CURRENT SURVEY

The widening spectrum of neurological damage in liver disease

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This occurs with all types of cirrhosis and the fixed neurological syndromes may sometimes appear without preceding episodes of hepatic pre-coma or coma.

Part of the symptom complex can be related to a chronic and progressive dementia. Initially there is loss of the sophisticated habits of civilized living. Some patients remain superficially alert but may have impairment of recent memory and paucity of spontaneous thought. In other patients reversible fluctuations of mood from apathy to wild excitement may occur whilst in a further group frank psychotic symptoms with hallucinations and paranoid delusions dominate the picture (Read et al., 1967).

Probably the most consistent neurological features of hepato-cerebral degeneration are related to disorders of the cerebellar and extrapyramidal systems. Tremors of the hands varying from a fine resting tremor, as seen in Parkinsonism, to the well-described flapping tremor may be encountered. Other patients may have tremor of the lips and tongue. Bizarre symptoms of choreo-athetosis may occur with facial grinning, lip-smacking, tongue protrusion and writhing sinusous or tortuous convulsions of the arms and legs (Gibson, 1963; Toghill, Johnston & Smith, 1967). Rarely there may be myoclonic jerks of the limbs which have been termed ‘intention or action mycolonus’ (Lance & Adams, 1963).

Disorders of the pyramidal system are common with brisk reflexes, ankle clonus and extensor plantar responses. Unilateral neurological signs are unusual but Pearce (1963) has observed transient hemiparesis, permanent hemiplegia and focal epilepsy in association with hepatic pre-coma and coma.

A true myelopathy can also occur. This is...
characterized by extreme spasticity, and Liver- 
sedge & Rawson (1966) have recently drawn at- 
tention to the late retention of flexor plantar 
responses. They suggest that the initial change in 
the myelopathy is an alteration in the \( \gamma \)-loop 
threshold with, at a later stage, demyelination of 
the pyramidal pathways but not to levels above 
the cervical cord.

Although peripheral neuropathy has been only 
rarely recorded in liver disease it may be more 
common than is generally recognized. Dayan & 
Williams (1967) found evidence of a demyelinating 
peripheral neuropathy in each of the ten 
patients they examined with widely differing 
types of hepatic disease. Retro-bulbar neuritis 
may also occur (Ortiz-Vázquez, 1967) and a 
Guillain-Barré syndrome complicating acute viral 
hepatitis has been described (Dragsted, 1950).

**Differential diagnosis**

Probably the most confusing situation in the 
diagnosis of patients with liver disease and neu- 
rological abnormalities is concerned with cases 
of Wilson's disease with no family history. The 
nervological signs of dementia, choreo-athetosis, 
tremor and myoclonus may be indistinguishable 
from acquired hepato-cerebral degeneration, 
though usually Wilson's disease presents at an 
éarlier age with less emphasis on hepatic symp- 
toms. Denny-Brown (1964) considers that the 
nervological abnormalities in Wilson's disease 
can be separated into two groups. The first ('pseudo-
sclerosis'), which tends to present in adult life, 
is characterized by a flapping wrist tremor, a 
'wing-beating' effect at the shoulders and dysar-
thria. The second ('progressive lenticular degene-
ration') begins earlier in childhood with dystonia 
and abnormal postures of the limbs, a fixed 
facial expression, inattentiveness and occasional 
schizoid symptoms. According to Denny-Brown 
the adult pseudosclerosis type which carries a 
better prognosis and is helped by treatment with 
chelating agents may be the direct effect of 
copper deposition in the brain, whereas the 
juvenile dystonic variety which carries a poor 
prognosis and may be aggravated by chelation 
is possibly related to the underlying liver disease. 
Unfortunately the serum caeruloplasmin level is 
not always low, but Kayser-Fleischer rings are 
diagnostic of Wilson's disease though they may 
require slit lamp examination for detection, and 
radio-copper studies can be helpful (Osborn & 
Walshe, 1967).

Further difficulties may occur in the diagnosis 
of hepatic neurological disease in subjects with 
chronic alcoholism but not necessarily cirrhosis. 
These patients may develop various neuro-
psychiatric syndromes such as delirium tremens, 
Wernicke's encephalopathy, and Korsakoff's psy-
chosis, whereas some may also show signs of a 
peripheral neuropathy or an alcoholic cerebellar 
When the patient has cirrhosis and hepatocere-
bral changes in addition, a complex neurological 
state results.

