NEUROLOGY AND MEDICINE

Neurology and the liver

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Neurological syndromes commonly occur in patients with liver disease. A neurological syndrome associated with a liver disease may be a complication of the disease, it may be induced by a factor that also contributes to the disease—for example, alcohol—or it may have no relation to the presence of the liver disease. Neurological deficits associated with liver disease may affect the CNS, the peripheral nervous system, or both. This review focuses on syndromes characterised by altered CNS function associated with structural liver diseases. Space does not permit consideration of peripheral neuropathies associated with liver disease (for example, xanthomatous peripheral neuropathy), diseases of childhood that affect the liver and CNS (for example, Reye's syndrome), or neurological consequences of hepatic lesions characterised by specific enzyme deficiencies (for example, congenital hyperammonaemias, the porphyrias, kernicterus, galactosaemia, and Zellweger's syndrome (cerebrohepatorenal syndrome)).

That there is a relationship between the functional status of the liver and that of the brain has been known for centuries.[1] The most widely recognised aspect of this relation is that hepatocellular failure may be complicated by the behavioural syndrome of hepatic encephalopathy, in which neurotransmission in the brain is altered.[2 3] Recently, it has been suggested that two other behavioural complications of liver disease, scratching due to pruritus in cholestatic patients[4 5] and profound fatigue in patients with chronic cholestasis,[6 7] may also be associated with altered neurotransmission in the brain.

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Hepatic encephalopathy

DEFINITIONS AND CLASSIFICATION

The term hepatic encephalopathy refers to the syndrome of neuropsychiatric disturbances that may arise as a complication of acute, subacute, or chronic hepatocellular failure. The syndrome is associated with increased portal-systemic shunting of gut derived constituents of portal venous blood, due to their impaired extraction by the failing liver and, in most instances, their passage through intrahepatic and/or extrahepatic portal-systemic venous collateral channels.

The term portal-systemic encephalopathy is often used interchangeably with hepatic encephalopathy, but portal-systemic encephalopathy can be defined to include encephalopathy associated with increased portal-systemic shunting in the absence of unequivocal evidence of hepatocellular insufficiency—for example, shunting secondary to a congenital portal-systemic shunt, extrahepatic portal hypertension or portal hypertension due to hepatic fibrosis (for example, schistosomiasis).

Subclinical hepatic encephalopathy is the term applied to a patient with chronic liver disease (for example, cirrhosis) when routine neurological examination is normal, but application of psychometric or electrophysiological tests discloses abnormal brain function that can be reversed by effective treatment for hepatic encephalopathy.[8]

Fulminant hepatic failure and subfulminant (or late onset) hepatic failure are terms used when the syndrome of acute liver failure is complicated by hepatic encephalopathy within one to several weeks of the first evidence of liver disease or the development of jaundice.[9 10]

Hepatic encephalopathy occurring in a patient with cirrhosis may be either acute or chronic. The acute form in such a patient is usually associated with a clearly identifiable precipitating factor and usually resolves when the precipitating factor is removed or corrected. Failure to find a precipitating factor may imply that a decrease in overall hepatocellular function has taken place. The term chronic hepatic encephalopathy (or chronic portal-systemic encephalopathy) is often applied to a patient with cirrhosis and substantial portal-systemic shunting, who has hepatic encephalopathy that is persistent or episodic, with or without complete resolution of encephalopathy between episodes.

It has been conventional to classify hepatic encephalopathy as a reversible metabolic encephalopathy. This definition excludes rare neurodegenerative disorders associated with chronic liver disease and extensive portal systemic shunting (see Degenerative disorders section). However, this widely accepted classification of hepatic encephalopathy may need reappraisal.[11 12] It is probably useful to classify cerebral oedema and raised intracranial pressure (ICP) occurring in patients with fulminant hepatic failure separately from hepatic encephalopathy. However, these complications of fulminant hepatic failure contribute to encephalopathy, occur together with hepatic encephalopathy, and may share pathogenic factors with hepatic encephalopathy (for example,

Table 1 The clinical stages of hepatic encephalopathy

Stage	*Mental state*
I	Mild confusion, euphoria or depression, decreased attention, slowing of ability to perform mental tasks, untidiness, slurred speech, irritability, reversal of sleep rhythm
II	Drowsiness, lethargy, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behaviour, intermittent disorientation (usually for time), lack of sphincter control
III	Somnolent but rousable, unable to perform mental tasks, persistent disorientation with respect to time and/or place, amnesia, occasional fits of rage, speech present but incoherent, pronounced confusion
IV	Coma, with (IVA) or without (IVB) response to painful stimuli

From Adams and Foley[13] with modifications.

raised ammonia concentrations) (see Fulminant hepatic failure section).

CLINICAL FEATURES

The term encephalopathy covers a wide range of neuropsychiatric disturbances ranging from minimal changes in personality or altered sleep pattern to deep coma[13] (table 1). The earliest clinical signs of hepatic encephalopathy (stage 1) are often subtle psychiatric and behavioural changes that may be more apparent to the patient's family and close friends than to the neurologist.[14 15] These changes are primarily due to mild impairment of intellectual function that reflect predominantly bilateral forebrain, parietal, and temporal dysfunction. In early stages of hepatic encephalopathy the presence of pronounced intellectual impairment may be masked by relatively well preserved verbal ability.[16 17] Whether patients with subclinical hepatic encephalopathy should be considered unfit to drive a car is uncertain.[17 18] As encephalopathy progresses, intellectual abilities deteriorate overtly (with deterioration of performance at school or work), motor function becomes impaired, and consciousness decreases. With further progression coma ensues. Neurological signs vary with progression of hepatic encephalopathy. Hypertonia, hyperreflexia, and positive Babinski signs may be elicited and tend to precede the occurrence of hypotonia and diminished deep tendon reflexes in late stages of hepatic encephalopathy. In contrast to most other metabolic encephalopathies, features of hepatic encephalopathy may include manifestations of extrapyramidal dysfunction, such as hypomimia, muscular rigidity, bradykinesia, hypokinesia, monotony of speech, a Parkinsonian-like tremor, and dyskinesia.

Asterixis or "liver flap" is often present in the early stages of hepatic encephalopathy. Asterixis consists of infrequent involuntary flexion-extension movements of the hand (one flap every one to two seconds), which may result in part from an impairment of the normal inflow of joint position sense to the brain stem reticular formation.[19] Asterixis should be classified as a negative myoclonus rather than a tremor. It is usually best demonstrated with the patient's arms outstretched, the wrists hyperextended, and the fingers separated (as if trying to stop traffic). Also, if the patient uses a hand to grip two of the neurologist's outstretched fingers, asterixis is indicated by rhythmic squeezing of the neurologist's fingers (milk maid's grip). This useful sign is characteristic, but not pathognomonic, of liver failure; it may occur in hypoxia, hypercapnia, uraemia, heart failure, or sedative overdosage.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hepatic encephalopathy includes alcohol intoxication and withdrawal syndromes, Wernicke's encephalopathy, Korsakoff's syndrome, intoxication with sedative/hypnotic drugs, other metabolic encephalopathies (for example, hypernatraemia or hyponatraemia, uraemia, hyperglycaemia or hypoglycaemia, hypercapnia), Wilson's disease, consequences of head trauma (for example, subdural haematoma) and organic intracranial lesions. Delirium tremens (DTs) may occur in a patient with underlying alcoholic liver disease. It is important, therefore, to distinguish this syndrome from hepatic encephalopathy. In contrast to asterixis associated with hepatic encephalopathy, patients with DTs have a rapid postural and action tremor. Furthermore, the manifestations of DTs, including delirium, suggest cortical excitation rather than the presumed cortical inhibition that seems to characterise hepatic encephalopathy. Benzodiazepines are commonly given in the management of DTs. Patients with chronic liver disease have increased sensitivity to the neuroinhibitory effects of these drugs.[20] Other CNS complications of alcoholism, such as Wernicke's encephalopathy and Korsakoff's psychosis, are also not dependent on the development of alcoholic liver disease.

