Review

The neurology of liver failure

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Introduction

That there is a relationship between the brain and the liver has been known for many years, and patients with chronic liver disease frequently experience neurological problems. The commonest and most widely recognized is the reversible syndrome of hepatic encephalopathy, and we will deal with this in some detail. There are also of course many conditions that affect both the liver and the nervous system, Wilson’s disease being one of the best known. This condition is a genetic disorder of copper metabolism; the abnormal gene is located on chromosome 13 and most of the symptoms seem to be due directly to the deposition of copper in various organs. Patients typically present early with liver disease or later with the neurological syndrome, which consists of various subtle neuropsychiatric symptoms such as a change in behaviour or performance at school and abnormality of movement. There are many other conditions where the brain and liver are damaged by the same or similar mechanisms, but these will not be examined by this review, which concentrates on the effect of a poorly functioning liver on the nervous system.

Overt hepatic encephalopathy

Overt hepatic encephalopathy is generally taken to refer to a syndrome of neuropsychiatric, neuropsychological and neurological disturbances that may arise as a complication of liver disease, and which is reversible. This definition is not entirely consistent with the current state of knowledge, however, as there is growing evidence that the reversibility of the syndrome is not complete.

A recent consensus statement, published following the World Congress of Gastroenterology in 1998, suggested that hepatic encephalopathy be divided into three main types, with further subdivisions within one of the categories (Table 1). Between 10 and 50% of patients with cirrhosis and/or porto-caval shunts will experience an episode of overt hepatic encephalopathy at some time during their illness, with the prevalence varying across the spectrum of severity of the cirrhosis.

The true incidence and prevalence of overt hepatic encephalopathy in these patients is difficult to establish, because of the considerable heterogeneity in aetiology and disease severity. It is also difficult to diagnose the more subtle forms of hepatic encephalopathy such as stage 1 (Table 2) and minimal hepatic encephalopathy. The lack of a gold standard for assessing the presence of hepatic encephalopathy means that the incidence of these more minor forms is difficult to ascertain.

The factors that can precipitate overt hepatic encephalopathy are well recognized, and include an oral protein load, gastrointestinal bleeding, electrolyte imbalance, infection and deteriorating liver function.

It is unlikely that a single mechanism underlies the whole syndrome of hepatic encephalopathy in all its various forms; a multifactorial pathogenesis is much more likely. Current thinking suggests that a combination of chronic low-grade glial oedema and potentiation of the effects of gamma amino butyric acid (GABA) on the central nervous system...
system by ammonia may be responsible for many of the symptoms of hepatic encephalopathy.

GABA is the major inhibitory neurotransmitter in the human brain. Increased GABA-mediated neurotransmission is known to cause impaired consciousness and psychomotor dysfunction. In animal models of hepatic encephalopathy, an increase in GABA-ergic tone has been demonstrated due to both an increase in GABA release and enhanced activation of the GABA-A receptor complex. Benzodiazepines can act at the GABA-A receptor complex, and increased concentrations of endogenous benzodiazepines are found in the brain in liver failure.

Ammonia is known to be neurotoxic, but usually at much higher levels than those found in liver failure, and even then it does not produce a syndrome like that seen in hepatic encephalopathy; in fact, it tends to cause neuronal excitation. However, at the lower concentrations seen in hepatic encephalopathy, ammonia potentiates the actions of GABA, possibly by enhancing ligand binding to the GABA-A receptor complex. It is probably for this reason that some patients with hepatic encephalopathy improve following administration of the GABA-A receptor antagonist flumazenil.

In addition there is some evidence for involvement of the glutamatergic system in hepatic encephalopathy. Glutamate is the major excitatory neurotransmitter in the human brain, and ammonia reduces its synthesis and down-regulates the glutamate receptor in vitro. This would result in reduced excitatory transmission in the brain. The dopaminergic, serotonergic and opioid neurotransmitter systems have also been implicated in the pathogenesis of hepatic encephalopathy, and it is likely that all of them and possibly others are involved in this complex syndrome.

