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Minimal hepatic encephalopathy and sleep disorders in patients with cirrhosis: Which comes first?

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Minimal hepatic encephalopathy (MHE), affecting up to 80% of patients with cirrhosis, impairs attention, alertness, response inhibition, and executive functions as well as the working memory, psychomotor speed, and visuospatial ability. Altered quality of life, falls, sleep disorders, erectile dysfunction in males, impairment in driving capacity, and car accidents have been found to be more frequent in patients with MHE than in those without. Moreover, MHE by reducing the patients' working ability may affect both patient's and caregiver's socioeconomic status. Finally, MHE appears linked with sarcopenia and is a clear risk factor for the development of overt HE or its recurrence, leading to frequent hospitalization of the patients. Therefore, MHE has a heavy burden both for the patients and their caregivers, resulting in the use of more healthcare resources than other complications of liver disease. The optimal measure for diagnosing MHE is still debated. In fact, none of the methods proposed (psychometric paper and pencil test, computerized test, electrophysiology) cover the wide complexity and heterogeneity of MHE-related cognitive impairment, as well as appropriate norms needed. Therefore, MHE is still ignored or underdiagnosed by most clinicians and the need for treatment is still under debate.^[1-7]

Between the computerized tests for MHE detection, the EncephalApp was easy to administer, quick to teach to patients, and simple to score and interpret.^[8,9] The anterior attention system is hypothesized to modulate response inhibition, behavioral selection, and executive control, which are cognitive skills necessary to perform the test. Abnormalities in attention and psychomotor speed are the hallmark of cognitive impairment in MHE and negatively affect patient's quality of life.

Luo *et al.*^[10] aimed to study the relationship between sleep quality and EncephalApp results in patients with MHE due to hepatitis B-induced cirrhosis. EncephalApp appears a useful diagnostic tool for diagnosing MHE when compared with the gold standard Psychometric Hepatic Encephalopathy Score (PHES) in patients with cirrhosis due to HBV infection, the most representative etiology of advanced liver disease in China. Moreover, 62 (63%) of

98 of MHE patients were diagnosed as poor sleepers by using the Pittsburgh Sleep Quality Index (PSQI), having a PSQI score >5, the threshold value to distinguish between poor and good sleepers. In addition, EncephalApp results discriminate better than PHES patients with different sleep quality. However, patients without MHE seem to have poor sleep quality, having a global PQSI score >5 (9.6 ± 3.05). The above evidence should be further evaluated, and highlights the need for further validation and analysis of this relationship.

Results of Luo *et al.*^[10] seem to be partially in line with previously published studies. In fact, in the paper by Samanta *et al.*,^[11] MHE was present in 40 (87%) of poor sleepers, vs. 6 (13%) of good sleepers and MHE emerged as a strong predictor of sleep disturbance among cirrhotic patients in multivariate analysis. Labenz *et al.*^[12] confirmed the presence of covert HE as an independent predictor of sleep quality measured by PSQI. Moreover, Singh *et al.*^[13] showed that lactulose therapy was effective not only in the amelioration of PHES score of patients with MHE and PSQI, but also in the overall evaluation and Health Related Quality of Life.

The study of Luo *et al.*^[10] is the first to describe a possible relationship between MHE as diagnosed by EncephalApp and poor sleep quality; therefore, validation series are needed to confirm these interesting and promising conclusions. However, the study only enrolled patients with HBV-related cirrhosis since this condition represents the major etiology in China. It should be noted that patients with alcoholic cirrhosis show a heavy cognitive impairment at the EncephalApp, carrying, as stated by the authors, scarce possibility to generalize the results of this study to the whole spectrum of cirrhosis. In addition, the authors showed that patients with MHE had a higher degree of liver impairment than those without (MELD scores 9.46 ± 3.54 vs. 7.03 ± 4.32 , $P = 0.02$, Child Pugh Class B/C 21 vs. 6 $P = 0.02$) as did patients with poor sleep quality compared to those with good sleep quality (MELD scores 11.7 ± 3.82 vs. 8.22 ± 3.67 , $P < 0.001$, Child Pugh Class B/C 14 vs. 7 $P = 0.03$). Moreover, the presence of ascites, a hallmark of advanced liver disease, seems to be strictly related both with MHE and poor sleep quality. These findings require further exploring, with analysis

of the relationship between liver disease “per se” and poor sleep quality, even beyond the presence of MHE. Finally, with the whole HE spectrum being considered as a “sleepiness syndrome”,^[14] it would be interesting to investigate the implications and relationship between HE, MHE, and sleep disturbances.

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