DIAGNOSIS

When patients, with and without known liver disease, present with neuropsychiatric symptoms or neurological signs, it is necessary to ask one of the following questions: (1) Does this patient have hepatic encephalopathy? or (2) Could this patient have hepatic encephalopathy? There are two components to making a diagnosis of hepatic encephalopathy: one is to determine that subclinical or overt encephalopathy is present (table 1 and sections on psychometric tests and electrophysiology), and the other is to obtain information consistent with hepatocellular insufficiency and increased portal-systemic shunting.

Initially it is mandatory to take a meticulous clinical history (usually from the patient's relatives and friends) and to conduct a detailed physical examination. Information elicited should include a history of past or present liver disease, any family history of liver disease, and potential exposure to a hepatotoxic drug or other hepatotoxin or to a hepatitis virus. There are no specific clinical features or patterns of laboratory test results that are diagnostic of hepatic encephalopathy. Accordingly, the diagnosis of hepatic encephalopathy requires clinical judgment and involves establishing the presence of hepatocellular insufficiency and excluding other causes of encephalopathy. The main clinical (non-encephalopathic) manifestations of liver failure, which may be associated with hepatic encephalopathy, are hepatocellular jaundice, fluid retention (ascites, ankle oedema), and an increased bleeding tendency

(bruises). Signs of increased portal-systemic shunting include ascites, dilated veins in the abdominal wall, in which blood flow is away from the umbilicus, and a venous hum, with or without a thrill, in the region of the umbilicus or xiphoid process. Furthermore, classic, but non-specific, stigmata of liver disease (for example, spider angiomata, palmar erythema) may be found. Hypoalbuminaemia and a prolonged prothrombin time are useful laboratory findings, which suggest impaired synthetic function of the liver and hence hepatocellular insufficiency.

Occasionally, when making a confident diagnosis of hepatic encephalopathy is difficult, the clinical and electrophysiological responses to a treatment for hepatic encephalopathy (for example, dietary protein restriction, evacuation of the bowel, or an intravenous injection of flumazenil—see Treatment section) may help to resolve the issue. Making a diagnosis of hepatic coma (stage IV hepatic encephalopathy) can be particularly challenging, as the differential diagnosis of coma is so large and a relevant history may be unavailable. In this clinical situation the finding of a raised plasma ammonia concentration can be useful in suggesting that liver disease may be the primary cause of the coma (see Laboratory section). The correct diagnostic approach to the comatose patient has been well described in the authoritative monograph of Plum and Posner.[21]

ASSESSMENT

Clinical

Classification of the severity of the encephalopathy in terms of four principal clinical stages is routine (table 1).[13] Asterixis may be elicited, particularly in the early stages (I and II) of hepatic encephalopathy. As asterixis represents a defect of neuromuscular function rather than a feature of disordered consciousness, asterixis should probably be assessed independently of the mental state and clinical stage of hepatic encephalopathy.

Laboratory

When encephalopathy is attributable to hepatic encephalopathy alone, abnormal results of serum biochemical tests reflect the underlying liver disease. Routine laboratory test results aid in the differential diagnosis of encephalopathies (for example, uraemia, hypoglycaemia, hypercapnia) and in the detection of factors that may precipitate hepatic encephalopathy (for example, hypokalaemic metabolic alkalosis). Plasma ammonia concentrations are not consistently raised in patients with hepatic encephalopathy; they correlate poorly with the stage of hepatic encephalopathy and they do not provide a reliable index of the efficacy of treatments for hepatic encephalopathy.[2]

Lumbar puncture

Lumbar puncture is not done unless indicated by atypical clinical or laboratory findings. Lumbar puncture carries increased risk because of the presence of coagulopathy and, if ICP is increased in fulminant hepatic failure, the possibility of precipitating cerebral herniation.

Brain imaging

Computed tomography is not useful for the diagnosis of hepatic encephalopathy. It should be done, however, in each case in which the differential diagnosis includes intracranial bleeding, especially the presence of a subdural haematoma.

Magnetic resonance imaging cannot be used for the diagnosis of hepatic encephalopathy. However, characteristic MRI abnormalities are found in patients with cirrhosis. The main abnormal finding is symmetric pallidal hyperintensities in T1 weighted images, which may be accompanied by similar changes in the region of the nigral substance and the dentate cerebellar nucleus.[23–25] These MRI abnormalities do not correlate closely with the stage of hepatic encephalopathy, but in individual cases seem to correlate with the degree of impairment of hepatocellular function. T1 weighted pallidal hyperintensities have been shown to disappear within one year in a cirrhotic patient undergoing liver transplantation.[26 27] The cause of the MRI abnormalities in the CNS of cirrhotic patients is unknown. Possibilities that are being considered include an increased deposition of manganese in the basal ganglia and regional changes in the relaxation time caused by an increase in the number of biological membranes (mitochondria, endoplasmic reticulum) as a consequence of astrocytic proliferation.[21]

Like MRI findings, studies in cirrhotic patients involving the application of magnetic resonance spectroscopy and 18-fluoro-deoxyglucose positron emission tomography have also disclosed abnormal findings in the basal ganglia. The relationship of these abnormalities to hepatic encephalopathy is uncertain. Details of these studies are beyond the scope of this article and the interested reader is referred to relevant literature.[28–32]

Psychometric tests

Psychometric tests can be applied to detect and quantitate subtle abnormalities of mental function in patients with liver diseases, who have subclinical hepatic encephalopathy or early prestupor stages of hepatic encephalopathy (that is, many ambulatory patients with cirrhosis).[15] Simple psychometric tests include orientation to time, person, and place, recall of current events, subtraction of serial sevens, handwriting, and figure drawing. The inability to draw a five pointed star (constructional or ideational dyspraxia) has received special attention.[33] Of the many quantitative psychometric tests available, one that is easy to apply and has been extensively used in the assessment of early hepatic encephalopathy is a modification of the Reitan trail making test, known as the number connection test.[34] Repeated application of this test can be useful, but care must be taken to exclude an effect of learning and age on test scores.[35 36] In addition, tests of reaction times to auditory or visual

Table 2 Grading of electroencephalographic changes in hepatic encephalopathy

Grade	*Features*
A	Generalised suppression of alpha rhythm
B	Unstable alpha rhythm with paroxysmal waves at 5 to 7 per second; occasional underlying fast activity
C	Runs of medium voltage 5 to 6 per second waves bilaterally over frontal and temporal lobes; alpha rhythm seen occasionally
D	Constant 5 to 6 per second waves in all areas
E	Bilaterally synchronous, 2 to 3 per second waves, predominating over frontal lobes and spreading backward to occipital lobes; occasional short-lived appearance of faster rhythms (5 to 6 per second)

From Parsons-Smith *et al.*[22]

Table 3 Factors that may precipitate hepatic encephalopathy

Oral protein load Upper gastrointestinal bleed Constipation	Act through gut factors
Diarrhoea and vomiting Diuretic therapy Abdominal paracentesis	Dehydration; electrolyte and acid/base imbalance (for example, hypokalaemic alkalosis)
Hypoxia Hypotension Anaemia Hypoglycaemia	Adverse effects on both liver and brain
Sedative/hypnotic drugs* Azotaemia† Infection‡ Induction of medical or surgical portal-systemic shunt General surgery	

