= Hepatic encephalopathy =

Hepatic encephalopathy (HE) is the occurrence of confusion , altered level of consciousness , and coma as a result of liver failure . In the advanced stages it is called hepatic coma or coma hepaticum . It may ultimately lead to death .

It is caused by accumulation in the bloodstream of toxic substances that are normally removed by the liver . The diagnosis of hepatic encephalopathy requires the presence of impaired liver function and the exclusion of an alternative explanation for the symptoms . Blood tests (ammonia levels) may assist in the diagnosis . Attacks are often caused by another problem , such as infection or constipation .

Hepatic encephalopathy is reversible with treatment . This relies on suppressing the production of the toxic substances in the intestine and is most commonly done with the laxative lactulose or with non @-@ absorbable antibiotics . In addition , the treatment of any underlying condition may improve the symptoms . In particular settings , such as acute liver failure , the onset of encephalopathy may indicate the need for a liver transplant .

= = Signs and symptoms = =

The mildest form of hepatic encephalopathy is difficult to detect clinically , but may be demonstrated on neuropsychological testing . It is experienced as forgetfulness , mild confusion , and irritability . The first stage of hepatic encephalopathy is characterised by an inverted sleep @-@ wake pattern (sleeping by day , being awake at night) . The second stage is marked by lethargy and personality changes . The third stage is marked by worsened confusion . The fourth stage is marked by a progression to coma .

More severe forms of hepatic encephalopathy lead to a worsening level of consciousness , from lethargy to somnolence and eventually coma . In the intermediate stages , a characteristic jerking movement of the limbs is observed (asterixis , " liver flap " due to its flapping character) ; this disappears as the somnolence worsens . There is disorientation and amnesia , and uninhibited behaviour may occur . In the third stage , neurological examination may reveal clonus and positive Babinski sign . Coma and seizures represent the most advanced stage ; cerebral oedema (swelling of the brain tissue) leads to death .

Encephalopathy often occurs together with other symptoms and signs of liver failure . These may include jaundice (yellow discolouration of the skin and the whites of the eyes) , ascites (fluid accumulation in the abdominal cavity) , and peripheral edema (swelling of the legs due to fluid build @-@ up in the skin) . The tendon reflexes may be exaggerated , and the plantar reflex may be abnormal , namely extending rather than flexing (Babinski 's sign) in severe encephalopathy . A particular smell (foetor hepaticus) may be detected .

= = Causes = =

In a small proportion of cases , the encephalopathy is caused directly by liver failure ; this is more likely in acute liver failure . More commonly , especially in chronic liver disease , hepatic encephalopathy is caused or aggravated by an additional cause , and identifying these causes can be important to treat the episode effectively .

Hepatic encephalopathy may also occur after the creation of a transjugular intrahepatic portosystemic shunt (TIPSS) . This is used in the treatment of refractory ascites , bleeding from oesophageal varices and hepatorenal syndrome . TIPSS @-@ related encephalopathy occurs in about 30 % of cases , with the risk being higher in those with previous episodes of encephalopathy , higher age , female sex and liver disease due to causes other than alcohol .

= = Pathogenesis = =

There are various explanations why liver dysfunction or portosystemic shunting might lead to

encephalopathy . In healthy subjects , nitrogen @-@ containing compounds from the intestine , generated by gut bacteria from food , are transported by the portal vein to the liver , where 80 ? 90 % are metabolised through the urea cycle and / or excreted immediately . This process is impaired in all subtypes of hepatic encephalopathy , either because the hepatocytes (liver cells) are incapable of metabolising the waste products or because portal venous blood bypasses the liver through collateral circulation or a medically constructed shunt . Nitrogenous waste products accumulate in the systemic circulation (hence the older term " portosystemic encephalopathy ") . The most important waste product is ammonia (NH3) . This small molecule crosses the blood ? brain barrier and is absorbed and metabolised by the astrocytes , a population of cells in the brain that constitutes 30 % of the cerebral cortex . Astrocytes use ammonia when synthesising glutamine from glutamate . The increased levels of glutamine lead to an increase in osmotic pressure in the astrocytes , which become swollen . There is increased activity of the inhibitory ? @-@ aminobutyric acid (GABA) system , and the energy supply to other brain cells is decreased . This can be thought of as an example of brain oedema of the " cytotoxic " type .

