory bowel disease (IBD) but could not distinguish between ulcerative colitis and Crohn's disease. Because his symptoms did not improve following steroid and azathioprine treatment, infliximab therapy was initiated. Six days after the initial infliximab infusion, temporary numbness of the right arm and the right perioral area developed, followed four days later by dysarthria and left sided weakness and sensory loss. Cerebral computed tomography imaging revealed no abnormalities. All neurological symptoms resolved spontaneously within a few days.

Because of ongoing complaints consistent with luminal disease activity, a second dose of infliximab was administered two weeks after the initial dose. Complaints related to IBD gradually diminished with this regimen. After three days, however, neurological symptoms recurred. Over the course of three weeks he developed a dysarthria, left sided hemianopia, and motor aphasia. His level of consciousness decreased gradually and generalised seizures occurred. At that time, cerebrospinal fluid analysis showed a mild pleiocytosis and meningoencephalitis was suspected. He was treated with acyclovir, but analysis of blood and cerebrospinal fluid cultures as well as polymerase chain reaction (PCR) did not reveal any infectious agent.

Seven months after the onset of gastrointestinal symptoms and 3.5 months after the first dose of infliximab, the patient was referred to our hospital. He had a normal blood pressure and was afebrile. On neurological examination he had reduced consciousness (Glasgow coma scale E2M4V2), no meningism, intact light and corneal reflexes, and a right hemiparalysis. Magnetic resonance imaging of the brain revealed bilateral hyperintense cortical and subcortical lesions on T2 weighted imaging that showed enhancement with gadolinium. There were no signs of cerebral sinus thrombosis. Cerebral angiography showed focal narrowing of branches of the middle cerebral arteries, suggestive of vasculitis. Because repeated cultures and PCR of cerebral tissue (obtained on biopsy), blood, and cerebrospinal fluid remained negative (including for JC and BK virus) it was decided to start treatment with cyclophosphamide and prednisone for a suspected cerebral vasculitis. Despite this treatment, the patient's condition deteriorated gradually and he died approximately one month later. An autopsy was performed.

Histopathological examination revealed necrosis of the cerebral cortex (fig 1) and mononuclear infiltration with macrophages and giant cells. As no causative infectious agent or evidence for cerebral vasculitis was found, the diagnosis aseptic meningoencephalitis was made.

Neurological complications related to infliximab are uncommon.[2] It has been suggested that treatment with infliximab may give rise to inflammatory demyelinating disease of the central nervous system.[3 4] Aseptic meningitis related to infliximab, as in our patient, has been reported twice,[5 6] but this is the first case of meningoencephalitis with a fatal outcome. In our patient, involvement of a broad range of infectious agents, including tuberculosis, was excluded.

The pathogenesis of infliximab related aseptic meningitis is unknown, and in the first case reported[5] generation of antibodies to neurones or to infliximab was excluded. Presumably, the inability of infliximab to pass the blood-brain barrier results in a failure to downregulate proinflammatory pathways in the brain while effectively blocking peripheral TNF-α. Based on the present case and the currently available literature, we conclude that infliximab therapy should be withdrawn permanently when (even transient) neurological symptoms occur.

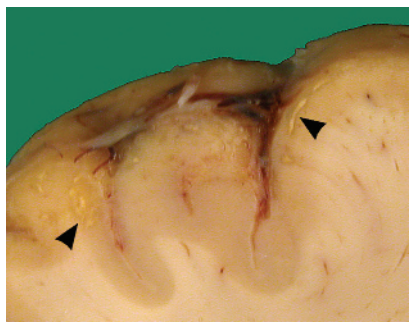

Figure 1 Cross section of the cerebral frontal cortex with multiple yellowish lesions (arrowheads) in the grey matter compatible with inflammatory infiltrate and tissue necrosis.

Acknowledgements

We thank RHWM Derksen, MD PhD, Department of Rheumatology and Immunology, UMC Utrecht, for critically reviewing our manuscript.

R Quispel
Department of Gastroenterology, University Medical Centre, Utrecht, the Netherlands

H B van der Worp, M Pruissen
Department of Neurology, University Medical Centre, Utrecht, the Netherlands

M E Schipper
Department of Pathology, University Medical Centre, Utrecht, the Netherlands

B Oldenburg
Department of Gastroenterology, University Medical Centre Utrecht, the Netherlands

Correspondence to: Dr R Quispel, Department of Gastroenterology, Huispostnr F.02.618, University Medical Centre, PO Box 85500, 3508 GA Utrecht, the Netherlands; R.Quispel@digd.azu.nl

doi: 10.1136/gut.2006.093294

Conflict of interest: None declared.

References

1 **Hanauer SB**, Feagan BG, Lichtenstein GR, *et al*. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet* 2002;**359**:1541–9.
2 **Colombel JF**, Loftus EV Jr, Tremaine WJ, *et al*. The safety profile of infliximab in patients with Crohn's disease: The Mayo Clinic experience in 500 patients. *Gastroenterology* 2004;**126**:19–31.
3 **Thomas CW Jr**, Weinshenker BG, Sandborn WJ. Demyelinisation during anti TNF-α therapy with infliximab for Crohn's disease. *Inflamm Bowel Dis* 2004;**10**:28–31.
4 **Mohan N**, Edwards ET, Cupps TR, *et al*. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum* 2001;**44**:2862–9.
5 **Marotte H**, Charrin JE, Miossec P. Infliximab-induced aseptic meningitis. *Lancet* 2001;**358**:1784.
6 **Hegde N**, Gayomali C, Rich MW. Infliximab-induced headache and infliximab induced meningitis: two ends of the same spectrum? *South Med J* 2005;**98**:564–6.

Optimising the therapy of exocrine pancreatic insufficiency by the association of a proton pump inhibitor to enteric coated pancreatic extracts

Fat maldigestion with steatorrhoea is the main problem in the management of exocrine pancreatic insufficiency (EPI).[1] When