In fulminant hepatic failure where hepatic encephalopathy develops within 8 weeks of the onset of liver disease, autopsy reveals brain oedema and astrocyte swelling. In patients with cirrhosis and portal-systemic shunts, the typical finding is the Alzheimer type II astrocyte, which is the pathological hallmark of hepatic encephalopathy.
are found in many locations, including the cortex and the lenticular, lateral thalamic, dentate and red nuclei.\textsuperscript{24} In turn, these abnormal astrocytes have been shown to be produced by ammonia.\textsuperscript{25} These findings are similar to those in the acquired hepatocerebral degeneration syndrome.\textsuperscript{26–29}

Recent studies have also shown increased levels of manganese in the basal ganglia and to a lesser extent other areas of the brain,\textsuperscript{30–32} but the relevance of these findings is undetermined.

Overt or symptomatic hepatic encephalopathy is traditionally graded into four stages (Table 2). The clinical picture is of a derangement of consciousness accompanied by decreased (or occasionally increased) psychomotor activity that if left untreated progresses through increasing drowsiness, stupor and coma.\textsuperscript{33} Sleep disturbance is one of the more common early signs and occurs in nearly 50\% of cases.\textsuperscript{34}

As the encephalopathy progresses along this path, signs of pyramidal tract dysfunction such as hypertonia, hyperreflexia and extensor plantar responses are common, eventually being replaced by hypotonia as coma develops.\textsuperscript{2} The familiar sign of asterixis is well described in hepatic encephalopathy, but unfortunately also occurs in other metabolic encephalopathies and is not therefore pathognomonic.\textsuperscript{20} One of the areas in which hepatic encephalopathy can differ from other metabolic encephalopathies is in the early stages when the psychomotor retardation that occurs can produce a striking Parkinsonian syndrome.\textsuperscript{2} In one study, these Parkinsonian features were shown to correlate with the degree of T1 hyperintensity seen in the basal ganglia on cerebral magnetic resonance imaging and the changes in choline/creatine ratios in the basal ganglia on cerebral magnetic resonance spectroscopy.\textsuperscript{35}

Focal neurological deficits and signs have been described in hepatic encephalopathy, but are probably rare,\textsuperscript{36,37} although a recent study has described fairly subtle abnormal neurological signs occurring quite frequently.\textsuperscript{38} Visual disturbances have also been reported in association with hepatic encephalopathy, both as a result of cortical\textsuperscript{39} and retinal dysfunction. The retinal dysfunction has been termed ‘hepatic retinopathy’ and probably results from damage to retinal glia or Muller cells.\textsuperscript{40,41}

Although seizures may occur, they are unusual outside the setting of fulminant hepatic failure, and should prompt the search for an alternative explanation. This relative rarity probably represents the balance of neurotransmitters being tipped in favour of inhibition as discussed above.

The diagnosis of overt hepatic encephalopathy is largely clinical, but some investigations are of use. Arterial blood ammonia is usually raised in hepatic encephalopathy, although not always, and the absolute level bears little relation to the severity of the encephalopathy.\textsuperscript{42} The use of the electroencephalogram is limited, as the alterations are non-specific, and triphasic waves are found in many other metabolic encephalopathies.\textsuperscript{43} The role of evoked potentials in the diagnosis and management of hepatic encephalopathy is controversial, and a complete discussion of these techniques is beyond the scope of this review. Visual (VEP), sensory (SEP) and brainstem auditory (BAEP) evoked potentials can all be recorded, and show various abnormalities depending on the waveforms analysed and the liver disease under examination. Generally speaking, these tests demonstrate delayed latencies (a slower response) which become more prolonged in relation to the degree of encephalopathy.\textsuperscript{44} They may therefore be of use in detecting minimal hepatic encephalopathy or monitoring treatment in established encephalopathy.\textsuperscript{44–52}

In addition, marked prolongation or absence of various waveforms can be an indicator of poor prognosis.\textsuperscript{4,53,54} Other tests such as lumbar puncture and neuroimaging are not usually indicated in overt hepatic encephalopathy unless the diagnosis is in doubt.

Treatment is largely supportive. Precipitating factors should be treated or removed, and absorption of nitrogenous substances from the bowel should be reduced.\textsuperscript{2,20} Treatments aimed at reversing the neurotransmitter defects such as by the use of flumazenil are unproven and remain experimental.\textsuperscript{23}

The outlook for patients who develop overt hepatic encephalopathy is grim.\textsuperscript{55,56} Following the first episode of overt hepatic encephalopathy, the 1-year survival is about 40\%, falling to about 15\% after 3 years.\textsuperscript{56,57} Interestingly, the studies by Saunders \textit{et al.} and Bustamante \textit{et al.} show very similar mortality rates, despite the improvements in intensive medical support that have occurred over the intervening 20 years.

