

*Progress report*

## Chronic portal systemic encephalopathy: update 1987

Neuropsychiatric dysfunction is a complication of cirrhosis. Treatment is by a largely vegetarian diet with limited animal protein and with lactulose, or preferably lactilol. Branched chain amino acids are not indicated to treat chronic hepatic encephalopathy. Acute episodes in the course of chronic portal systemic encephalopathy indicate a search for a precipitant, dietary protein withdrawal, enemas, lactulose and a short course of oral neomycin. Benzodiazepine antagonists are under study.

### **Aetiology**

In a cirrhotic patient the brain may be intoxicated by substances of gut origin and derived from the action of bacteria, largely colonic, on dietary protein (portal systemic encephalopathy). The toxic metabolites reach the brain either through portal systemic venous channels or by failure of removal by the diseased liver.<sup>1,2</sup> Despite decades of research endeavour, the nature of the toxic, gut derived, substances defies identification. Ammonia is often incriminated. Recently, after studies on a rat model of fulminant hepatitis, gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter present in 30–50% of all cerebral synapses, has been invoked as responsible for the features of hepatic encephalopathy.<sup>3</sup> It is produced by bacterial action in the gut and concentrations are increased in the blood of patients with hepatic encephalopathy. There are, however, certain difficulties in accepting this hypothesis.<sup>4</sup> The methodology for measuring serum GABA is suspect as other substances, including glutamine, may also be estimated. Serum GABA concentrations do not correlate well with the grade of encephalopathy as seen in man. Gamma-aminobutyric acid may not pass the human blood brain barrier into the cerebrospinal fluid. Finally, there are obvious difficulties in equating a rabbit model with man.

An increased number of binding sites for GABA can be shown in the brains of the rat model of fulminant hepatitis, although this is not consistent. An increased number of binding sites for benzodiazepines and barbiturates is also found. This could account for the increased sensitivity of patients with cirrhosis to benzodiazepines and barbiturates. Gamma-aminobutyric acid and benzodiazepines share the same terminals promoting chloride conductance across the postsynaptic neural membrane so increasing membrane depolarisation and inhibiting postsynaptic potential. Benzodiazepine antagonists have therefore been suggested for the treatment of hepatic encephalopathy. While interacting with binding sites for benzodiazepines on the GAB-receptor complex, they might be expected to modulate GABA-ergic neurotransmission. Intravenous administration of

one such antagonist (Ro 15-178) was indeed followed by rapid amelioration of hepatic encephalopathy monitored clinically and by EEG changes.<sup>5</sup> A limited observation in a patient with chronic encephalopathy suggested benefit but the effect was not consistent (personal communication). Side effects such as convulsions, may prevent its wider use. Ro 15-178 has a half-life of only three minutes and longer acting benzodiazepine antagonists are under development. Further work is needed and the results are eagerly awaited.

### **Diet**

Dietary protein is reduced to the limit of tolerance. In most instances, this is the normal 70-90 g day. In the more severely encephalopathic, only 30-40 g divided between three meals, can be allowed. No longer should cirrhotics be encouraged to eat large steaks.

Vegetable protein seems to be better tolerated than animal in terms of cerebral function.<sup>6</sup> This may be explained by the increased intake of dietary fibre and increased incorporation and elimination of nitrogen contained in faecal bacteria.<sup>7</sup> Vegetable protein is less ammoniagenic and contains smaller amounts of methionine and aromatic amino acids. Carnivorous man, however, is not well adapted to living the life of a rabbit. Side effects include the bulk that has to be consumed, abdominal distension, flatulence and diarrhoea; these reduce compliance. Moreover, in the winter, the cost of salads may be prohibitive. Nevertheless, all patients with cirrhosis should be encouraged to eat as much fruit and vegetables as possible.