### 2. Neuropathological changes

The detailed studies of Victor et al. (1965) 
have shown that there are two abnormalities; 
firstly, a diffuse increase in the size and number 
of the protoplasmic astrocytes and, secondly, a 
patchy vacuolar degeneration and necrosis of the 
nerve cells which usually occurs in bands in the 
dereper layers of the cerebral cortex and, to a 
lesser extent, in the basal ganglia and in the 
cerebellum.

There is some, but not complete, correlation 
between the type of neurological disorder ex-
perienced in life and the site of lesions at 
autopsy. The slowly progressive dementia is pro-
bably dependent on the widespread cortical 
lesions. The hippocampal and diencephalic 
systems which appear to be critical for memory 
and learning are affected less than other regions, 
and this would explain why these functions are 
not disproportionately affected as in Korsakoff's 
psychosis (Victor et al., 1965). The cerebellar 
symptoms also correlate with lesions in the cere-
bellar cortex but there is a poor correlation be-
tween choreoathetosis and lesions of the basal 
ganglia.

The changes in the astrocytes are perhaps the 
most fascinating and puzzling feature of this 
disorder. These may be the only finding in patients 
dying in acute hepatic coma though presumably 
there is some functional impairment of the 
neuronal parenchymal cells with changes too 
slight to be visible on light microscopy. In patients 
dying after a protracted but single episode of 
hepatic coma widespread parenchymal changes 
can occur, and in the various chronic syndromes 
there is a fairly close correlation between the 
topography of the parenchymal and astrocytic 
lesions (Victor et al., 1965). The exact function 
of the protoplasmic astrocytes is unknown but 
they may be concerned with the transport of 
esential substances from capillary to neurone, 
in which case it could be postulated that the 
nerve cell injury is secondary to a pathological 
process acting primarily on the astrocytes. What-
ever the exact relationship it is important to 
remember that chronic clinical syndromes with 
dysarthria or ataxia do not necessarily have irre-
versible morphological changes in the nerve cells.
and some cases are reported in which considerable improvement occurred after colonic exclusion (McDermott, Victor & Point, 1962).

Neuropathological distinction from Wilson's disease

In general, changes in the basal ganglia are usually more pronounced in Wilson's disease. Intranuclear glycogenic inclusions in the astrocytes are less common and Opalski cells (a form of lipid-laden degenerating nerve cell) are more frequent. However, there are many cases which are indistinguishable from acquired hepatocerebral degeneration and this raises many problems in relation to the exact role of copper toxicity in the pathogenesis of the disorder. The close pathological similarity of the two diseases is not, as might be suggested, a reflection of a limited range of response of cerebral tissue to injury. The protoplasmic astrocytic changes are seen only in these two disorders and the overall neuropathological picture, as Victor and his colleagues stress, is quite different from that resulting from other types of toxic or metabolic cerebral injury such as following anoxia or hypoglycaemia.

3. Biochemical disorder

The increased incidence of encephalopathy in cirrhosis after portacaval anastomosis (Grace, Muench & Chalmers, 1966) and the development of a typical chronic hepatocerebral degeneration after a shunt operation in two patients who had a normal liver (Adams, 1965) shows the importance of the collateral circulation as opposed to hepatocellular impairment in the pathogenesis of this disorder. The complete diversion of portal blood as in a shunt operation may, however, impair liver function even in a previously normal liver. The liver decreases in size after a portacaval shunt and in one of Adams' cases severe hypoproteinaemia developed. Furthermore studies by Thompson, Williams & Sherlock (1964) in the closely comparable situation of extrahepatic portal hypertension due to a portal-vein thrombosis showed definite and progressive impairment of liver function.

Much evidence points to ammonia as a toxic substance responsible for hepatic coma (reviewed by Summerskill, 1966). The blood ammonia level is usually raised in acute hepatic coma, the disorder can be precipitated by the feeding of ammonium salts, and neomycin, which reduces bacterial breakdown of protein in the large bowel, is undoubtedly effective in controlling both clinical symptoms and in reducing blood ammonia level. Furthermore, patients with certain inborn errors of metabolism involving the urea cycle, of which argininosuccinic aciduria is one example, may have a raised blood ammonia and neurological disorders including episodes of confusion and coma, which resemble hepatic encephalopathy (Moser et al., 1967). On the other hand, numerous workers have been worried by the lack of exact correlation between neurological signs and ammonia levels, and there can be no doubt that substances such as methionine when given orally, and sedative drugs like morphine, can precipitate hepatic coma in cirrhosis without any change in ammonia metabolism (Read, 1965).