**Minimal hepatic encephalopathy**

Minimal hepatic encephalopathy is the term that has replaced the old terms of latent or sub-clinical hepatic encephalopathy. It was felt that these older terms did not reflect the important effects of this syndrome on patients’ lives.\textsuperscript{13} It has been recognized for some time that with appropriate neuropsychological tests, patients who were felt clinically to be free from hepatic encephalopathy do in fact demonstrate signs of cognitive impairment.\textsuperscript{58,59}
Only quite recently, however, were these more subtle deficits shown to affect patients’ lives, and the current consensus is that they should be treated. Depending on the tests used and the population studied, minimal hepatic encephalopathy seems to affect between about 20% and 70% of patients with liver disease.

The pathogenesis of minimal hepatic encephalopathy is not understood. It would seem likely, however, that the same mechanisms affecting neurotransmission in overt hepatic encephalopathy also underlie minimal hepatic encephalopathy. There is no reason to think that hepatic encephalopathy is an all-or-nothing phenomenon, and a continuous scale of impairment would seem more likely. Alterations in the pattern of cerebral blood flow have been demonstrated in patients with minimal hepatic encephalopathy, and it would seem likely that this also plays a role in its pathogenesis.

Because the syndrome of minimal hepatic encephalopathy has only recently been defined, its clinical characteristics are poorly described. If different neuropsychological tests are used to identify the syndrome in each study, then different cognitive deficits might be detected. A common finding in most of the studies is impairment of visuospatial functioning, attention and psychomotor speed. Unfortunately this is not universal, and others have not demonstrated visuo-spatial dysfunction. The causes of liver failure are heterogeneous and the severity of liver disease within even a single cause can vary hugely. This could explain the difficulty in establishing the nature of the cognitive dysfunction that exists in these patients.

It is now generally agreed that neuropsychological tests offer the best option for diagnosing minimal hepatic encephalopathy, but there is considerable debate about which tests should be used and how the results should be interpreted. Generally, any battery of neuropsychological tests should assess a broad range of cognitive functions and in the case of liver dysfunction, should probably include tests of psychomotor speed, visuoperception, attention and concentration. It has been suggested that tests of language and memory need not be included in assessing minimal hepatic encephalopathy. We believe that at the moment we do not know enough about the characteristics of the cognitive impairment in these patients to exclude major areas of cerebral function from any assessment.

The role of the EEG and evoked potentials in making the diagnosis is also uncertain, but the current feeling is that neuropsychological tests are more sensitive and specific. However, in the absence of a ‘gold standard’, these comparisons are very difficult. It could be that the neuropsychological tests are actually achieving the correct level of sensitivity and specificity, and the neuropsychological tests are overdiagnosing the condition. A recent study has suggested that using the technique of critical flicker frequency might be effective in identifying cases of minimal hepatic encephalopathy. This technique establishes the frequency at which a flashing light appears to stop flashing and becomes continuous (fusion frequency). The authors plotted this against the severity of hepatic encephalopathy and also for normal controls, and showed that the fusion frequency dropped with increasing cognitive impairment. They went on to suggest appropriate cut-off scores for identifying minimal and overt hepatic encephalopathy with varying degrees of sensitivity and specificity. This is a promising technique, and will probably have a role in screening patients who may then need more formal neuropsychological assessment.

Neuroimaging techniques such as magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) have been used in the assessment of minimal hepatic encephalopathy, but at the moment they are more useful in research and in further establishing the pathophysiology of the condition.

How these patients should be treated is uncertain. Studies have shown an improvement in cognitive functioning with dietary protein restriction or lactulose treatment. If there is a scale of neurological and cognitive dysfunction with minimal hepatic encephalopathy at one end and overt hepatic encephalopathy at the other, it would seem reasonable that similar treatments would work in each condition.

The prognosis of minimal hepatic encephalopathy has recently been studied, and 30% of patients who showed signs of minimal hepatic encephalopathy went on to develop overt hepatic encephalopathy. Unfortunately, in this study the authors do not make it clear over what period this occurred, as they followed patients until one of three endpoints occurred (death, transplantation or overt hepatic encephalopathy). The mean time taken to develop hepatic encephalopathy was about 2 years from the initial assessment. This is of limited use, as we can not know when these patients actually developed their initial cognitive impairment. Other studies have also shown that minimal hepatic encephalopathy is an independent predictor of poor survival in patients with liver disease.

