International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Unraveling Hepatic Encephalopathy: From Pathogenesis to Patient Care

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Abstract: ***Hepatic encephalopathy (HE) is a reversible syndrome of impaired brain function occurring in patients with advanced liver diseases. The precise pathophysiology of HE is still under discussion; the leading hypothesis focus on the role of neurotoxins, impaired neurotransmission due to metabolic changes in liver failure, changes in brain energy metabolism, systemic inflammatory response and alterations of the blood brain barrier. HE produces a wide spectrum of nonspecific neurological and psychiatric manifestations. Minimal HE is diagnosed by abnormal psychometric tests. Clinically overt HE includes personality changes, alterations in consciousness progressive disorientation in time and space, somnolence, stupor and, finally, coma. Except for clinical studies, no specific tests are required for diagnosis. HE is classified according to the underlying disease, the severity of manifestations, its time course and the existence of precipitating factors. Treatment of overt HE includes supportive therapies, treatment of precipitating factors, lactulose and/or rifaximin. Routine treatment for minimal HE is only recommended for selected patients.***

Keywords: Hepatic encephalopathy, pathophysiology, diagnostic tests, management strategy

1. Introduction

Hepatic encephalopathy (HE) or portosystemic encephalopathy (PSE) is a reversible syndrome of impaired brain function occurring in patients with advanced liver failure. However, HE is not a single clinical entity. It may reflect either a reversible metabolic encephalopathy, brain atrophy, brain edema or any combination of these conditions. The mechanisms causing brain dysfunction in liver failure are still unknown. These factors are directly related to liver failure (e. g. decreased metabolism of ammonia). Unless the underlying liver disease is successfully treated, HE is associated with poor survival and a high risk of recurrence [1, 2]. Even in its mildest form, HE reduces health - related quality of life and is a risk factor for bouts of severe HE [3, 4].

Pathogenesis

In spite of more than 100 years of research, the pathogenesis of HE is still not well understood. This reflects the limitation to study the brain of patients with HE *in vivo*. Most of the published data are derived from experimental models of HE, which are far from perfect. The most common suggestions include the role of neurotoxins, impaired neurotransmission due to metabolic changes in liver failure, changes in brain energy metabolism, systemic inflammatory response and alterations of the blood brain barrier. The pathogenesis of HE is not allowed to be reviewed in detail due to the huge number of published data (for a detailed discussion, see [5–7]). The various hypotheses of the pathogenesis of HE are not mutually exclusive. It seems likely that many of the described abnormalities may be present at the same time and may ultimately be responsible for the development of HE.

Neurotoxins

Ammonia is the best characterized neurotoxin linked to HE. The gastrointestinal (GI) tract is the primary source of ammonia. Ammonia is produced by enterocytes from glutamine and by colonic bacterial catabolism of nitrogenous sources (such as blood after GI bleeding) [8]. The intact liver clears almost all of the portal vein ammonia, converting it into glutamine and preventing entry into the systemic circulation. The increase in blood ammonia in advanced liver disease is a consequence of impaired liver function and of the shunting of blood around the liver. Muscle wasting, a common occurrence in these patients, also may contribute, since muscle is an important site for extrahepatic ammonia removal.

Swelling of astrocytes as consequence of hyperammonemia may be a key event in the development of HE in patients with cirrhosis [9–12]. One possible explanation for brain edema is an increase in intracellular osmolarity resulting from the metabolism of ammonia in astrocytes to form glutamine [13]. Brain glutamine concentrations are significantly increased in acute liver disease whether assessed biochemically in autopsy material [13] or by 1H - magnetic resonance spectroscopy [14]. These data are supported by *in vivo*measurements in cirrhotic patients in whom proton magnetic resonance spectroscopy of the brain showed depletion of myoinositol (a sign of increased osmolarity) and increased glutamine [14]. One protein strongly implicated in cell swelling is the water channel protein aquaporin - 4, which is abundantly expressed in astrocytes [15, 16]. Ammonia also directly affects neuronal electric activity by inhibiting the generation of both excitatory and inhibitory postsynaptic potentials [17] and cortical hemichannels [18].

Impairment of neurotransmission

Several neurotransmitter systems have been studied in various experimental models of (mostly) acute liver failure, including investigations of neurochemical, neurobehavioral and electro phy si ological methods. Most reports describe changes in the GABA - benzodiazepine - ergic [19], dopaminergic [20], serotoninergic and glutamate - ergic neurotransmitter systems [5]. For obvious reasons, very few data exist in humans suffering from HE.