*Includes drugs acting on the $GABA_A$/benzodiazepine receptor complex.
†Blood urea is a source of intestinal ammonia.
‡May cause dehydration and augmented release of nitrogenous substances.

stimuli may also be useful.[8] Detailed psychometric testing, involving the application of a battery of psychometric tests, is more sensitive in the detection of subtle deficits of mental function than either conventional clinical assessment of the mental state or the EEG.[8 37] Results of quantitative psychometric tests should be assessed in relation to age related data on normal subjects and an assessment of cognitive dysfunction should be based on a test set that allows the assessment of several different cerebral functions.[38]

Electrophysiology

Electrophysiological evaluation of hepatic encephalopathy is not routine.[15] The EEG may be abnormal in subclinical hepatic encephalopathy and early stages of hepatic encephalopathy. It is usually abnormal in late stages of hepatic encephalopathy. The EEG abnormalities that occur in hepatic encephalopathy are non-specific, being found in other metabolic encephalopathies. The main EEG abnormalities in hepatic encephalopathy are a progressive bilaterally synchronous decrease in wave frequency and an increase in wave amplitude. Preterminally there is a loss of wave amplitude (table 2).[22] In common with other metabolic encephalopathies, paroxysmal triphasic waves may occur, even in the early stages of hepatic encephalopathy, and are characteristically associated with a frontal to occipital phase shift.[39] A good correlation between the clinical stage of hepatic encephalopathy and the degree of abnormality of the EEG is not invariable.[33] Abnormalities of event related potentials (for example, the P300 wave) may be detected in patients with subclinical hepatic encephalopathy.[40 41]

PRECIPITATING FACTORS

Any factor which increases portal-systemic shunting (for example, surgically created portal-systemic shunt or transjugular intrahepatic portal-systemic shunt (TIPSS)) or further impairs hepatocellular function (for example, surgery under general anaesthesia) will tend to precipitate or exacerbate hepatic encephalopathy. Table 3 shows some of the many recognised precipitating factors. These tend to be more readily apparent in patients with chronic, rather than acute, liver failure. With the notable exception of sedative-hypnotic drugs that act on the γ-aminobutyric acid A ($GABA_A$)/benzodiazepine receptor complex (for example, benzodiazepines and barbiturates), the relationship of common precipitating factors to pathogenesis is poorly understood.

PROGNOSIS

In a patient with chronic hepatocellular disease an episode of hepatic encephalopathy usually resolves if overall hepatocellular function remains relatively well maintained and a precipitating factor can be identified and corrected. Alternatively, if an obvious precipitating factor cannot be identified, a poor prognosis is likely. About 50% of patients with cirrhosis die within one year of their first episode of hepatic encephalopathy and about 80% within five years, not as a direct consequence of hepatic encephalopathy, but as a consequence of chronic hepatocellular failure.[42]

NEUROPATHOLOGY

Structural changes in neurons, as assessed by light microscopy, are not found in the brains of patients who had hepatic encephalopathy when they died.[13] However, in patients who die with cirrhosis and portal-systemic shunts, an increase in the number and size of astrocytes, particularly Alzheimer type 2 astrocytes is commonly found.[13] Such changes may be induced by raised concentrations of ammonia,[43] but they are not a feature of the brain in fulminant hepatic failure.

PATHOGENESIS

A normally functioning liver is necessary to maintain normal brain function. Theoretically, hepatic encephalopathy might occur as a consequence of (1) reduced synthesis by the failing liver of a substance(s) necessary for normal brain function; (2) synthesis by the failing liver of an encephalopathogenic substance(s); and (3) reduced extraction and metabolism by the failing liver of encephalopathogenic substances or precursors of such substances. Available data that have potential relevance to the pathogenesis of hepatic encephalopathy apply predominantly to the last of these three possibilities.

Traditionally gut factors have been considered to play important roles in pathogenesis, because hepatic encephalopathy may be precipitated by an oral protein load, a gastrointes-

Table 4 Treatment of hepatic encephalopathy

	Treatment	Comment
I.	Correction or removal of precipitating factors	Mandatory
II.	Minimise absorption of nitrogenous substances Dietary protein restriction Evacuation of bowel Lactulose (or a related sugar) and/or oral broad spectrum antibiotic (for example, neomycin)	Routine
III.	Reduction of portal-systemic shunting	Rarely practical
IV.	Direct reversal of neuropathophysiology Flumazenil	Experimental

tinal haemorrhage, or constipation (table 3) and may be ameliorated by evacuation of the bowel and dietary protein restriction (table 4).[33] The relationship of portal-systemic encephalopathy in the absence of hepatocellular failure to hepatic encephalopathy is uncertain. For example, in contrast to patients with chronic hepatic insufficiency, encephalopathy that develops in dogs with an Eck fistula (a portacaval shunt) fed a standard diet can be prevented by giving a palatable nutritious diet that prevents weight loss and malnutrition, but not hepatic atrophy.[44] It has been proposed that in liver failure some gut derived neuroactive substances (for example, ammonia, GABA), that are present in increased concentrations in peripheral blood plasma, cross the blood-brain barrier and modulate brain function.[2 45] The blood-brain barrier is normally highly permeable to non-polar substances, such as non-ionic ammonia and benzodiazepine receptor ligands, but has a low permeability to polar compounds. However, in liver failure the permeability of this barrier to polar compounds, some of which are neuroinhibitory (for example, GABA), may increase.[46]

It is widely thought that the pathogenesis of hepatic encephalopathy is multifactorial. Currently, the two factors considered to be most important in pathogenesis are raised brain concentrations of ammonia and increased GABA mediated neurotransmission. The hypotheses implicating these two phenomena have appeared to be unrelated, but recent evidence suggests that they may be interrelated and mutually compatible.[46]

Increased GABA mediated neurotransmission is associated with impairments of motor function and decreased consciousness,[2 47] two of the cardinal manifestations of hepatic encephalopathy. There are four lines of evidence, largely from studies in animal models, which support the hypothesis that increased GABA mediated neurotransmission contributes to the manifestations of hepatic encephalopathy.[47] Potential mechanisms for increased GABAergic tone in hepatic encephalopathy include increased availability of GABA in synaptic clefts, due to loss of presynaptic feedback inhibition of GABA release associated with a decrease in $GABA_B$ receptors and/or increased blood to brain transfer of GABA,[46] increased astrocytic synthesis, and release of neurosteroids[43] and increased brain concentrations of natural benzodiazepine receptor agonist ligands.[2 48] The distribution of increased concentrations of natural benzodiazepines in the brain in liver failure may be heterogeneous[2] and specific factors, such as increased synaptic concentrations of GABA and the modestly increased concentrations of ammonia that occur in liver failure (see below), may potentiate the neuroinhibitory actions of natural benzodiazepines in liver failure.[2 48] Increased sensitivity of the brain of patients with cirrhosis to an exogenously administered benzodiazepine has been demonstrated.[20] In assessing the potential role of natural benzodiazepines in an encephalopathic patient with liver disease, it may not be easy to ascertain whether the patient had taken pharmaceutical benzodiazepines recently, as several of the natural benzodiazepines present in increased concentrations not only in the brain,[2 48] but also in plasma[49] in liver failure, seem to be identical to pharmaceutical benzodiazepines.