These findings are not consistent with another study that showed that the presence of minimal
hepatic encephalopathy was of limited prognostic significance. In this study however, patients with minimal hepatic encephalopathy had more episodes of overt hepatic encephalopathy, and as we know that overt hepatic encephalopathy is associated with a very poor prognosis, it could be that the authors’ negative findings simply reflect a lack of long-term follow-up.

Hepatic encephalopathy and liver transplantation

The effect of liver transplantation in patients with varying degrees of hepatic encephalopathy is uncertain. There have been few studies in this area and none in the UK. The work that has been done suggests a significant improvement in cognitive function following liver transplantation, but patients do not return to normal.

A recent study has suggested that these improvements occur quickly after transplantation and are maximal by about 3 months. In some respects the fact that patients do not return to normal is not surprising, but it is somewhat at odds with the current theory regarding the complete reversibility of hepatic encephalopathy.

Fulminant hepatic failure

Patients with fulminant hepatic failure form a distinct group, compared to patients with chronic liver disease. The syndrome is said to occur when hepatic encephalopathy develops within 8 weeks of the onset of liver disease. The most prominent neurological problem is cerebral oedema and subsequent raised intracranial pressure. The exact mechanism by which the cerebral oedema occurs is unknown, but once again ammonia is thought to play a role. This time, levels of ammonia tend to be higher, and may contribute to the neuro-excitatory symptoms seen in this state, such as agitation, seizures and multifocal muscle twiching, via direct toxicity. In these situations ammonia also has an adverse effect on osmoregulation via its reaction with glutamate to form glutamine, thus exacerbating cerebral oedema. Mortality is high at around 70–80%, but many of these patients are now being transplanted, and survival rates are improving. In addition, there is also evidence that if provided with support, the native liver can regenerate, and auxiliary partial liver transplantation is sometimes used to treat these patients.

Acquired hepatocerebral degeneration and hepatic myelopathy

Acquired (non-Wilsonian) hepatocerebral degeneration (AHCD) is a clinical-pathological syndrome of brain dysfunction associated with a variety of liver diseases, originally characterised by Victor et al. in 1965. The typical clinical features of this chronic and largely irreversible syndrome are dementia, dysarthria, ataxia of gait, intention tremor and choreoathetosis. The main neuropathological findings include diffuse but patchy cortical necrosis, diffuse proliferation of Alzheimer type II glial cells and uneven neuronal loss in the cerebral cortex, basal ganglia and cerebellum.

A hepatic or portal-systemic myelopathy (HM) has also been described, initially by Zieve et al. in 1960, and is characterized clinically by a spastic paraparesis with minimal sensory involvement. The pathology is somewhat different, however, and consists mainly of symmetrical demyelination, predominantly of the lateral pyramidal tracts, sometimes associated with axonal loss, generally going no higher than cervical cord level. There have been suggestions, however, that the acquired hepatocerebral degeneration syndrome simply represents the damage accumulated from multiple episodes of hepatic encephalopathy.

In most of the reported cases, episodes of overt hepatic encephalopathy have preceded the development of the myelopathy or the hepatocerebral degeneration. However, there have been cases where this has not occurred, and thus another mechanism may be at work. It would seem most likely that it is chronic exposure to toxic substances bypassing the liver that causes both AHCD and HM. Or more specifically, that these toxins are resulting in one pathological response in the brain and a different pathological response in the spinal cord.

Treatment of these patients is difficult. There have been case reports of transplantation being used with varying degrees of success, but if liver transplantation does have a role to play in the management of this condition, one needs to bear the underlying pathology in mind. In the early stages, demyelination seems to predominate, but as the disease progresses axonal loss occurs, and this is likely to be irreversible. This might go some
way towards explaining the different experiences reported in the literature. In the case reported by Counsell et al., liver transplantation was performed at least 18 months after the onset of symptoms, and there was no improvement in the myelopathy. In a more recent case, the liver transplant was performed after no more than 10 months of neurological symptoms, and the authors documented good improvement. If, as seems likely, it is the portal-systemic venous shunting that underlies these conditions, then with the development of procedures such as transjugular intrahepatic portal-systemic shunting (TIPSS), and the increasing survival of these patients, such long-term neurological sequelae may be encountered more often. In fact there is growing evidence that this is already starting to occur, with several studies reporting neurological and neuropsychological dysfunction in patients who have undergone shunting procedures such as TIPSS. As the time between shunting and the development of AHCD can be many years, we will need to wait and see whether this syndrome becomes a common and significant problem for these patients.

