Minimal/Covert Hepatic Encephalopathy – Impact of Comorbid Conditions

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Mild cognitive dysfunction as in minimal or covert hepatic encephalopathy (HE) can be found in a variety of metabolic disturbances, several neurological diseases, and even older age. Because liver cirrhosis usually is accompanied by one or the other of these, a differentiation between HE and cognitive decline because of comorbidities is difficult. Somehow discriminating is the impairment of motor speed and accuracy, which is more prominent in HE than in any of the comorbidities. The observation that, for example, diabetes mellitus, renal dysfunction, infections, or hyponatremia as well as older age increase the risk of developing HE indicates the interaction between these factors and liver dysfunction in the development of HE and the necessity to adjust the therapy accordingly. (J CLIN EXP HEPATOL 2019;9:109–111)

Neither neuropsychological nor neurophysiological findings characteristic for hepatic encephalopathy (HE) are specific. Thus, consideration of comorbidities is mandatory in diagnosing HE. Montagnese et al. reported that 95 of 177 prospectively recruited patients with cirrhosis and HE in their center had comorbidities that could add to their symptoms besides HE.¹ Most important are renal dysfunction, hyponatremia, diabetes mellitus (DM), infection, and thiamine deficiency. But, of course, also genuine neurological disorders such as dementia could play a role in an individual case. By analyzing the data of about 15,000 patients with alcoholic or cryptogenic cirrhosis, Jepsen et al. found a 10% prevalence of DM, while 5% of their patients had cerebrovascular disease and 1% had severe renal dysfunction.² The rate of diabetes and renal dysfunction in a population of patients with liver cirrhosis varies with the underlying liver disease and the severity of liver dysfunction. In patients with hepatitis C virus, cirrhosis diabetes was observed in up to 1/3 of the patients,³ and patients on the waiting list for transplantation showed significant renal dysfunction in about 20%.⁴ Hyponatremia (serum sodium level < 135 mmol/l) was observed in 31% of patients with cirrhosis on the waiting list for liver transplantation in a survey in the United States and has been shown to be

correlated with both HE and mortality.^{5,6} The rate of bacterial infections in patients with liver cirrhosis has been reported as 25% to 35%⁷ and may rise to 45% in patients with gastrointestinal bleedings.⁸ Thiamine deficiency is usually considered in patients with alcoholic cirrhosis presenting with the characteristic triad of neurological symptoms—ophthalmoplegia, ataxia, and confusion/memory loss. But thiamine deficiency may as well present with milder signs of brain dysfunction such as fatigue, apathy, difficulty in concentration, and memory and in these cases is at risk to be overlooked by clinical routine examination.⁹ Of note, thiamine deficiency is not restricted to patients with alcoholic cirrhosis but may be present in other cirrhotic patients as well because of malnutrition and loss of hepatic thiamine stores.⁹ Data on the prevalence of thiamine deficiency in patients with cirrhosis are missing.

The mentioned comorbidities may significantly affect brain function themselves (Table 1), but—even more importantly—they enhance the effect of metabolic and inflammatory alterations associated with end-stage liver disease on brain function.

Attention, executive function, and memory are significantly altered in patients with chronic kidney disease grade 4 and 5 and further decline in patients on hemodialysis.^{10,11} The psychometric profile of patients with liver cirrhosis and renal dysfunction has not been separately studied in detail. But Kalaitzakis and Björnsson were able to show that, for example, the time needed to perform the number connection test B correlated with serum creatinine levels in their patients with liver cirrhosis and that serum creatinine was independently related to the presence of HE.¹² Serum creatinine levels have also been shown to indicate the risk for the development of HE.¹³

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Abbreviations: DM: diabetes mellitus; HCV: hepatitis C virus; HE: hepatic encephalopathy; NCT B: number connection test B

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Table 1 Pattern of (Subclinical) Cognitive Dysfunction That has Been Observed in Various Comorbidities of Liver Cirrhosis.