### **Amino acids**

Neurotransmitter synthesis is controlled by the brain concentration of the precursor amino acids. The aromatic amino acids, tyrosine, phenylalanine and tryptophan, are increased in liver disease, perhaps because of failure of hepatic deamination. The branched chain amino acids, valine, leucine, and isoleucine, are decreased, possibly related to increased catabolism by skeletal muscle and kidneys secondary to the hyperinsulinism of chronic liver disease. The aromatic amino acids have a profound effect on cerebral metabolism. For example, tryptophan is metabolised to serotonin, an inhibitory neurotransmitter, and phenylalanine and tyrosine are precursors of catecholamines. A reduced ratio of branched chain to aromatic amino acids has been related to the development of hepatic encephalopathy.<sup>8</sup> Infusions of solutions containing a high concentration of branched chain amino acids have been used to treat the acute and chronic conditions. Results have been extremely conflicting perhaps related to differences in the nature of the amino acid solutions, the ways of administration and the patients studied. In the acute situation, results of two randomised controlled trials showed no benefit in respect of encephalopathy.<sup>9,10</sup> In a third trial of 40 patients, a parenterally administered branched chain amino acid enriched mixture was claimed to be beneficial as regards encephalopathy and mortality.<sup>11</sup> With respect to encephalopathy, results were significant only between days one and two, and not in patients whose coma was precipitated by gastrointestinal haemorrhage. Considering the high cost of intravenous amino acid mixtures, it is difficult to justify their use in acute hepatic

encephalopathy, particularly as such patients have high blood levels of branched chain amino acids anyway.<sup>12</sup> Oral branched chain amino acid preparations have been recommended to treat chronic hepatic encephalopathy and to maintain nitrogen balance in cirrhosis but with confusing results. Two randomised crossover trials showed no significant effect on encephalopathy.<sup>13,14</sup> In one short study of patients with latent portal systemic encephalopathy, some tests of psychomotor function and practical intelligence improved, but the overall rating of fitness to drive a car did not change significantly.<sup>15</sup> Branched chain amino acids preparations are however, able to maintain a high positive nitrogen balance<sup>14,16</sup> and seem to be of more value in nutrition than in controlling encephalopathy. If the patient can eat 40–50 g natural protein daily extra branched chain amino acids are unnecessary.

### **Lactulose and lactilol**

For the last decade, lactulose therapy has been the standby for the treatment of chronic hepatic encephalopathy.<sup>17</sup> The mode of action remains uncertain. Degradation of disaccharides results in the production of fatty acids, some of which are absorbed. The osmotic volume of the colon is increased. The acidification results in reduced absorption of ammonia, urea synthesis in the colon decreases and nitrogen excretion is increased. Lactulose, prescribed as a syrup, is costly, unpleasant to take and oversweet. The patient is tied to large bottles of medicine. Side effects include nausea, flatulence, and intestinal pain. Diarrhoea can be so profound, that serum sodium increases to over 145 mg/l, serum potassium falls, and alkalosis develops.<sup>18</sup> The blood volume falls so impairing renal function, an undesirable feature in cirrhotic patients who are at risk of developing functional renal failure. These side effects are particularly likely if the daily dose of lactulose exceeds 100 ml. Some of the side effects may be related to contamination of lactulose syrup with other sugars, principally galactose and lactose.

Lactilol is a disaccharide analogue of lactulose which is easily produced in a chemically pure form and can be dispensed as a powder. It is less sweet than lactulose. It does not appear to be absorbed in the small intestine, but is extensively metabolised by colonic bacteria.<sup>19,20</sup> In an uncontrolled comparison with lactulose, the lactilol proved as efficacious, had a less sweet taste, and was more acceptable because the catharsis was more predictable.<sup>21</sup> The powder was more convenient to take than the syrup. A double blind randomised crossover study comparing lactilol with lactulose in the treatment of chronic hepatic encephalopathy showed both sugars to be equally effective.<sup>22</sup> Gastrointestinal side effects were less with lactilol, but events leading to hepatic decompensation seemed to be more. All these results need confirmation. Lactulose is being prepared in crystalline form. The absence of contaminants will reduce the side effects and a powder will add to the convenience, but the preparation will still be costly. Its efficacy relative to lactulose syrup and to lactilol remains to be reported.