Substances involved in the activation of the GABAA - ergic neurotransmission have been isolated, characterized and positively identified by gas chromatography–mass spectroscopy as benzodiazepines in brain, sera and cerebrospinal fluid of humans with type A and type C HE

[21]. Some of them may be of exogenous origin but endogenous benzodiazepine - like compounds such as neurosteroids have been identified [22]. Neurosteroids are potent selective positive allosteric modulators of the GABAA receptor complex. Allopregnanolone and pregnenolone (a neurosteroid precursor) pathophysiologically relevant concentrations were increased in the brains of hepatic coma patients [22]. Activation of the astrocytic 18 - kDa translocator protein (formerly referred to as peripheral - type benzodiazepine receptors) contributes to the pathogenesis of the central nervous system symptoms of HE [23].

Some of the extrapyramidal symptoms in patients with cirrhosis may be due to altered dopaminergic function, which is closely related to accumulation of manganese in basal ganglia [24]. Manganese appears to normalize low striatal levels of dopamine. Thus, manganese accumulation in basal ganglia may represent an attempt of the brain to correct dopamine deficiency in liver disease [25].

Systemic response to infections and neuroinflammation
Other possible causes of brain dysfunction include alterations in cerebral blood flow, brain metabolites and the release of inflammatory mediators; importantly, these processes occur without the direct infection of brain tissue [9, 26]. Infection is a well - known precipitant of HE, but the mechanisms involved are incompletely understood [27]. Patients with cirrhosis are known to be functionally immunosuppressed and prone to developing infections. Whether infections themselves or the inflammatory response exacerbate HE is unclear. The systemic inflammatory response syndrome results from the release and circulation of proinflammatory cytokines and mediators. Sepsis - associated encephalopathy is characterized by changes in mental status and motor activity, ranging from delirium to coma [28].

Small bowel bacterial overgrowth may contribute to minimal HE [29, 30]. Patients with cirrhosis had significantly fewer autochthonous and more pathogenic genera than controls [31]; *Alcaligenaceae* and *Porphyromonadaceae* were positively associated with cognitive impairment [32]. Dysbiosis, represented by reduction in autochthonous bacteria, is present in both saliva and stool in patients with cirrhosis, compared to controls; thus investigating microbiota in saliva can be used in clinical practice [33].
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2. Clinical Presentation

HE produces a wide spectrum of nonspecific neurological and psychiatric manifestations [34]. In its lowest expression [35, 36], HE alters only psychometric tests oriented towards attention, working memory, psychomotor speed and visuospatial ability, as well as electrophysiological and other functional brain measures [37, 38].

As HE progresses, personality changes, such as apathy, irritability and disinhibition, may be reported by the patient's relatives [39], and obvious alterations in consciousness and motor function occur. Disturbances of the sleep–wake cycle with excessive daytime sleepiness are frequent [40], whereas complete reversal of the sleep–wake cycle is less consistently seen [41, 42]. Patients may develop progressive disorientation to time and space, inappropriate behavior, acute confusional state with agitation or somnolence, stupor and, finally, coma [43]. The recent ISHEN (International Society for Hepatic Encephalopathy and Nitrogen Metabolism) consensus uses the onset of disorientation or asterixis as the initial sign of overt HE [44].

In non - comatose patients with HE, motor system abnormalities such as hypertonia, hyperreflexia and a positive Babinski sign can be seen. In contrast, deep tendon reflexes may diminish and even disappear in coma [45], although pyramidal signs can still be seen. Rarely, transient focal neurological deficits can occur [46]. Seizures are very rarely reported in HE [47–49]. Extrapyramidal dysfunction, such as hypomimia, muscular rigidity, bradykinesia, hypokinesia, monotony and slowness of speech, Parkinsonian - like tremor and dyskinesia with diminished voluntary movements are common findings [45].

Asterixis or 'flapping tremor' is often present in the early–middle stages of HE that precede stupor or coma, and is in actuality not a tremor, but a negative myoclonus consisting of loss of postural tone. It is easily elicited by actions that require postural tone, such as hyperextension of the wrists with separated fingers, or the rhythmic squeezing of the examiner's fingers. However, asterixis can be seen in other areas such as the feet, legs, arms, tongue and eyelids. Asterixis is not pathognomonic of HE, as it can be seen in other diseases, such as uremia.

Notably, the mental (either cognitive or behavioral) and motor signs of HE may not be expressed or do not progress in parallel in each individual, therefore producing difficulties in staging the severity of HE.

Apart from less usual manifestations of HE, it is widely accepted in clinical practice that all forms of HE and their manifestations are completely reversible, and this assumption still is a well - founded operational basis for treatment strategies. However, research on liver - transplanted HE patients and on patients after resolution of repeated bouts of overt HE casts doubt on the full reversibility.

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