Disorder	Attention	Memory	Executive function	Visuoconstruction	Processing speed	Motor speed	Motor accuracy
Hepatic encephalopathy	X		X	X	X	X	X
Diabetes mellitus	X	X	X		X	X	
Renal dysfunction	X	X	X		X	X	
Hyponatremia	X				X		
Sepsis ^a	X	X	X	X	X		
Wernicke's encephalopathy	X	X	X	X	X	X	

HE, hepatic encephalopathy.

The table lists those domains that may be affected in HE compared with various comorbidities. Obviously there is a significant overlap regarding the domains affected in the different conditions. Especially attention, executive function, and processing speed are impaired, irrespective of the underlying disorder. Although also patients with diabetes mellitus, renal dysfunction, and Wernicke's encephalopathy show alterations of motor function, these are less pronounced than in patients with HE.

^aData referring to septic encephalopathy were achieved after the patients' recovery.

In subjects with type 2 DM, global cognition, semantic and episodic memory, working memory, and visuospatial ability were found to be impaired.¹⁴ In patients with type 1 DM, visual attention and perception, psychomotor efficiency, speed of information processing, and cognitive flexibility were affected.¹⁵ Both, type 1 and type 2 DM increase the risk of developing dementia.^{16,17} In regard to HE, an association with diabetes has been shown for minimal and overt HE.^{18,19} Considering possible mechanisms behind this association, the hypothesis that diabetes could increase ammonia production by enhancing small intestine glutaminase type K is of special interest.¹⁹ Metformin, which reduces glutaminase activity *in vitro*, has been shown to decrease the incidence of HE in patients with cirrhosis. Another important factor is the increased release of proinflammatory cytokines in type 2 DM and insulin resistance. Several studies indicate a relationship between the levels of proinflammatory cytokines and severity of HE in patients with cirrhosis and in acute liver failure.^{18,19}

Proinflammatory cytokines are related to cognitive dysfunction also apart from HE. Alterations of cognition and consciousness have been observed even in patients with uncomplicated infections of the urinary tract, although predominantly in subjects with pre-existing brain disorder.²⁰ And, up to 70% of patients with bacteremia and fever show neurological symptoms ranging from lethargy and mild inattention to coma.^{21,22} Of note, the incidence of sepsis-associated encephalopathy is highest with biliary or intestinal infections and pneumonia, and sepsis-associated encephalopathy carries the risk of long-term cognitive impairments, including alterations in mental processing speed, executive function, memory, attention, and visuospatial abilities.^{21,22} These findings are of interest regarding the strong association between infection and HE on the one side and the ongoing discussion on the reversibility of cognitive dysfunction in patients with HE after successful liver transplantation on

the other.^{23–25} In patients with liver cirrhosis, infections are considered as significant risk factors for the development of HE.²³ Shawcross et al. showed that hyperammonemia induced by administration of an amino acid solution to cirrhotic patients results in a deterioration in neuropsychological function in the presence of a systemic inflammatory response but not after resolution of the infection.²⁴

Hyponatremia is another significant risk factor for the development of HE.^{6,13} Per se hyponatremia may stay without any symptoms or may lead to severe neurological complications including disorientation, seizures, and disturbance of consciousness depending on the rate and extent of alterations.²⁶ But, even mild hyponatremia may affect cognitive function, especially attention.²⁷ In patients with liver cirrhosis, hyponatremia adds to the ammonia effect on astrocyte volume and exacerbates astrocytic swelling because of a loss of organic osmolytes, such as myo-inositol.⁶

Finally, the most frequent comorbidities present in patients with liver cirrhosis share neurological symptoms with HE and tend to add to the mechanisms behind the development of HE, thus increasing the risk for HE. The significant alteration of motor speed and accuracy together with increased plasma ammonia levels helps differentiate HE from other metabolic encephalopathies. But even if these motor deficits are present, the impact of comorbidities on other domains such as attention, for example, cannot be determined. Thus, HE therapy has to consider the comorbidities as well.

CONFLICTS OF INTEREST

The author has none to declare.

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