About 75% of the non-white world population are lactose intolerant and in these individuals lactose will have the same effects as lactulose in producing acidification of the colonic contents, and increasing bacterial ammonia metabolism.<sup>23</sup> Lactose is inexpensive and a dose of 50–100 g is given daily. Twenty per cent lactose solution may also be given in an enema.

### **Levodopa and bromocriptine**

Chronic encephalopathy has been treated by drugs which replenish cerebral dopamines. Levodopa is sometimes of limited benefit in a few patients. Bromocriptine may be of value in the rare patient with chronic hepatic encephalopathy and good stable liver function who is resistant to dietary protein restriction and lactulose.<sup>24</sup>

### **Surgical procedures**

Encephalopathy after surgical portal-systemic shunting has been treated by ligation of the shunt but with considerable operative mortality.<sup>25, 26</sup> A mesocaval shunt can be occluded by a balloon introduced radiologically into the narrow, synthetic interposition graft. In one patient so treated, encephalopathy was reversed and liver function improved.<sup>27</sup> In this patient there was no encephalopathy and no rebleeding 10 months later. Varices may of course still recur and rebleed in the future.

Hepatic transplantation has been used to treat chronic intractable hepatic encephalopathy. In one patient, there was marked improvement.<sup>28</sup> This is surprising considering the changes in cerebral structure present in patients with longstanding hepatic encephalopathy.

### **Acute episodes**

During their course patients with chronic portal-systemic encephalopathy may suffer episodes of acute deterioration. These may be precipitated by an infection, electrolyte imbalance (often diuretic induced), a gastrointestinal haemorrhage, a large protein meal, constipation or sedative drugs. All these are sought and treated. Dietary protein is withdrawn completely for three days and then built up slowly by 20 g every three days until the limit of tolerance is reached.

A magnesium sulphate purge or lactulose enemas may be used. All enemas must be neutral or acid to reduce ammonia absorption.

The tetracyclines have shown to be effective in controlling gut flora, although they carry the risk of opportunistic bowel infections, particularly staphylococcal. Neomycin decreases the concentration of urease containing bacteria in the intestinal flora, thus decreasing the production of ammonia from proteins and amino acids. Intestinal hydrolysis of urea can account for the equivalent of 35 g of extra dietary protein daily.<sup>29</sup> Neomycin, 4 g daily for one week is safe and effective, but because of ototoxicity should not be given long term. Metronidazole, 0.2 g four times a day is equally effective, but because of central nervous system toxicity is also only given for short periods.<sup>30</sup>

Lactulose or lactilol is given to ensure a catharsis.<sup>31</sup> It is surprising that lactulose which, theoretically, depends on colonic bacteria for its therapeutic benefit should be effective in the presence of neomycin which reduces such bacteria. Nevertheless, neomycin and lactulose seem to act synergistically, perhaps because they affect different bacterial populations.<sup>32</sup>

## Spectrum of hepatic encephalopathy

At one end the patient suffers episodes of deep coma and between them is so mentally disordered that he cannot manage his affairs. Such patients usually have a large portal-systemic venous shunt, either surgically induced or developing naturally and slowly over the years in preformed venous channels. At the other end of the spectrum, about 60% of all patients with cirrhosis show some impairment of cerebral function sufficient to cause disruption in the routine of everyday living.<sup>32</sup> This has been termed 'latent portal-systemic encephalopathy'.<sup>34</sup> Clinically such patients seem normal, and the EEG shows no change. Verbal intelligence is preserved, but memory, performance IQ and psychomotor ability are impaired. Thus the measures used to manage clinical hepatic encephalopathy may have to be extended to include the majority of patients with cirrhosis.

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