Despite numerous studies demonstrating the central role of ammonia , ammonia levels don 't always correlate with the severity of the encephalopathy ; it is suspected that this means that more ammonia has already been absorbed into the brain in those with severe symptoms whose serum levels are relatively low . Other waste products implicated in hepatic encephalopathy include mercaptans (substances containing a thiol group) , short @-@ chain fatty acids and phenol .

Numerous other abnormalities have been described in hepatic encephalopathy , although their relative contribution to the disease state is uncertain . Loss of glutamate transporter gene expression (especially EAAT 2) has been attributed to acute liver failure . Benzodiazepine @-@ like compounds have been detected at increased levels as well as abnormalities in the GABA neurotransmission system . An imbalance between aromatic amino acids (phenylalanine , tryptophan and tyrosine) and branched @-@ chain amino acids (leucine , isoleucine and valine) has been described ; this would lead to the generation of false neurotransmitters (such octopamine and 2 @-@ hydroxyphenethylamine) . Dysregulation of the serotonin system , too , has been reported . Depletion of zinc and accumulation of manganese may play a role . Inflammation elsewhere in the body may precipitate encephalopathy through the action of cytokines and bacterial lipopolysaccharide on astrocytes .

= = Diagnosis = =

= = = Investigations = = =

The diagnosis of hepatic encephalopathy can only be made in the presence of confirmed liver disease (types A and C) or a portosystemic shunt (type B) , as its symptoms are similar to those encountered in other encephalopathies . To make the distinction , abnormal liver function tests and / or ultrasound suggesting liver disease are required , and ideally liver biopsy . The symptoms of hepatic encephalopathy may also arise from other conditions , such as cerebral haemorrhage and seizures (both of which are more common in chronic liver disease) . A CT scan of the brain may be required to exclude haemorrhage , and if seizure activity is suspected an electroencephalograph (EEG) study may be performed . Rarer mimics of encephalopathy are meningitis , encephalitis , Wernicke 's encephalopathy and Wilson 's disease ; these may be suspected on clinical grounds and confirmed with investigations .

The diagnosis of hepatic encephalopathy is a clinical one , once other causes for confusion or coma have been excluded ; no test fully diagnoses or excludes it . Serum ammonia levels are elevated in 90 % of patients , but not all hyperammonaemia (high ammonia levels) is associated with encephalopathy . A CT scan of the brain usually shows no abnormality except in stage IV encephalopathy , when cerebral oedema may be visible . Other neuroimaging modalities , such as magnetic resonance imaging (MRI) , are not currently regarded as useful , although they may show abnormalities . Electroencephalography shows no clear abnormalities in stage 0 , even if minimal

HE is present ; in stages I , II and III there are triphasic waves over the frontal lobes that oscillate at 5 Hz , and in stage IV there is slow delta wave activity . However , the changes in EEG are not typical enough to be useful in distinguishing hepatic encephalopathy from other conditions .

Once the diagnosis of encephalopathy has been made , efforts are made to exclude underlying causes (such as listed above in " causes ") . This requires blood tests (urea and electrolytes , full blood count , liver function tests) , usually a chest X @-@ ray , and urinalysis . If there is ascites , diagnostic paracentesis (removal of a fluid sample with a needle) may be required to identify spontaneous bacterial peritonitis (SBP) .

= = = Classification = = =

= = = = West Haven criteria = = = =

The severity of hepatic encephalopathy is graded with the West Haven Criteria ; this is based on the level of impairment of autonomy , changes in consciousness , intellectual function , behavior , and the dependence on therapy .

Grade 1 - Trivial lack of awareness ; euphoria or anxiety ; shortened attention span ; impaired performance of addition or subtraction

Grade 2 - Lethargy or apathy ; minimal disorientation for time or place ; subtle personality change ; inappropriate behaviour

Grade 3 - Somnolence to semistupor , but responsive to verbal stimuli ; confusion ; gross disorientation

Grade 4 - Coma

= = = = Types = = = =

A classification of hepatic encephalopathy was introduced at the World Congress of Gastroenterology 1998 in Vienna . According to this classification , hepatic encephalopathy is subdivided in type A , B and C depending on the underlying cause .

