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Neurological disorders in liver transplant candidates: Pathophysiology and clinical assessment☆

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A B S T R A C T

Compromised liver function, as a consequence of acute liver insufficiency or severe chronic liver disease may be associated with various neurological syndromes, which involve both central and peripheral nervous system. Acute and severe hyperammoniemia inducing cellular metabolic alterations, prolonged state of "neuroinflammation", activation of brain microglia, accumulation of manganese and ammonia, and systemic inflammation are the main causative factors of brain damage in liver failure. The most widely recognized neurological complications of serious hepatocellular failure include hepatic encephalopathy, diffuse cerebral edema, Wilson disease, hepatic myelopathy, acquired hepatocerebral degeneration, cirrhosis-related Parkinsonism and osmotic demyelination syndrome. Neurological disorders affecting liver transplant candidates while in the waiting list may not only significantly influence preoperative morbidity and even mortality, but also represent important predictive factors for post-transplant neurological manifestations. Careful pre-transplant neurological evaluation is essential to define severity and distribution of the neurological impairment, to identify the abnormalities still responsive to current treatment, and to potentially predict the inherent post-operative prognosis. The preferred specific indices of neurological pre-transplant assessment may vary among centers, however, even with the aid of the current biochemical, neurophysiological, neuropsychological and neuroimaging diagnostic tools, the correct diagnosis and differential diagnosis of various syndromes may be difficult. In this article the relevant pathophysiological and clinical aspects of the most frequent brain and peripheral nervous system diseases affecting liver transplant candidates with acute or advanced chronic liver failure are briefly reported. The practical diagnostic findings useful for the preoperative assessment and treatment, as well as the expected neurological evolution after liver transplantation are also evaluated.

1. Introduction

Compromised liver function as a consequence of either acute hepatic failure or severe chronic liver disease and liver cirrhosis leads to insufficient detoxification of some substances and catabolic products, which accumulate in the blood and are responsible for a broad range of neurological and neuropsychiatric manifestations [1]. A strict relationship between brain functioning and integrity of the liver is well known, and a pathological liver may be responsible for various neurological syndromes, which affect both the central nervous system (CNS) and the peripheral nervous system [2,3].

Liver transplant candidates may experience a great variety of neurological disorders while on the waiting list, which may significantly influence preoperative morbidity and even mortality. It has been recognized that many neurological disorders associated with acute or chronic liver failure tend to improve or disappear after successful orthotopic liver transplantation (OLT); however, some minor "residual" clinical signs may persist postoperatively in a variable percentage of liver transplanted patients. Furthermore, pre-transplant subclinical neurological symptoms may become apparent in the event of graft dysfunction or severe postoperative metabolic disturbances [4,5].

Liver transplant recipients are affected by the highest rate of CNS complications among solid organ transplants (incidence between 10% and 85%), with focal and diffuse neurological deficits sometimes representing a major obstacle to the improvement of short- and long-term outcomes [6]. Relevant adverse post-OLT neurological events occur due to brain edema, increase of intracranial pressure, metabolic encephalopathy, cerebrovascular complications, osmotic demyelination syndrome, and opportunistic infections. Moreover, some pre-operative neurological alterations such as dysarthria or akinetic mutism, confusion and seizures, may worsen due to the neurotoxic effects of calcineurin inhibitors drugs required to prevent graft rejection [4,7]. Full

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comprehension of the pathophysiology and proper management of the neurological manifestations of end stage liver failure has not yet been completely attained. In fact, multiple factors have been associated with brain damage, such as a prolonged state of brain "neuroinflammation", activation of brain microglia and inflammatory cells, accumulation of manganese and ammonia, altered permeability of the blood–brain barrier, altered neurotransmission, and inflammation of the peripheral nervous system [8]. Other negative direct or indirect neurologic effects are caused by chronic malnutrition, gastrointestinal hemorrhages, cerebral hypoperfusion and renal dysfunction [9–12]. The most widely recognized neurological complication of serious hepatocellular failure is the complex syndrome of hepatic encephalopathy (HE), but many other brain alterations associated with liver cirrhosis may occur, as listed in Table 1 [13].