Ammonia was originally implicated in the pathogenesis of hepatic encephalopathy because it was recognised to be neurotoxic, plasma concentrations tend to be raised in patients with liver failure, and plasma ammonia readily enters the brain.[2 46] However, plasma ammonia concentrations higher than those usually found in liver failure (>1 mM) are associated with effects that do not mimic hepatic encephalopathy; in particular, they suppress inhibitory postsynaptic potential formation and hence promote phenomena attributable to neuronal excitation, such as a preconvulsive state and seizures.[2 46 50 51] Interestingly, administration of ammonium salts to cirrhotic patients does not readily induce EEG changes similar to those found in hepatic encephalopathy.[52]

The question arises whether the modestly raised plasma ammonia concentrations typically found in patients with precomatose hepatic encephalopathy (stages I-III) (100-400 μM)[46] can be associated with an ammonia induced enhancement of neuronal inhibition. This could occur if ammonia at these concentrations promotes astrocytic synthesis of neurosteroids that activate the $GABA_A$ receptor complex[43 46] or acts directly on this complex to enhance neuronal inhibition.[46] Recently, ammonia, in concentrations that commonly occur in plasma in liver failure (but not higher concentrations), has been shown to facilitate GABA-gated Cl^- currents in cultured cortical neurons[46] and to increase selectively the binding of agonist ligands, including the benzodiazepine receptor agonist, flunitrazepam, to the $GABA_A$/benzodiazepine receptor complex.[46] Thus in liver failure ammonia may potentiate GABAergic neurotransmission as a consequence of direct synergistic interactions with agonist ligands of the $GABA_A$/benzodiazepine receptor complex. Furthermore, ammonia appears to increase the binding of agonist ligands, such as diazepam binding inhibitor, to astrocytic peripheral benzodiazepine receptors,[43] the density of which is increased in patients who die with cirrhosis and hepatic encephalopathy.[53] These findings raise the possibility that in liver failure there may be an increase in peripheral benzodiazepine receptor mediated astrocytic synthesis

and release of neurosteroids, such as 3-α-hydroxysteroids. Such compounds, by interacting with specific steroid binding sites on the $GABA_A$ receptor complex, induce positive modulation of the $GABA_A$ receptor[54] and hence may contribute to increased inhibitory neurotransmission in hepatic encephalopathy.[2 43 46]

It has been postulated that additional disturbances of neuron-astrocyte interactions, some of which may be induced by ammonia, may also contribute to hepatic encephalopathy.[3 43 55] In addition, possible roles for neurotransmitter systems, other than the GABA system, in hepatic encephalopathy have been postulated—for example, the glutamate, dopamine, serotonin, and opioid systems.[3] The demonstration of impaired astrocytic uptake of glutamate and down regulation of glutamate binding sites in animal models of hepatic encephalopathy,[3] may imply a decrease in excitatory glutamatergic neurotransmission. Furthermore, some of the symptomatology of hepatic encephalopathy can be explained by disturbances in functional loops of basal ganglia, which could arise as a consequence of an imbalance between glutamatergic and GABAergic neurotransmission. Evidence supporting hypotheses of pathogenesis that implicate primary roles for impaired brain energy metabolism, the synergistic action of neurotoxins such as mercaptans and short chain fatty acids with ammonia, and false neurotransmitters (including an imbalance of adrenergic, serotoninergic, and dopaminergic neurotransmission) is currently considered to be less strong than evidence supporting the ammonia and GABAergic neurotransmission hypotheses.[2] Decreased cerebral oxygen consumption and glucose metabolism may be consequences of hepatic encephalopathy rather than primary pathogenic factors.[2] Roles for zinc[56] and manganese[3] in hepatic encephalopathy have also been suggested.

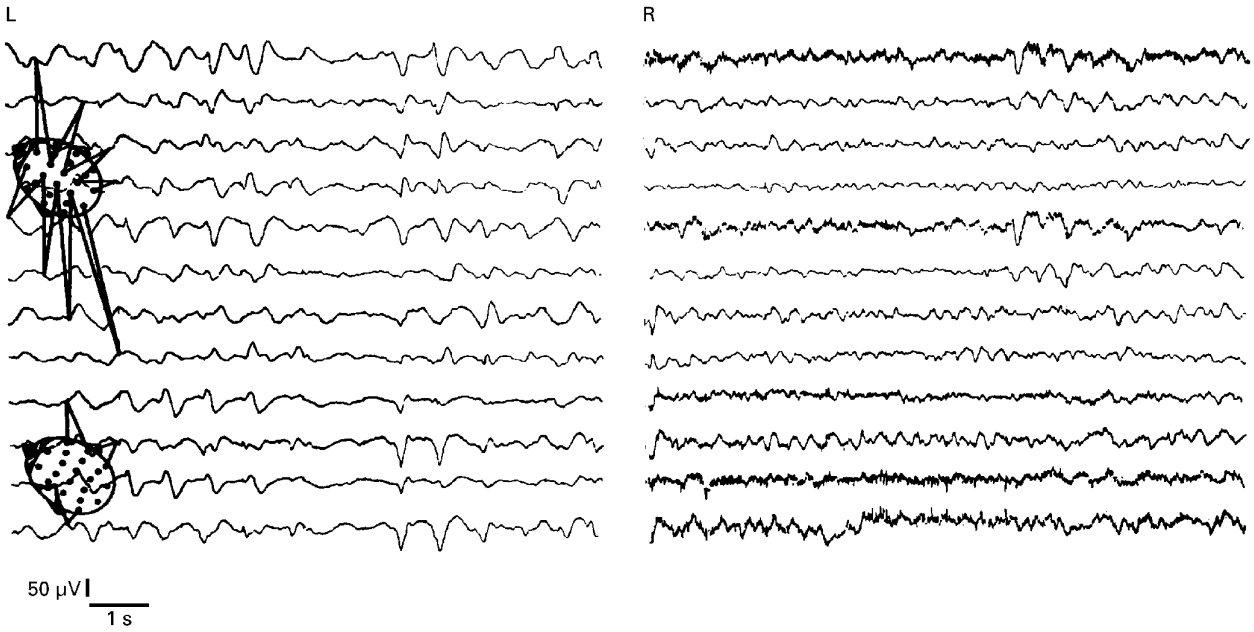
TREATMENT

The following general principles are relevant to the management of hepatic encephalopathy (table 4): (1) removal or correction of any precipitating factors (table 3); (2) reduction of absorption of nitrogenous substances from the intestinal tract (for example, evacuation of the bowel by purgation, enemas, and elimination of dietary protein);[57] (3) reduction of increased portal-systemic shunting; and (4) reversal of contributing neuropathophysiological events by administration of drugs that act directly on the brain. Approach (1) is mandatory; (2) is routine; (3) is rarely practical; and (4) is still experimental. The section on pathogenesis above provides rationales for treatments for hepatic encephalopathy that decrease GABA mediated inhibitory neurotransmission and/or lower ammonia concentrations.