Type A (= acute) describes hepatic encephalopathy associated with acute liver failure , typically associated with cerebral oedema

Type B (= bypass) is caused by portal @-@ systemic shunting without associated intrinsic liver disease

Type C (= cirrhosis) occurs in patients with cirrhosis - this type is subdivided in episodic , persistent and minimal encephalopathy

The term minimal encephalopathy (MHE) is defined as encephalopathy that does not lead to clinically overt cognitive dysfunction , but can be demonstrated with neuropsychological studies . This is still an important finding , as minimal encephalopathy has been demonstrated to impair quality of life and increase the risk of involvement in road traffic accidents .

= = = = Minimal HE = = = =

The diagnosis of minimal hepatic encephalopathy requires neuropsychological testing by definition . Older tests include the " numbers connecting test " A and B (measuring the speed at which one could connect randomly dispersed numbers 1 ? 20) , the " block design test " and the " digit @-@ symbol test " . In 2009 an expert panel concluded that neuropsychological test batteries aimed at measuring multiple domains of cognitive function are generally more reliable than single tests , and tend to be more strongly correlated with functional status . Both the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and PSE @-@ Syndrom @-@ Test may be used for this purpose . The PSE @-@ Syndrom @-@ Test , developed in Germany and validated in several other European countries , incorporates older assessment tools such as the number connection test .

= = Treatment = =

Those with severe encephalopathy (stages 3 and 4) are at risk of obstructing their airway due to decreased protective reflexes such as the gag reflex . This can lead to respiratory arrest . Transferring the patient to a higher level of nursing care , such as an intensive care unit , is required and intubation of the airway is often necessary to prevent life @-@ threatening complications (e.g. , aspiration or respiratory failure) . Placement of a nasogastric tube permits the safe administration of nutrients and medication .

The treatment of hepatic encephalopathy depends on the suspected underlying cause (types A , B or C) and the presence or absence of underlying causes . If encephalopathy develops in acute liver failure (type A) , even in a mild form (grade 1 ? 2) , it indicates that a liver transplant may be required , and transfer to a specialist centre is advised . Hepatic encephalopathy type B may arise in those who have undergone a TIPSS procedure ; in most cases this resolves spontaneously or with the medical treatments discussed below , but in a small proportion of about 5 % , occlusion of the shunt is required to address the symptoms .

In hepatic encephalopathy type C , the identification and treatment of alternative or underlying causes is central to the initial management . Given the frequency of infection as the underlying cause , antibiotics are often administered empirically (without knowledge of the exact source and nature of the infection) . Once an episode of encephalopathy has been effectively treated , a decision may need to be made on whether to prepare for a liver transplant .

= = = Diet = = =

In the past , it was thought that consumption of protein even at normal levels increased the risk of hepatic encephalopathy . This has been shown to be incorrect . Furthermore , many people with chronic liver disease are malnourished and require adequate protein to maintain a stable body weight . A diet with adequate protein and energy is therefore recommended .

Dietary supplementation with Branched @-@ chain amino acids has shown improvement of encephalopathy and other complications of cirrhosis . Some studies have shown benefit of administration of probiotics (" healthy bacteria ") .

= = = Lactulose / lactitol = = =

Lactulose and lactitol are disaccharides that are not absorbed from the digestive tract . They are thought to decrease the generation of ammonia by bacteria , render the ammonia inabsorbable by converting it to ammonium (NH_4^+) ions , and increase transit of bowel content through the gut . Doses of 15 @-@ 30 ml are administered three times a day ; the result is aimed to be 3 ? 5 soft stools a day , or (in some settings) a stool pH of < 6 @.@ 0 . Lactulose may also be given by enema , especially if encephalopathy is severe . More commonly , phosphate enemas are used . This may relieve constipation , one of the causes of encephalopathy , and increase bowel transit .

A 2004 review by the Cochrane Collaboration concluded that there was insufficient evidence to determine whether lactulose and lactitol are of benefit for hepatic encephalopathy , but it remains the first @-@ line treatment for type C hepatic encephalopathy . In acute liver failure , it is unclear whether lactulose is beneficial . Furthermore , it may lead to bloating and as such interfere with a liver transplant procedure if required .