It has been suggested that ammonia acts by producing a depletion of the Krebs' cycle intermediate α-ketoglutarate as a result of excess conversion to glutamic acid and glutamine. High glutamine levels have been demonstrated both in the brain and in the cerebrospinal fluid in hepatic coma, but liberation of ketoglutarate from the brain rather than uptake occurs (Dastur, Seshadri & Talageri, 1963).

Recently, Schenker et al. (1967) have produced direct evidence that toxic doses of ammonia can in vivo actually affect cerebral energy metabolism. They showed a substantial decrease in adenosine triphosphate and phosphocreatine concentration in the base of the brain but not in the cortex of ammonia-intoxicated rats. Whatever the initial basic injury the final picture is a complicated one and includes respiratory alkalosis and electrolyte disturbances, particularly hypokalaemia, together with various changes in carbohydrate, short-chain fatty acid and amino-acid metabolism (reviewed by Read, 1965; Zieve, 1966).

4. Advances in treatment

Standard therapy at present consists of dietary protein restriction, emptying of the bowel by purgation and neomycin therapy, together with attention to electrolyte imbalance and correction of precipitating factors such as over-diuresis, infection or haemorrhage. Remarkable improvement can occur both in acute coma and in some of the various chronic syndromes. Nevertheless, the mortality of coma due to infective hepatitis or massive necrosis from drug toxicity remains about 80% and in these conditions some form of temporary liver support is needed. The recent developments of exchange transfusion and extracorporeal hepatic perfusion afford some hope.

Improvement with exchange transfusion may result from the addition of deficient factors to the circulation, possibly antibody (Morris, Gocke & Sardi, 1967), or from the removal of toxic substances. Saunders (1967) in Cape Town, whose group were largely responsible for intro-
Producing the technique, continues to get good results. Eleven of the twenty-two patients treated to date recovered consciousness completely and six patients are alive and well. They found that fresh frozen plasma was of help in controlling the haemorrhagic tendency and that intravenous albumin was needed to correct hypoalbuminaemia. Some patients developed hypoglycaemia and the blood sugar should be estimated routinely. Most of the patients were children with infections and the experience reported from this country, mainly in adults, is less encouraging. Three of the seven patients treated by Jones et al. (1967) showed striking improvement in the level of consciousness but all seven died. Necropsy in six showed such distortion of hepatic architecture as to suggest that macronodular cirrhosis would have been inevitable. Indeed, two of Saunders' successful cases now have cirrhosis and it may well be that at a certain stage of lobular disorganization restitution of normal structure is impossible. However, exchange transfusion is a relatively simple procedure and in our view is worthwhile when the patient fails to respond to standard measures within 24 hr.

Perfusion of the patient's blood through a cooled isolated pig or cadaver human liver in an extracorporeal circuit, unlike exchange transfusion, requires extensive facilities and a large team. Such isolated perfused livers can function satisfactorily for periods of up to 8 hr. Oxygen is utilized, bile is produced and bilirubin and ammonia are removed from the patient's blood. Approximately a third of the patients treated have shown neurological improvement although relatively few have recovered completely (Eisenman, 1966; Watts et al., 1967).

Chronic encephalopathy

A number of attempts have been made to reduce ammonia production in the large bowel by altering the bacterial flora. Lactobacillus acidophilus has been given in milk (Macbeth, Kass & McDermott, 1965) or as the freeze-dried preparation Enpac (Read et al., 1966). The lactobacilli are thought to impede coliform multiplication as a result of lowering faecal pH but clinical improvement has not necessarily correlated with coliform stool counts. Fenton, Knight & Humpherson (1966) produced some improvement in three patients by feeding a diet containing milk and cheese protein instead of the normal mixed animal protein. The beneficial action may be due to the high bacterial content of the diet altering the bacterial flora.

Alternatively faecal pH may be changed by giving lactulose (1-4-beta-galactosidofructose). This is a synthetic disaccharide which cannot be hydrolysed by the small intestinal enzymes in man and is split in the large bowel into organic acids. Some diarrhoea results due to fermentation of carbohydrates and an improvement in encephalopathy comparable with neomycin was obtained in two patients (Bircher et al., 1966).

A more complete and possibly more permanent response can be obtained by surgical exclusion of the colon with an ileo-sigmoidostomy. Cirrhotic patients in general withstand surgical operations badly and this operation should be restricted to patients with good liver function. In some of the patients reported there has been a striking improvement in mental status and ability to tolerate protein. Symptoms such as dysarthria, ataxia and extra-pyramidal symptoms may or may not improve (MacDermott et al., 1962; Walker et al., 1965). Blood ammonia falls though it may rise later as a result of colonization of the small bowel by urea-splitting organisms.

References


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