Careful pre-transplant evaluation of the CNS and peripheral nervous system disorders is essential for identifying the abnormalities still responsive to current medical treatment, and potentially predicting the inherent post-operative prognosis. An accurate assessment of baseline neurological features increases the understanding of how brain disorders can interfere with post-hospitalization quality of life in case of potential incomplete recovery after OLT. Patients with end-stage liver disease are usually evaluated with indices that predict advanced disease, such as the Child–Turcotte–Pugh score, or those that predict prognosis, such as the Model for End-stage Liver Disease score (MELD, MELD-Na). Preoperative neurological assessment is based on the specific evaluation of both CNS and peripheral nervous system functions. Examination of motor (pyramidal and extrapyramidal) and sensory system integrity, cranial nerves evaluation, as well as analysis of superficial and deep-tendon reflexes and cerebellar signs should always be performed as first step neurological assessment before searching for more specific neurological features. Evaluation of the mental status, cognitive functions, speech characteristics, etc., is also extremely useful in obtaining a detailed baseline neurological status and monitoring possible disease progression. Clinical and biochemical diagnostic tools, neurophysiological assessments (electroencephalography (EEG) and visual, auditory, and somatosensory-evoked potentials (EPs) and neuroimaging, have been adopted to correctly diagnose different stages of neurological impairment. However, the choice of the preferred clinical or instrumental parameters for neurological pre-transplant assessment may vary among centers, and the differential diagnosis of various syndromes may be difficult and critical, even with the use of "modern" technologies. This article mainly focuses on the most frequent CNS and peripheral nervous system diseases affecting liver transplant candidates with acute severe or advanced liver dysfunction. Patients with severe liver dysfunction can have a great range of neurologic manifestations due to direct effects of hepatic disease on the central and peripheral nervous system (i.e. HE or acquired hepato-cerebral degeneration) or to diseases with concomitant hepatic and neurological involvement (i.e. Wilson disease). The neurological syndromes may require a specific management, such in the case of acute liver failure, or in the context of chronic liver cirrhosis or portosystemic shunting. The relevant pathophysiological and clinical aspects, the practical diagnostic findings useful for the preoperative clinical assessment and treatment, as well as the expected neurological evolution after liver transplantation, are briefly described.

Table 1
Neurological manifestations associated with liver cirrhosis, from [13] with modifications.

Hepatic encephalopathy and minimal hepatic encephalopathy
Cirrhosis-related parkinsonism
Raised intracranial pressure, cerebral edema
CNS infectious complications
Acquired hepatocerebral degeneration
Cirrhotic or hepatic myelopathy
Cirrhosis related intracranial bleeding
Neurologic complications related to specific aetiologies of liver disease
Neurologic symptoms of Wilson disease
Hepatitis C infection related CNS complications
Osmotic demyelination syndrome
Marchiafava-Bignami disease
Wernicke encephalopathy
Neurological disorders associated with malnutrition
Alcoholic cerebellar degeneration, amblyopia, polyneuropathy, Wernicke–Korsakoff Disease
Alcohol related cerebral atrophy and cognitive decline

2. Neurological aspects of hepatic encephalopathy

HE is a complex syndrome characterized by neuropsychiatric, neuropsychological and neurological disturbances caused by different underlying liver diseases or peri-hepatic vascular shunting, and influenced by a variety of precipitating factors. The development of HE may manifest with a wide range of neurologic manifestations, which are characterized by potential reversibility once the abnormality of liver function is corrected. Sudden onset of confusion evolving rapidly into coma is a frequent presentation of acute HE episodes, often under the trigger of some precipitating factors; in other circumstances, the signs and symptoms may fluctuate slowly, with long periods without HE events [14]. Based on the clinical practice guidelines of the American Association for the study of liver diseases (AASLD) and the European Association for the study of the liver (EASL) [15], HE should be classified according to four factors:

(1) the underlying disease; with type A HE resulting from acute liver failure, type B resulting predominantly from portosystemic bypass or shunting, and type C resulting from cirrhosis;
(2) the severity of manifestations; a summarized grading of severity of clinical manifestations of HE, according to both the West Haven criteria (Old Classification) and International Society for Hepatic Encephalopathies and Nitrogen Metabolism (ISHEN) classification, is reported in Table 2 [15],
(3) the time course; subdivided into episodic (spontaneous or precipitated), recurrent (episodes occurring with a time interval of 6 months or less), persistent (>2 weeks of mental status changes),
(4) the existence of precipitating factors; subdivided into spontaneous non precipitated or precipitated (with specification of the precipitating factors).

The so-called overt form of HE (OHE), defined when neurological and psychiatric abnormalities are detected at the bedside, was divided into four stages of severity based on the New Haven scale. However, given the largely subjective criteria for classifying a cirrhotic patient as stage 1 HE, it was decided to abolish this stage of HE. Every cirrhotic patient with disorientation to time has to be considered with definite OHE [16].

Minimal HE (MHE), once called covert HE, and defined when minimal or no symptoms are detected [17,18], occurs in nearly 70% of cirrhotic patients; it has grown in importance over the recent years as it may precede the development of OHE. MHE is defined as the presence of test-dependent or clinical signs of brain dysfunction in patients with chronic liver disease who are not disoriented or display asterixis. According to the ISHEN classification, covert HE (CHE) is essentially the amalgamation of stage 1 HE and MHE.

3. Neurological manifestations of acute liver failure (type HE)

Acute liver failure (ALF) is characterized by a rapid hepatocellular necrosis that leads to the severe deterioration of liver function, alterations of coagulation and encephalopathy, which occurs within days or weeks of the primary insult (less than 26 weeks) without evidence of pre-existing cirrhosis [19]. The most common aetiologies are drug-induced liver injury (acetaminophen overdose being observed in <45%), food intoxication, viral hepatitis, autoimmune liver disease and ischemic hepatitis. Neurologic manifestations are those of encephalopathy