

Recent Advances of Diagnosis and Treatment in Minimal Hepatic Encephalopathy of Cirrhotic Patients in Japan

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Abstract

Minimal hepatic encephalopathy (MHE) is a common cognitive disorder in cirrhotic patients, but is clinically asymptomatic. In Japan, It can be diagnosed by computer-based simple neuropsychiatric test with high specificity. Moreover, we recently established much more available and routine screening tool of MHE, using chronic liver disease questionnaire (CLDQ), from the viewpoint of less time-consuming. Cirrhotic patients diagnosed as MHE can be medicated by several supplementations. L-carnitine is one of the treatment modalities of MHE. It would stimulate mitochondrial function, and reinforce the activity of the antioxidant enzymes, leading to the amelioration of MHE. Cases with MHE amelioration after the treatment had a significantly higher serum level of taurine before treatment, not only supporting pre-therapeutic prediction of MHE amelioration, but also being beneficial from a financial perspective.

Mini Review

Minimal hepatic encephalopathy (MHE) is a neuropsychiatric and cognitive disorder as a result of decompensated cirrhosis. MHE shows abnormalities in intellectual function, such as memory reduction, personality changes, and impairment of concentration and reaction times [1,2]. Driving and quality of life are also affected due to impairment of cognitive function and psychomotor slowing, becoming serious problem in social settings [3,4]. MHE is a risk factor for the more serious overt hepatic encephalopathy. Moreover, increased mortality rate was recently reported in MHE patients [5]. However, MHE is often unrecognized because the patients are usually asymptomatic and only represents coma grade 0 or less. They are just diagnosed by specialized tests, as various neuropsychiatric and neurophysiologic evaluations and imaging [6-8]. The neurophysiological tests have advantages from the standpoint of the lack of learning effects and specificity of response. However, phycologists are required for administration and interpretation. Moreover, electroencephalography is an expensive modality. Functional magnetic resonance imaging was also reported to be effective to diagnose MHE. However, strict thresholds for diagnosis of MHE by the imaging technique are under consideration. In Japan, Kato et al developed a simple computer-aided neuropsychiatric test (NP-test) system, consisting eight tests that can be performed easily by outpatients using

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touch panel [9]. The NP-test is useful to diagnose MHE in clinical settings. The test has higher specificity in MHE diagnosis (30-35% of cirrhotic patients) than other modalities (30-85% of cirrhotic patients). However, it takes almost 30 minutes for outpatients to complete, which would be a key barrier to routine testing for MHE in social settings such as workplace examinations of employees.

It was recently reported that MHE was associated with decreased health-related quality of life (HRQL) [10,11]. The chronic liver disease questionnaire (CLDQ) is widely used to assess HRQL of cirrhotic patients, which was developed by Younossi and colleagues [12]. The CLDQ is in a question format with seven-category response scales. The scale has been applied in several countries, and the validity, reproducibility, reliability, and sensibility has been identified [13-15]. CLDQ is also more responsive to small clinical change. Recently, we showed that CLDQ worry (WO), one of the categories of CLDQ, was the best predictive factor of MHE diagnosed by the NP test [16]. The CLDQ is less time-consuming of less than 10 minutes. It is thought that

the CLDQ WO can become an alternative routine screening tool of MHE before performing NP-test in social settings.

As the treatment modalities of MHE, various supplementations have been tried for the disease [17-19]. In the meeting of the International Society for the Study of Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) in 2014, branched-chain amino acids, lactulose, L-ornitine L-aspartate, rifaximin, and probiotics were reported to be effective for the amelioration of MHE. A majority of these attempts were aimed at reducing blood ammonia, which plays a key role in the pathogenesis of MHE. We reported that L-carnitine (300mg/tablet) (Otsuka Pharmaceutical, Tokyo, Japan) at a dose of two tablets three times daily after meals improved 45.8% of MHE patients three months after L-carnitine administration [20]. Similar to the other treatment modalities, L-carnitine reduced blood ammonia level to some extent, but our data showed that the level before and after the treatment did not differ between the MHE-ameliorated group and non-ameliorated group. The other pathogenesis of MHE is thought to be undetoxified reactive oxygen species (ROS) due to mitochondrial dysfunction, which was found in the process of liver fibrosis [21-23]. L-carnitine is not an oxidative stress scavenger

but it would stimulate mitochondrial function, and reinforce the activity of the key ROS-scavenging antioxidant enzymes such as superoxide dismutase [24]. Cases without MHE-ameliorated effect by L-carnitine administration could be explained by much fewer incorporation of L-carnitine because of the much less mitochondrial permeability. In these cases, mitochondrial L-carnitine would remain to be insufficient even after L-carnitine administration. On the other hand, cases with MHE-ameliorated effect by L-carnitine administration had significantly higher serum taurine level before L-carnitine administration. Taurine is a potent free radical scavenger that attenuates the damage caused by excessive mitochondrial oxidative stress [25]. We speculate that oral administration of L-carnitine plus taurine might become a new therapeutic method in cirrhotic patients with MHE.

In conclusion, CLDQ WO can become an alternative routine screening tool of MHE before performing NP-test in social settings. L-carnitine is one of the treatment modality of MHE, and cases with MHE amelioration after the treatment had a significantly higher serum level of taurine before treatment, not only supporting pre-therapeutic prediction of MHE amelioration, but also being beneficial from a financial perspective.

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