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Scientific Basis of Clinical Practice

Hepatic Encephalopathy

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The Syndrome

In severe liver disease neuropsychiatric changes may occur and may progress to coma. These effects are termed hepatic encephalopathy. An early manifestation is defects of behaviour. Later there may be euphoria or drowsiness, confusion, ataxia, and a characteristic flapping tremor, before progression to coma. The course often fluctuates and may be arrested or reversed at any stage. The flapping tremor is characteristic but not pathognomonic of hepatic encephalopathy. It may also occur in severe heart failure, severe respiratory failure, or severe renal failure.^{1,2}

In hepatic encephalopathy there is a characteristic abnormality of the electroencephalogram consisting of paroxysms of bilaterally synchronous, symmetrical, high-voltage, slow waves in the delta range of 1½ to 3 per second interspersed with, or superimposed on, relatively normal alpha waves.³ Again, these changes are not pathognomonic of hepatic encephalopathy but may occur in other severe metabolic disturbances.

OBSERVATIONS

The mechanism of hepatic encephalopathy is not established, but any proposition must take account of the following observations:

(1) The liver is the only organ which can remove ammonia from the blood and convert it to urea.^{1,4,5}

(2) In liver disease, particularly if there is significant portal-systemic shunting of blood, the blood ammonia concentration may rise.⁶⁻⁹ Hepatic encephalopathy occurs in virtually all patients in whom the blood ammonia concentration exceeds 3 or 3.5 µg/ml,⁷⁻⁹ and in an individual patient as encephalopathy progresses the blood ammonia concentration rises. Perhaps 20% of patients with severe hepatic encephalopathy, however, have ammonia levels within the normal range.⁷⁻⁹

(3) In the absence of liver disease, encephalopathy may occasionally develop if there are appreciable portal-systemic communications due to extrahepatic obstruction in the portal venous system,¹⁰ but in most patients with encephalopathy there is evidence of both liver disease and portal-systemic communications.

(4) Several orally administered nitrogenous compounds have been shown to produce encephalopathy in susceptible subjects: ammonium chloride, ammonium-containing cation-exchange resins, diammonium citrate, urea,¹¹ and dietary protein.¹² These all yield ammonia in the gut and are associated with raised blood ammonia levels. However, methionine may provoke encephalopathy without causing a significant rise in blood ammonia concentration and this effect can be prevented by chlortetracycline.¹³

SUGGESTED MECHANISMS

Toxic products of bacterial degradation of nitrogenous material within the bowel are normally absorbed, pass into the portal vein, and are removed by the liver (fig. 1). In chronic liver disease, because of failure of removal by the diseased liver—and also because of direct access to the systemic circulation by collateral vessels, surgical shunts, or intrahepatic communications—these toxic products reach the brain, where they exert a deleterious effect.

There is suggestive evidence that ammonia is one of the toxic products responsible for hepatic encephalopathy, but

FIG. 1—Mechanism and methods of treatment of hepatic encephalopathy.

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it is almost certainly not the only one and there remain facts which are difficult to explain.

Ammonia can be produced in the tissues and in the bowel.¹⁴ About 4 g of ammonia is normally produced from the bowel each day.¹⁵ This originates predominantly from the colon and is generated by bacterial—and to a lesser extent mucosal—enzymes acting on various nitrogenous substrates.¹⁶ One important substrate is dietary protein,¹² but a more important substrate may be urea since possibly about 3.5 g of ammonia is produced every day from this source.¹⁷ Ammonia is able to move bidirectionally across the large bowel wall by ionic diffusion, according to the concentration gradient, and by non-ionic diffusion to the more acidic side.^{18, 19} Thus ammonia normally passes from the large bowel into the blood, both because of the greater concentration of ammonia in the large bowel and because of the alkalinity of its contents. Ammonia is normally secreted into the upper part of the gastrointestinal tract, where its movement is influenced particularly by concentration gradients, the pH gradient being less important.²⁰

In the rat acute ammonia intoxication is known to result in a significant and consistent depletion of ATP in parts of the brain.²¹ Possibly ammonia exerts its effect on cerebral energy production by amination of alpha-ketoglutarate to glutamic acid, resulting in the impairment of the tricarboxylic acid cycle and decreased ATP synthesis.²² Although this hypothesis is attractive, other studies do not lend support to it.²³

Examination of patients dying after prolonged hepatic encephalopathy shows swelling and increase in number of the protoplasmic astrocytes in various parts of the brain and, in severe cases, degeneration of nerve cells of the basal ganglia and cerebral cortex. The changes show some relation to the duration and severity of the encephalopathy and, though not specific, are highly characteristic of advanced liver disease. Possibly these structural changes are related to the permanent neurological sequelae of prolonged encephalopathy rather than to the usual reversible signs.

Precipitating Factors

In many patients encephalopathy may be due to progression of the liver disease without a definable precipitating factor. Nevertheless, factors known to precipitate encephalopathy must be sought and if found must be treated promptly.

GUT BLEEDING

Bleeding into the gastrointestinal tract may precipitate encephalopathy, the blood acting as protein available for bacterial degradation in the large bowel. In addition, if the bleeding is severe, there may be hypotension and hypoxia which adversely affect both cerebral and hepatic functions.

POTASSIUM DEPLETION

Potassium depletion is a frequent accompaniment of drug-induced diuresis. Potassium depletion is accompanied by an extracellular alkalosis, which may aid diffusion of ammonia into the brain, and in potassium depletion there is also an intracellular acidosis, which may help to trap ammonia within the brain cells. Furthermore, in potassium depletion ammonium ions may substitute for potassium ions within the cells.