Certain treatments for hepatic encephalopathy have relevance to specific hypotheses of pathogenesis. For example, evacuation of the bowel or oral administration of lactulose or broad spectrum antibiotics (for example, neomycin) tend to reduce intestinal absorption of ammonia.[57] However, these therapeutic interventions affect the metabolism of many compounds other than ammonia and, consequently, they do not have specificity for the ammonia hypothesis. Potential treatments that induce relatively selective decreases in plasma ammonia concentrations include arginine, ornithine, and sodium benzoate.[58–60] The rationales for levodopa, bromocriptine, and infusions of branched chain amino acids are based on the false neurotransmitter hypothesis; the efficacy of none of these three treatments has been convincingly shown.[2] The rationale for the benzodiazepine receptor antagonist flumazenil is based on the GABAergic neurotransmission hypothesis.[61]

The association of increased brain concentrations of natural benzodiazepine receptor agonists with hepatic encephalopathy[2 48] provides a strong justification for giving a benzodiazepine receptor antagonist in the management of hepatic encephalopathy. The imidazobenzodiazepine, flumazenil, is a selective, high affinity, competitive antagonist of central benzodiazepine receptors on the $GABA_A$/benzodiazepine receptor complex. It rapidly gains access to these receptors after its intravenous administration.[2 62] It competes with high specificity with benzodiazepine receptor agonist ligands (for example, diazepam) for binding to these receptors and rapidly reverses neurological effects attributable to benzodiazepine agonist induced enhancement of GABAergic neurotransmission.[62] Current evidence suggests that GABAergic tone may be increased in hepatic encephalopathy, not only by benzodiazepine agonists, but also by mechanisms that are independent of these ligands (see Pathogenesis section). Thus the reduction in GABAergic tone in hepatic encephalopathy induced by antagonising the effects of natural benzodiazepine receptor agonists may be insufficient to normalise GABAergic tone and, consequently, may be associated, at the most, with only a partial amelioration of hepatic encephalopathy. It should be noted that antagonists of the central benzodiazepine receptor with weak partial agonist actions, such as flumazenil have an acceptable safety profile, because an overdose is likely to be associated with only mild diazepam-like effects.

Anecdotal reports of uncontrolled observations have suggested that a benzodiazepine antagonist may be useful in the management of hepatic encephalopathy. When flumazenil has been given parenterally, usually as intravenous bolus injections, clinical and electrophysiological ameliorations of hepatic encephalopathy have been documented in patients with clinically and electrophysiologically stable hepatic encephalopathy due to fulminant hepatic failure or cirrhosis (fig 1).[2 61–64] Characteristics of the responses to intravenous injections of this drug are as follows:[65] (1) they are often reproducible in an individual patient; (2) they are inconsistent, occurring in only about 60% of patients; (3) they occur rapidly, within four minutes of drug administration; (4) substantial ameliorations occur after low doses—for example, 0.3-0.5 mg—suggesting that only small amounts of the drug are necessary to occupy a large proportion of central benzodiazepine



Electrophysiological amelioration of hepatic encephalopathy in a 58 year old woman with cirrhosis after intravenous flumazenil. L Before treatment, when the patient was in stage IV hepatic encephalopathy, the EEG showed continuous 1 to 2 Hz triphasic activity. R Forty seconds after the administration of 0.3 mg flumazenil, the severity of hepatic encephalopathy had improved to stage II, and the EEG showed 4 to 5 Hz theta background activity. From Bansky G, Meier PJ, Ziegler WH, Walser H, Schmid M, Huber M. Lancet 1985;i:1324-5. © by the Lancet Ltd, 1985.

receptors; (5) ameliorations are always of short duration, consistent with the rapid rate of metabolism of the drug;[62] and (6) ameliorations are usually partial (for example, one or two clinical stages). In addition, an intravenous infusion of flumazenil (0.2 mg) has been shown to improve the cognitive component of a reaction time task in patients with subclinical hepatic encephalopathy.[66] Controlled trials have confirmed that the mean severity of hepatic encephalopathy in cirrhotic patients after treatment with parenteral flumazenil was significantly less than that after treatment with placebo.[67] In a single case study oral flumazenil (25 mg twice daily) successfully reversed the manifestations of chronic intractable hepatic encephalopathy and normalised oral protein tolerance.[68]

Because of the specificity of the action of flumazenil on the central benzodiazepine receptor and its weak partial agonist properties at this receptor, the most logical explanation for a flumazenil induced amelioration of hepatic encephalopathy is that the drug reduces increased GABAergic tone by displacing natural benzodiazepine agonist ligands from central benzodiazepine receptors. This phenomenon would lead to a dysinhibition of neurons and hence an increase in their spontaneous activity. Furthermore, the transient anxiety that consistently occurred shortly after the oral administration of flumazenil to a patient with chronic portal-systemic encephalopathy[68] can also be explained by this mechanism. The efficacy of flumazenil in reversing manifestations of hepatic encephalopathy may be related primarily to brain concentrations of natural benzodiazepine agonists.

The available data suggest that augmentation of GABAergic tone by natural benzodiazepine agonists makes a substantial contribution to the manifestations of hepatic encephalopathy in a majority of patients with liver failure. The data on the effects of flumazenil on hepatic encephalopathy in humans may, however, underestimate the magnitude of this phenomenon for the following reasons: (1) other complicating metabolic disturbances in liver failure may mask the contribution of natural benzodiazepine agonist ligands; (2) the design of the published controlled trials of flumazenil in patients with hepatic encephalopathy[67] may not have been optimal; (3) flumazenil does not have the properties of an ideal benzodiazepine antagonist for administration to patients with hepatic encephalopathy;[47 65] and (4) factors other than natural benzodiazepines may contribute to increased GABAergic tone in hepatic encephalopathy (see Pathogenesis section). None of the traditional treatments for hepatic encephalopathy, such as lactulose and neomycin, induce such substantial ameliorations of hepatic encephalopathy so often and so rapidly after their administration as those that have been documented after intravenous flumazenil. Demonstration of the efficacy of other more appropriate benzodiazepine receptor ligands[69] and/or specific antagonists of other neurotransmitter systems in reversing manifestations of hepatic encephalopathy may open up new pharmacological horizons in the management of this syndrome.

Fulminant hepatic failure

Convincing evidence that hepatic encephalopathy in fulminant hepatic failure and hepatic encephalopathy complicating cirrhosis involve different mechanisms is not available. However, fulminant hepatic failure is a syndrome of multiorgan failure, the neurological manifestations of which are not limited to hepatic

encephalopathy. In particular, raised ICP due to cerebral oedema, and hypoglycaemia may also contribute to neurological deficits, including encephalopathy. Thus in general, neurological abnormalities associated with fulminant hepatic failure tend to be more complex than those associated with hepatic encephalopathy complicating chronic liver failure. Accordingly, the neurological status of patients with fulminant hepatic failure usually requires more extensive evaluation than that of patients with cirrhosis and some of the treatments indicated for neurological deficits associated with fulminant hepatic failure are not indicated for neurological consequences of chronic liver disease.

At least three potential roles of ammonia in the pathophysiology of fulminant hepatic failure have been proposed: (1) it is postulated to contribute to hepatic encephalopathy (see section on pathogenesis of hepatic encephalopathy); (2) it may contribute to the pathogenesis of cerebral oedema and raised ICP by promoting increased conversion of glutamate to the organic osmolyte glutamine in astrocytes, thereby inducing impaired cellular osmoregulation;[70 71] and (3) ammonia concentrations higher than those usually associated with hepatic encephalopathy in cirrhotic patients may occur and may be responsible for neuroexcitatory phenomena, such as psychomotor agitation, multifocal random muscle twitching, mania, delirium, and/or seizures, that sometimes occur during the course of fulminant hepatic failure, particularly in children.[46]

CEREBRAL OEDEMA AND RAISED INTRACRANIAL PRESSURE

Cerebral oedema and raised ICP seem to occur rarely in patients with chronic liver failure.[71] They are much better recognised as serious complications of fulminant hepatic failure, occurring in 75%-80% of cases that progress to stage IV encephalopathy.[71] Cerebral oedema and raised ICP are probably manifestations of the same pathological process. Cerebral oedema leads to raised ICP once the compliance of the brain cavity has been exceeded.[70] It seems that rapid rather than slow loss of hepatocellular function favours the development of cerebral oedema and raised ICP, possibly because an appreciable time interval is required for osmolar compensation to take place in response to changes in metabolites in the brain when the liver fails.[71] An acute or chronic increase in ICP in fulminant hepatic failure may lead to brain ischaemia due to compression of cerebral vasculature[72] and/or brain stem herniation. Indeed, herniation of the cerebellum or uncinate process secondary to raised ICP is a common cause of death in patients with fulminant hepatic failure.[73] The pathogenesis of cerebral oedema in fulminant hepatic failure is currently uncertain; potential mechanisms include a breakdown of the blood-brain barrier (vasogenic oedema) and impaired cellular osmoregulation (cellular or cytotoxic oedema),[70 71] with the latter mechanism being favoured by evidence from an electron microscopic study.[74] In the late stages of encephalopathy loss of autoregulation of the cerebral circulation[75] may contribute to neurological deficits. The development of cerebral oedema and raised ICP occurs together with hepatic encephalopathy in fulminant hepatic failure. Clinical signs often preceding or occurring with increases in ICP in fulminant hepatic failure include psychomotor agitation, hypertension, hyperventilation, vomiting, and increased muscle tone.[76] However, clinical signs are unreliable in the evaluation of raised ICP in patients with fulminant hepatic failure, particularly if the patient is receiving artificial ventilation.