= = = Antibiotics = = =

The antibiotic rifaximin is typically recommended . It is a nonabsorbable antibiotic from the rifamycin class . This is thought to work in a similar way to other antibiotics , but without the complications attached to neomycin and metronidazole . The use of rifaximin is supported by better evidence than lactulose . Due to the long history and lower cost of lactulose use , rifaximin is only used as a

second @-@ line treatment if lactulose is poorly tolerated or not effective . When rifaximin is added to lactulose , the combination of the two may be more effective than each component separately . Rifaximin is more expensive than lactulose , but the cost may be offset by reduced hospital admissions for encephalopathy .

The antibiotics neomycin and metronidazole were previously used as a treatment for hepatic encephalopathy . The rationale of their use was the fact that ammonia and other waste products are generated and converted by intestinal bacteria , and killing these bacteria would reduce the generation of these waste products . Neomycin was chosen because of its low intestinal absorption , as neomycin and similar aminoglycoside antibiotics may cause hearing loss and renal failure if used parenterally . Later studies showed that neomycin was indeed absorbed enterally , with resultant complications . Metronidazole , similarly , was abandoned because prolonged use could cause peripheral neuropathy (nerve damage) , in addition to gastrointestinal side effects .

= = = LOLA = = =

A preparation of L @-@ ornithine and L @-@ aspartate (LOLA) is used to increase the generation of urea through the urea cycle , a metabolic pathway that removes ammonia by turning it into the neutral substance urea . It may be combined with lactulose and / or rifaximin if these alone are ineffective at controlling symptoms .

= = Epidemiology and prognosis = =

In those with cirrhosis , the risk of developing hepatic encephalopathy is 20 % per year , and at any time about 30 ? 45 % of people with cirrhosis exhibit evidence of overt encephalopathy . The prevalence of minimal hepatic encephalopathy detectable on formal neuropsychological testing is 60 ? 80 % ; this increases the likelihood of developing overt encephalopathy in the future . Once hepatic encephalopathy has developed , the prognosis is determined largely by other markers of liver failure , such as the levels of albumin (a protein produced by the liver) , the prothrombin time (a test of coagulation , which relies on proteins produced in the liver) , the presence of ascites and the level of bilirubin (a breakdown product of hemoglobin which is conjugated and excreted by the liver) . Together with the severity of encephalopathy , these markers have been incorporated into the Child @-@ Pugh score ; this score determines the one- and two @-@ year survival and may assist in a decision to offer liver transplantation .

In acute liver failure , the development of severe encephalopathy strongly predicts short @-@ term mortality , and is almost as important as the nature of the underlying cause of the liver failure in determining the prognosis . Historically , widely used criteria for offering liver transplantation , such as King 's College Criteria , are of limited use and recent guidelines discourage excessive reliance on these criteria . The occurrence of hepatic encephalopathy in patients with Wilson 's disease (hereditary copper accumulation) and mushroom poisoning indicates an urgent need for a liver transplant .

= = History = =

The occurrence of disturbed behaviour in people with jaundice may have been described in antiquity by Hippocrates of Cos (ca . 460 ? 370 BCE) . Celsus and Galen (first and third century respectively) both recognised the condition . Many modern descriptions of the link between liver disease and neuropsychiatric symptoms were made in the eighteenth and nineteenth century ; for instance , Giovanni Battista Morgagni (1682 ? 1771) reported in 1761 that it was a progressive condition .

In the 1950s , several reports enumerated the numerous abnormalities reported previously , and confirmed the previously enunciated theory that metabolic impairment and portosystemic shunting are the underlying mechanism behind hepatic encephalopathy , and that the nitrogen @-@ rich compounds originate from the intestine . Many of these studies were done by Professor Dame

Sheila Sherlock (1918 ? 2001) , then at the Royal Postgraduate Medical School in London and subsequently at the Royal Free Hospital . The same group investigated protein restriction and neomycin .

The West Haven classification was formulated by Prof Harold Conn (1925 ? 2011) and colleagues at Yale University while investigating the therapeutic efficacy of lactulose .