In addition, after the administration of thiazide or mercurial diuretics, increased blood ammonia levels have been shown to be partly due to increased production of ammonia by the kidneys—and this may be related either directly to the hypokalaemia²⁴ or to the accompanying cellular acidosis.²⁵ Correction of the hypokalaemia by potassium supplements is associated with a decrease in renal ammonia production.²⁶

Potassium depletion due to other causes, such as associated renal tubular acidosis, low dietary potassium intake, or ion exchange resins has a similar effect on ammonia production.^{24, 27}

ACETAZOLAMIDE

Acetazolamide, a carbonic anhydrase inhibitor, can produce a rise in blood ammonia and encephalopathy in susceptible subjects with liver disease.²⁸ The rise in blood ammonia may be due to blocking of peripheral ammonia uptake.²⁹ Prolonged treatment causes a metabolic acidosis, which is a stimulus to renal ammonia production.^{25, 30}

URAEMIA

Urea and its products undergo an enterohepatic circulation (fig. 2). It has been estimated that 25% of the urea produced in the body passes into the gastrointestinal tract, where it is almost completely hydrolysed to ammonia by urease—which is mainly but not entirely of bacterial origin. The ammonia is absorbed, passes into the portal vein, and is resynthesized in the liver to urea.¹⁷ Possibly in states of protein malnutrition some of this ammonia may contribute to nutrition by being converted into protein.³¹

Ammonia production from urea increases many-fold in uraemia,^{32, 33} which may thus contribute to hepatic encephalopathy.³⁴ In cirrhosis of the liver uraemia may be caused by the associated impairment of renal function.³⁵ It is important to remember that tetracycline may contribute to renal impairment. An additional way in which tetracycline may cause a rise in blood urea is by its antianabolic effect, preventing the utilization of urea for protein synthesis.³⁶

FIG. 2—The normal enterohepatic circulation of urea and ammonia.

FLUID AND ELECTROLYTE ABNORMALITIES

Fluid and electrolyte abnormalities in patients with chronic liver disease are frequently associated with encephalopathy, particularly after diuretic therapy, and it seems likely that there are effects additional to those produced by hypokalaemia.³⁷

A diminution of hepatic blood flow after rapid diuresis may well contribute to encephalopathy. Hyponatraemia is a frequent finding in severe liver disease, and there is evidence that hyponatraemia may augment tissue catabolism, thereby increasing blood urea and hence ammonia concentration.³⁸

SEDATIVES

Many sedative and hypnotic drugs are metabolized by the liver, and their depressant action on cerebral function may

thus be enhanced in liver disease and precipitate encephalopathy. In addition, in patients with a tendency to hepatic encephalopathy the brain may be more sensitive to such drugs.

INFECTION

Intercurrent infection is often associated with the development of encephalopathy, possibly by reducing hepatic function and increasing protein catabolism.

CONSTIPATION

Constipation increases the opportunity for bacterial degradation of the nitrogenous contents of the large bowel.

Physiological Basis of Treatment

The following measures, which are designed to reduce the amount of nitrogenous products in the bowel, their breakdown by bacteria, or their absorption, are effective in the management of hepatic encephalopathy. Response to the commonly used measures is important confirmatory evidence that the particular symptoms and signs are due to hepatic encephalopathy.

- (1) Dietary protein restriction.
- (2) Emptying the lower bowel—for example, by enemata and purgatives.
- (3) Antibiotics, particularly non-absorbable antibiotics such as neomycin, administered orally or rectally.^{20 39}
- (4) Oral lactulose. This disaccharide has been shown to be effective in the treatment of encephalopathy.⁴⁰ Lactulose is not a normal dietary constituent and there is no enzyme lactulase in man, so that lactulose is neither digested nor absorbed and reaches the colon unchanged. It was initially thought that lactulose acts by encouraging the growth of lactose-fermenting organisms in the colon, at the expense of other organisms which produce the toxins responsible for encephalopathy. However, encephalopathy appears to improve before a detectable change in the intestinal bacteria.⁴¹
In the colon lactulose is broken down by bacteria to lactic and other organic acids. Improvement in encephalopathy may thus be due to trapping of ammonia, and perhaps other toxins, within the lumen of the colon by the more acidic stool content.⁴¹ Nevertheless, Agostini *et al.*⁴² were unable to confirm this, and suggested that lactulose acts simply as a cathartic and reduces ammonia absorption by decreasing colonic transit time—so reducing the amount of ammonia generated by colonic bacteria.
- (5) Lactobacilli given either freeze-dried⁴³ or as milk infected with lactobacilli,⁴⁴ can improve encephalopathy, presumably by displacing colonic organisms which produce ammonia or other toxins. A milk and cheese diet, claimed to be effective in encephalopathy, may also act by encouraging the growth of lactobacilli.⁴⁵
- (6) Colectomy⁴⁶ or colonic bypass⁴⁷ reduces the contact of nitrogenous residue with a relatively stagnant reservoir of colonic bacteria. Though not of general application, such operations may be of value in rare cases in which, despite other forms of therapy, constipation repeatedly precipitates encephalopathy.
- (7) Urease inhibition. Urease is the enzyme which splits urea to ammonia in the gastrointestinal tract. It may be inhibited biochemically (with a reduction in the formation of

ammonia) by the orally administered drug acetohydroxamic acid.^{18 48} It may also be inhibited immunologically by repeated injections of urease from the jack bean, thus stimulating the formation of antiurease antibodies—which probably enter the lumen of the gastrointestinal tract and inactivate the urease present there.⁴⁹ While of considerable theoretical interest these techniques are not much used in clinical practice.

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