PROGNOSIS

In general, when hepatic encephalopathy is associated with fulminant hepatic failure the mortality is high, particularly if encephalopathy is severe and prolonged, if encephalopathy develops rapidly after the onset of jaundice,[10] and if encephalopathy rapidly progresses to stage IV. In fulminant hepatic failure no relationship has been found between the presence or absence of motor responses to pain, the pupillary light reflex, and the oculocephalic reflex and subsequent recovery of consciousness.[77] However, loss of the oculovestibular reflex in fulminant hepatic failure is usually associated with a fatal outcome.[77] Resolution of intracranial hypertension, as indicated by an epidural pressure transducer (see Management section), may be a reliable prognostic indicator of recovery without liver transplantation.[78 79]

MANAGEMENT

Frequent and precise monitoring of neurological status, using an appropriate coma profile, is desirable.[80] It is essential to estimate blood sugar at frequent intervals so that hypoglycaemia can be detected early and its neurological consequences corrected promptly by administration of hypertonic dextrose into a central vein.

Continuous bipolar EEG monitoring may facilitate the early detection and treatment of complications, such as hypoglycaemia or intracranial hypertension, in patients not receiving ventilatory support. The development of these complications is usually heralded by a sudden increase in the degree of abnormality of the EEG.[81] The EEG may disclose the presence of complex partial seizures.

Cerebral oedema is not reliably detected by CT.[82] As sudden and repeated increases of ICP, that require immediate treatment, are to be expected, CT cannot be recommended.

Ideally, ICP should be monitored by direct measurement in the late stages of encephalopathy, and this is considered mandatory by some authorities when liver transplantation is under serious consideration.[78 79 83 84] The creation of a burr hole and placement of a stable, drift free, pressure transducer intracranially enables direct, accurate, and continuous measurements of ICP. When a decision to embark on such measurements is made, it is first necessary to correct, at least partially, the associated coagu-

lopathy by giving fresh frozen plasma, or platelets, or both so that the prothrombin time is prolonged less than three seconds (Quick score at least 50%) and the platelet count at least 50 000/cu mm when the burr hole is made.[76] Epidural transducers are safer but less precise than subdural or parenchymal monitors.[85] Direct measurements of ICP enable the indications for treatment of raised ICP to be clearly defined and facilitate monitoring the effects of treatments on ICP.

The patient is nursed supine with the head and upper body raised 20°-30° above the horizontal.[76 86] Factors that increase ICP are avoided.[76] If psychomotor agitation becomes a problem, great caution must be exercised with the use of sedatives (for example, a small dose of a short acting benzodiazepine or a small dose of morphine) or paralysing agents and appropriate antidotes should be available (for example, flumazenil, naloxone).[76] Sedation or paralysis confound the use of changes in neurological status to monitor progression or recovery.[21] Cerebral perfusion pressure (mean arterial pressure minus intracranial pressure) should be maintained above 50 mm Hg to avoid hypoperfusion of the brain.[76] The ICP should be maintained below 20 mm Hg.[76] The efficacy of mannitol (0.5-1.0 g/kg intravenously over five minutes in the absence of renal failure) but not dexamethasone in lowering raised ICP in patients with fulminant hepatic failure has been shown in a controlled trial.[87] The value of controlled hyperventilation[88] or barbiturates[76 89] in the management of raised ICP has not been established.

As an indirect index of ICP, cerebral perfusion may be assessed non-invasively by continuous transcranial Doppler monitoring.[90 91]

It is sometimes uncertain whether the severely abnormal complex neurological status exibited by a patient with fulminant hepatic failure would be completely reversed either by a spontaneous improvement in hepatocellular function or by liver transplantation.[92 93] Whether certain clinical findings—for example, fixed dilated pupils, a low cerebral perfusion pressure (for example, <50 mm Hg), or a flat EEG recording for a specified period of time—imply neurological injury that is not reversible by liver transplantation has not been clearly defined (R Williams, personal communication) and the interpretation of such findings may be confounded if barbiturates are used in the management of raised ICP.[76] However, in this context it has been suggested that liver transplantation is contraindicated if medical therapy has failed to control intracranial hypertension.[79]

Degenerative disorders

Rare CNS degenerative disorders that may occur in patients with longstanding cirrhosis and increased portal-systemic shunting include hepatocerebral degeneration and transverse myelitis. The former disorder is associated with irreversible neuronal injury or degeneration and the latter with demyelination. Patients may have chronic cerebellar and basal ganglia signs with parkinsonism, focal cerebral symptoms, epilepsy, dementia, and/or paraplegia. The neurological deficits in these syndromes respond only partially to treatment for hepatic encephalopathy. The precise relationship of these syndromes to chronic hepatic insufficiency or chronic hepatic encephalopathy is uncertain.[94–97]

Wilson's disease

Wilson's disease is a genetic disorder of copper metabolism. The responsible gene has been identified and cloned and is located on chromosome 13.[98] Most of the clinical manifestations of Wilson's disease appear to be the direct result of excessive accumulation of copper in various organ systems, particularly the liver and brain.

CLINICAL FEATURES

Presentation is unusual before the age of 5 years or after the age of 30 years.[99] Typically, patients present with hepatic and/or neurological dysfunction.[100]

Hepatic

Hepatic dysfunction tends to become manifest at a younger age than neurological dysfunction. The best recognised hepatic lesions due to Wilson's disease are a fulminant hepatic failure-like syndrome, chronic active hepatitis, and cirrhosis.[100]

Neurological

Neurological Wilson's disease usually presents in the second or third decade of life and may occur without overt clinical signs of liver disease.[101] Initial symptoms may be subtle, such as abnormal behaviour and deteriorating performance at school. Subsequently more overt neurological deficits occur; in particular, incoordination (especially involving fine movements), clumsiness, slowness of voluntary limb movements and speech, tremor, dysarthria, excessive salivation, ataxia, dysphagia, and mask-like facies.[101–104] Movement disorders tend to dominate the neurological features (table 5). In patients who have been inadequately treated, late neurological manifestations include dystonia, spasticity, grand mal seizures, rigidity, and flexion contractures. Neurological deterioration is progressive without treatment. However, chelation therapy

Table 5 Neurological symptoms and signs in Wilson's disease

Symptoms and signs	*Patients (%)*
Dysdiadochokinesia	51
Dysarthria	49
Bradykinesia	38
Posture tremor	31
Wing beating	31
Action tremor	31
Writing tremor	29
Resting tremor	20
Hyomimia	20
Gait disturbance	18
Hypersalivation	18
Chorea	13
Head tremor	13
Dystonia	11

Data based on a study of 45 patients (from Oder *et al* [101]).

often reverses the neurological sequelae of the disease, particularly if treatment is instituted at an early stage.[105 106]

Recently, by the application of exploratory factor analysis to correlate neuropsychiatric symptoms with structural lesions found on MRI, three distinct subsets of patients with Wilson's disease have been recognised:[107]

Pseudoparkinsonian—These patients, with dilatation of the third ventricle, have signs of bradykinesia, rigidity, cognitive impairment, and an organic mood syndrome.