Osmotic demyelination disorders

Central pontine myelinolysis manifests as a rapidly evolving paraparesis or quadriparesis, pseudobulbar palsy and impaired responsiveness. It is characterized pathologically by loss of myelin in the basis pontis, often in a strikingly symmetrical fashion (Figure 1). The degree of neurological impairment can range from minimal symptoms to a full ‘locked in’ syndrome, where the patient can experience the horror of being fully aware but be unable to move. The underlying cause is not fully understood, but most cases involve a change in osmolality, often rapid and often involving correction of hyponatraemia. This does not explain all the cases, however, and in addition many patients survive rapid correction of hyponatraemia without developing signs and symptoms of central pontine myelinolysis. Other conditions are likely to predispose to development of the syndrome, and liver disease and transplantation are commonly described in this role. The prognosis of this condition has probably been described in overly bleak terms, with many standard texts suggesting that most patients die. However, this has not been our experience, and in a recent large series, 32 out of 44 patients with central pontine myelinolysis survived. Twenty-one had various degrees of permanent neurological impairment, but 11 recovered completely.

Other neurological disorders in liver disease

There has also been recent interest in two other symptoms that can occur in liver disease and that

Figure 1. A T2-weighted MRI scan showing high signal in the brainstem (arrows) consistent with osmotic demyelination.
might have a neurological basis. The pruritus of cholestasis may at least in part have its origins in the central nervous system. The authors suggest several mechanisms whereby this might be the case: opioid agonists induce pruritus by a central mechanism, central opioidergic tone is increased in cholestasis and opioid antagonists can improve the symptom. Clearly this theory remains to be proven.

Many patients with chronic liver disease also complain of fatigue, and the mechanisms of this symptom are poorly understood. It would seem unlikely to have a single cause, but may be due in part to altered central neurotransmission involving the serotonergic system. Fatigue is a common complaint in many medical and psychiatric conditions. It is particularly common in neurological disorders such as multiple sclerosis, and the mechanisms involved may be similar.

There is an increased incidence of neuromuscular dysfunction in patients with liver disease. Whether the liver disease itself causes these problems is difficult to establish. Many of the causes of liver disease, such as alcohol, hepatitis C, porphyria and so on, are also known to cause peripheral neuropathies and myopathies. There is some evidence, however, that the worse the liver disease, the worse the neuropathy, independent of the aetiology of the liver disease. This suggests that the liver disease itself is causing, or at least contributing to, the neuropathy.

Neuroimaging abnormalities associated with liver disease

It is becoming widely recognized that patients with chronic liver disease and portal-systemic shunts exhibit typical abnormalities on cerebral magnetic resonance imaging (MRI). These consist of an abnormally high signal on T1-weighted imaging in the basal ganglia, particularly the globus pallidus (Figure 2). This high signal is now believed to be due to manganese deposition, and post-mortem studies have shown levels up to seven times normal in the globus pallidus. Interestingly, chronic manganese poisoning produces a syndrome very similar to the acquired hepatocerebral degeneration syndrome, with mental slowing, tremor and bradykinesia. It also has very similar neuroimaging characteristics, and chelation therapy has been effective in improving both the clinical syndrome and the globus pallidus high signal.

With successful liver transplantation, the abnormalities seen in liver disease also resolve.

In the acquired hepatocerebral degeneration syndrome, the typical findings described above are found, often with more extensive high signal in the white matter, best seen on T2-weighted imaging. In hepatic myelopathy, there are usually no MRI abnormalities, and this probably represents the current technical limitations of this technique and the relatively small magnet strengths of current clinical scanners.

Conclusions

Neurological syndromes are common in patients with liver failure, and are an important cause of morbidity. Our understanding of their pathogenesis is improving, but much work remains to be done, particularly as regards management of these problems. The link between the liver and the
brain, described many years ago by Dr Friedrich Frerichs, is still only partially understood.

References


