Fatigue is probably the most intriguing symptom affecting patients with chronic cholestatic disorders, in particular those with primary biliary cirrhosis. It is postulated that fatigue in patients with primary biliary cirrhosis may be associated with morphological abnormalities of the central nervous system secondary to accumulation of manganese. However, we are still far from understanding this complex issue.

The aetiology of fatigue in individuals with liver disease remains a puzzle and its comparison with an enigma seems to be fully justified. There is increasing evidence that this phenomenon may be mediated centrally. Animal studies in the bile duct ligated rat model have shown aberrant central neurotransmission involving 5-HT1A receptors to be present and administration of a serotonin receptor agonist can improve fatigue in a "swim test" model. Also, small doses of interleukin 1β (a cytokine involved in "sickness behaviours") were found to cause a significant decrease in locomotor function in acutely cholestatic rats. In the model of acute cholestasis in rats, that central rather than peripheral mechanisms mediate fatigue. Nevertheless, studies on fatigue in the rat model should be interpreted with caution as models of acutely induced cholestasis in animals are far from ideal for the study of chronic cholestasis.

Impaired biliary excretion which occurs in chronic cholestasis may predispose to accumulation of several compounds, including heavy metals. In this issue of Gut, Forton and colleagues postulate that fatigue in patients with PBC may be associated with morphological abnormalities of the central nervous system secondary to accumulation of manganese.
of the central nervous system (CNS), secondary to accumulation of manganese (Mn) \[\text{see page 587}\]. As effective treatment of fatigue does not exist, the hypothesis that fatigue is a result of increased accumulation of Mn is very attractive in terms of potential application of new therapeutic modalities, including chelating agents. Mn is a neurotoxic heavy metal with increased affinity to dopaminergic neurons. In their study, Forton and colleagues\(^{13}\) apply sophisticated brain imaging technologies, including proton magnetic resonance spectroscopy (\(1^\text{H} \text{MRS}\)) and magnetisation transfer ratio (MTR). \(1^\text{H} \text{MRS}\) can provide helpful information about cerebral metabolism, and abnormal \(1^\text{H} \text{MRS}\) patterns have been found to correlate with severity of hepatic encephalopathy.\(^{14,15}\) In this study, there was no difference in MRS choline/creatinine ratios between stage I–II PBC and healthy controls, suggesting an absence of even subclinical portosystemic encephalopathy (PSE) in these subjects to explain their fatigue. MTR is considered to be superior to conventional magnetic resonance imaging in detecting parenchymal abnormalities in the CNS as it incorporates a measurement of the exchange of protons between water and solid constituents of brain tissue. It has been demonstrated that patients with minimal hepatic encephalopathy have a reduced MTR, possibly due to increased brain water.\(^{15}\) The major findings of the study by Forton and colleagues\(^{13}\) is that globus pallidus (GP) MTR is significantly reduced in stage I and II patients with PBC compared with healthy controls. As this phenomenon can be secondary to accumulation of paramagnetic substances, the authors measured plasma Mn levels and found that the number of points scored in the Fatigue impact score (both in cirrhotic and non-cirrhotic stages and found that the number of points scored in the Fatigue impact score (both in cirrhotic and non-cirrhotic levels and found that the number of points scored in the Fatigue impact score (both in cirrhotic and non-cirrhotic levels and found that the number of points scored in the Fatigue impact score (both in cirrhotic and non-cirrhotic levels and found that the number of points scored in the Fatigue impact score (both in cirrhotic and non-cirrhotic levels and found that the number of points scored in the Fatigue impact score (both in cirrhotic and non-cirrhotic levels and found that the number of points scored in the Fatigue impact score (both in cirrhotic and non-cirrhotic levels and found that the number of points scored in the Fatigue impact score (both 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Management of swallowed razor blades—retrieve or wait and see?

Question

A 16 year old boy with a long history of self harm was admitted for the third time in four weeks with a history of ingestion of a number of shaving blades (fig 1). On previous occasions, endoscopic intervention with the use of an overtube under general anaesthesia had been successful in their safe retrieval. However, on the third occasion, a delay to endoscopy of 36 hours (due to a combination of late presentation and lack of access to the operating theatre) allowed the blades to progress beyond the pylorus into the small bowel, beyond the reach of a standard upper gastrointestinal endoscope (fig 2).

How should this young man now be managed?

- Push enteroscopy with the use of an overtube and removal of the blades?
- Laparotomy and surgical removal of the blades?
- Conservative management?

See page 486 for answer

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Fatigue in chronic cholestasis

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