Pseudosclerosis—These patients, with focal thalamic lesions, exhibit ataxia, tremor, and reduced functional capacity.

Dyskinesia—These patients, with focal abnormalities in the putamen and globus pallidus, exhibit dyskinesia, dysarthria, and an organic personality syndrome.

The incidence of seizures in patients with Wilson's disease (about 6%) is about 10-fold greater than that in the general population.[108] The seizures usually have a focal cortical origin, with or without secondary generalisation.[109]

Psychiatric

In about a third of cases psychiatric or behavioural symptoms are the presenting or predominant manifestation of the disease.[102 110] At the time of presentation at least one half of patients have some evidence of psychiatric or behavioural disturbance.[111 112] Psychiatric manifestations of Wilson's disease are protean, but are predominantly personality changes. Four basic categories of disturbance have been described: behavioural/personality, affective, schizophrenia-like, and cognitive.[113 114] The incidence of schizophrenia-like symptoms may not be increased in Wilson's disease and depression and cognitive impairment may largely reflect the degree of hepatocellular insufficiency. Patients often exhibit personality changes with lability of mood, emotionalism, and sometimes impulsive and antisocial behaviour.[109] Psychiatric symptoms often correlate with the severity of the neurological disturbances.[111 114] Both the effects of cerebral copper deposition and the reaction to progressive neurological deficits may contribute to the psychobehavioural disturbances. The incidence of psychoneuroses, depression, and schizophrenia-like psychosis is low[111] and the incidence of delusional disorders and affective disorders may not be increased.[109] Psychometric analyses have disclosed minimal impairment of cognitive function in Wilson's disease.[109 115–117]

Ophthalmological

The Kayser-Fleischer ring is a golden brown or greenish discolouration in the limbic region of the cornea due to copper deposition in Descemet's membrane. The rings are almost invariably present in untreated patients with neurological manifestations of the disease.[110 118] Kayser-Fleischer rings may not be visible to the naked eye; their presence should be sought or confirmed by an ophthalmologist using a slit lamp or gonioscopy. Sunflower cataracts, another ocular manifestation of the disease, are less common than Kayser-Fleischer rings.[119]

Haematological

Intravascular haemolysis, which may be acute, often occurs.[100]

NEUROPATHOLOGY

Histological studies of the brain at necropsy have disclosed degeneration and cavitation involving the putamen, globus pallidus, caudate nucleus, thalamus, and, less often, the frontal cortex.[120] The most severely affected regions of the brain are the basal ganglia, particularly the putamen.[109 121] Abnormalities of the white matter and cerebral cortex occur in about 10% of cases.[110] Total cerebral copper content seems to correlate with the severity of both the histological abnormalities and neurological symptoms,[106 120] but copper concentrations in affected and unaffected regions of the brain are similar.[110]

CEREBRAL IMAGING

Cerebral CT abnormalities seem to correlate with neurological deficits and histological findings in the CNS.[122 123] The cranial lesions are typically bilateral and have been divided into two categories:[124] (1) well defined slit-like low attenuation foci involving the basal ganglia, particularly the putamen, and (2) larger regions of low attenuation in the basal ganglia, thalamus, or dentate nucleus. Widening of the frontal horns of the lateral ventricles and diffuse cerebral and cerebellar atrophy have also been reported.[122 123] Brain CT is likely to be abnormal in 50% of asymptomatic patients and 75% of patients with hepatic dysfunction.[123] MRI of the brain seems to be more sensitive than CT in detecting early lesions[125] and has shown an apparently distinct "face of the giant panda" sign.[126] In contrast to CT findings, MRI abnormalities and neurological deficits correlate poorly.[127] Cranial CT and MRI findings (other than brain atrophy) are usually reversed by chelation therapy.[128 129] Involvement of the CNS in Wilson's disease has also been evaluated using PET[129 130] and SPECT.[129] The abnormalities found using these techniques improve with chelation therapy.[129]

DIAGNOSIS

The diagnosis of Wilson's disease should be based on confirmatory clinical and biochemical data.[131] In a patient with neurological symptoms or signs a diagnosis of Wilson's disease can be made if Kayser-Fleischer rings are present and the caeruloplasmin concentration is <20 mg/dl. Eighty to ninety per cent of patients with the disease have low serum caeruloplasmin concentrations (<20 mg/dl).[102 110] Urinary copper excretion is >100 μg/24 hours (normal <40) in most patients with symptomatic disease.[124] Measurement of the hepatic copper concentration is necessary to establish a diagnosis of Wilson's disease in the absence of Kayser-Fleischer rings, a low serum caeruloplasmin, or neurological abnormalities. The demonstration of a lack of incorporation of

radiocopper (^{64}Cu) into caeruloplasmin can be used to confirm the diagnosis in rare difficult cases.[132] Kayser-Fleischer rings may be found in certain other chronic liver diseases, notably chronic cholestatic disorders, such as primary biliary cirrhosis, that are not associated with focal CNS functional deficits and are usually readily distinguished from Wilson's disease.

PATHOGENESIS

The fundamental cause of the copper overload in Wilson's disease is thought to be impaired biliary secretion of copper due to a hepatocellular lysosomal defect.[133] Confirmation that the primary defect resides within the liver is provided by the prompt reversal of the abnormalities of copper metabolism after orthotopic liver transplantation.[134]

NATURAL HISTORY

The natural history of Wilson's disease can be divided into four stages.[124]

Stage I

During this initial phase copper accumulates at cytosolic hepatocellular binding sites and patients are usually asymptomatic.

Stage II

When cytosolic binding sites become saturated further accumulation of copper occurs in hepatocellular lysosomes and there may be release of copper into the systemic circulation. These phenomena may lead to hepatocellular necrosis and intravascular haemolysis, respectively. Thus stage II disease may be associated with hepatic and haematological abnormalities.

Stage III

During this stage there is not only continuing accumulation of copper in the liver, but also chronic accumulation of copper in the brain and other extrahepatic tissues. The clinical presentation of the disease depends on the rate of copper accumulation in different organ systems. It is typically during stage III disease that neurological abnormalities occur. However, if an inactive cirrhosis develops and cerebral accumulation of copper is slow, patients may remain asymptomatic for years.[135]

Stage IV

This is the stage in which normal copper balance has been achieved as a result of chelation therapy. Some patients continue to have residual neurological or hepatic dysfunction as a result of irreversible organ damage, whereas other patients, who previously had symptomatic disease, are asymptomatic.

TREATMENT

Once the diagnosis of presymptomatic or symptomatic Wilson's disease is established, lifelong chelation therapy should be commenced forthwith. It is routine to advise patients undergoing copper chelation therapy to avoid foods with a high copper content. Oral therapy with the copper chelating drug, D-penicillamine (250-500 mg four times a day before meals), usually results in complete reversal or substantial alleviation of hepatic, neurological, and psychiatric manifestations of the disease.[100] Supplementation with 25 mg oral pyridoxine daily is given routinely to counteract the antipyridoxine effect of D-penicillamine.[99] In about 20% of patients with neurological symptoms, worsening of neurological dysfunction may occur during the first four weeks of treatment,[106 136] and rarely neurological dysfunction may first become apparent shortly after initiating chelation therapy.[137] When neurological symptoms appear to be precipitated or exacerbated by D-penicillamine treatment, the dose can be decreased to 250 mg daily and subsequently increased by 250 mg/day every four to seven days until urinary copper excretion is >2 mg/day. An alternative approach is to initiate D-penicillamine treatment at a low dose in asymptomatic patients and patients with mild symptomatology[110 136 137] and gradually increase the dose to within the therapeutic range. Even if early clinical deterioration occurs, continued chelation therapy is mandatory.[106] Although various side effects[100 110] sometimes limit its use, D-penicillamine remains the treatment of first choice for this disorder. Chelation therapy should not be interrupted. Cessation of therapy may precipitate rapid and irreversible hepatic or neurological deterioration.[138 139] Trientine (triethylene tetramine dihydrochloride) is an alternative chelating agent that can be given to patients who experience severe toxic reactions to D-penicillamine.[139] Oral zinc may be given to the rare patient who cannot tolerate either D-penicillamine or trientine.[99 121] Oral zinc is the preferred treatment for Wilson's disease in some countries—for example, The Netherlands.

When psychiatric disturbances are troublesome psychotherapy together with tranquillisers or antidepressant drugs may be indicated in addition to copper chelation therapy. Phenothiazines may exacerbate both neurological and psychiatric manifestations of the disease. Most of the psychiatric manifestations, but particularly behavioural and cognitive deficits, usually respond to copper chelation therapy.[113 115] Psychometric testing in treated patients may be normal.[115] However, when patients with combined neurological and psychiatric abnormalities are diagnosed late in the clinical course of the disease, some psychiatric dysfunction may remain after treatment.[109 113]

Pregnancy is not contraindicated. Chelation therapy must be continued during pregnancy and pregnancy is not an indication to change the chelating agent being given.[140]

General surgery should, if possible, be avoided as it may precipitate neurological deterioration. However, liver transplantation must be seriously considered for patients who develop manifestations of acute or chronic hepatocellular failure[141 142] and for patients in whom conventional treatment has not achieved adequate copper chelation.[143] In general, liver transplantation is not recommended for patients with neurological deterioration alone.[141 142] Liver transplantation is associated with reversal of abnormalities of copper

metabolism,[134] although the reversal may not be complete.[143] It is also associated with substantial improvement in most symptoms and signs of the disease, including neurological abnormalities.[141 142]

SCREENING FOR WILSON'S DISEASE

It is imperative that all first degree relatives of a patient with Wilson's disease, who are older than 3 years, and especially siblings of the patient, be screened for the presence of the disease.[144] A simple screening evaluation for Wilson's disease consists of a slit lamp examination of the eyes, and measurements of serum caeruloplasmin and aminotransferases (ALT, AST). It is prudent to screen for Wilson's disease all patients with psychiatric disease, who have evidence of hepatic or neurological disease, who have a family history of Wilson's disease, or who are refractory to therapy for their psychiatric disease.

The pruritus of cholestasis

Pruritus is a common complication of intrahepatic or extrahepatic cholestatic disorders. The aetiology of this complication of cholestasis has not been established and conventional treatments tend to be empirical. Unrelieved pruritus of cholestasis may lead to severe sleep deprivation and even suicidal ideation. A recent hypothesis of the pathogenesis of the pruritus of cholestasis suggests that the neural events that initiate this form of pruritus may originate centrally in the CNS, rather than peripherally in the skin.[4] Three lines of evidence provide support for this hypothesis: (1) opioid agonists (for example, morphine) induce pruritus by a central mechanism;[4] (2) central opioidergic tone is increased in cholestasis;[4] and (3) opiate antagonists ameliorate the pruritus of cholestasis.[5] That central opioidergic tone is increased in patients with chronic cholestatic liver disease is illustrated by the striking opioid withdrawal-like syndrome that can be abruptly induced in such patients by the oral administration of a potent opiate antagonist.[145]

Fatigue

Patients with chronic liver disease, particularly chronic cholestatic liver diseases such as primary biliary cirrhosis, often complain of incapacitating fatigue that seems to be out of proportion to their general medical condition. Whether excessive fatigue has specificity for the syndrome of chronic cholestasis is uncertain. However, there is some evidence which suggests that altered central neurotransmission, possibly involving the serotonin system, may contribute to fatigue in patients with chronic liver disease.[6 7]

Summary

Hepatic encephalopathy is a syndrome of neuropsychiatric disturbances that complicates hepatocellular failure; it is associated with increased portal-systemic shunting. The spectrum of hepatic encephalopathy varies from mild intellectual impairment to deep coma, and includes manifestations of motor dysfunction, especially extrapyramidal signs, and asterixis. The diagnosis requires evidence of hepatocellular insufficiency and exclusion of other causes of encephalopathy. Hepatic encephalopathy occurs most often in cirrhotic patients with a precipitating factor. A cirrhotic patient with a normal neurological examination but abnormal results of psychometric or neuroelectrophysiological tests may have subclinical hepatic encephalopathy. The syndrome has been classified as a reversible metabolic encephalopathy with a multifactorial pathogenesis. Major hypotheses of pathogenesis implicate raised brain concentrations of ammonia and increased GABA mediated neurotransmission. Modestly raised concentrations of ammonia, increased brain concentrations of natural benzodiazepines, and increased availability of GABA at $GABA_A$ receptors appear to be factors which enhance GABAergic tone in liver failure, and hence contribute to impairments of motor function and decreased consciousness. Routine treatments correct precipitating factors and reduce intestinal absorption of nitrogenous compounds. Treatment with flumazenil is experimental. Fulminant hepatic failure is the syndrome of acute liver failure and hepatic encephalopathy, in which additional factors may contribute to encephalopathy, notably cerebral oedema and raised intracranial pressure, and hypoglycaemia. Rare degenerative neurological disorders in patients with longstanding cirrhosis include hepatocerebral degeneration and transverse myelitis.

Neurological manifestations of Wilson's disease are attributable to accumulation of copper in the brain as a consequence of a congenital impairment in the hepatocellular secretion of copper into bile. Movement disorders predominate and psychiatric disturbances are common. In untreated patients with neurological deficits, Kayser Fleischer rings and serum caeruloplasmin <20 mg/dl are diagnostic. The diagnosis is an indication for lifelong chelation therapy.

In patients with cholestatic liver diseases increased central opioidergic neurotransmission may contribute to pruritus.

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NEUROLOGICAL STAMP

Allesandro Volta (1745-87)

Lulgi Galvani (1738-98) thought that muscles contained animal electricity secreted by the brain and distributed by the nerves. Volta, a friend of Galvani, had difficulty with this concept of animal electricity. Volta showed that production of electric current did not need the presence of animal tissue, as Galvani and others had supposed. He also showed that muscles would contract with electrical stimulation but Galvani had also shown that the muscles of a frog twitched when touched by a spark from an electric machine or condenser such as a Leyden jar. Volta produced the famous voltaic pile consisting of alternating columns of zinc and silver discs separated by porous cardboard soaked in brine. This was essentially the first electrical battery and it revolutionised the study of electricity by producing a steady available source of current. This led almost immediately to William Nicholson's decomposition of water by electrolysis, and later the discovery by Humphrey Davy of potassium and other metals by the same process.

Volta was philatelically honoured in 1927 (Stanley Gibbons 209, Scott 189). It is in his honour that the unit of electrical potential or potential difference is called the volt.

L F HAAS

STAMP 1