

MINIMAL HEPATIC ENCEPHALOPATHY IN PATIENTS WITH DECOMPENSATED LIVER CIRRHOSIS

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SUMMARY – Minimal hepatic encephalopathy (mHE) is characterized by some minimal unspecific alterations of cerebral functions that can only be detected by neuropsychological or neurophysiological diagnostic tests, which dysfunctions nevertheless interfere with the patient's daily living. Early recognition of these impairments may prevent the progression or delay the development of the disease to overt hepatic encephalopathy. The aim of this study was to diagnose mHE in patients with decompensated liver cirrhosis. The study was conducted in 60 patients aged 40-65, divided into two groups: experimental group and control group. Patients in the experimental group were divided into Child-Pugh groups A, B or C: 53% were classified as Child-Pugh B and 47% as Child-Pugh C. Patients were tested using three neuropsychological tests: Mini Mental Score for quick assessment of cognitive status and two tests specific for mHE changes, Trail Making Test – Part A (TMT-A) and Symbol Digit Test (SDT). Electroencephalography (EEG) was performed in all patients. Limits for completing the test were set by using the formula $X_{\text{control group}} + 2 \text{ SD}$ for TMT-A and $X_{\text{control group}} - 2 \text{ SD}$ for SDT. All the three tests disclosed statistically significantly different results between the two groups. All patients with cirrhosis had some changes in EEG. Study results showed 80% of cirrhosis patients to have signs of mHE. The Child-Pugh score influenced performance on the neuropsychological tests. SDT more readily identified patients with mHE. Our findings pointed to the frequency of mHE and the importance of early diagnosis in the prevention of mHE progression to overt hepatic encephalopathy.

Key words: *Hepatic encephalopathy; Psychomotor disorders; Neuropsychological tests; Electroencephalography*

Introduction

Hepatic encephalopathy (HE) is defined as a group of neuropsychological disturbances occurring in patients with acute or terminal hepatic insufficiency. The histopathologic basis of HE is a combination of proliferation and edema of astrocytes. This type of proliferation and degradation of glial cells is

known as Alzheimer type II astrocytosis. Astrocytes have enlarged nuclei with prominent nucleolus and suppressed chromatin. Astrocytic edema is due to the toxic effects of ammonia and other neurotoxins, but is also a result of disturbances in cerebral circulation and glucose metabolism. The extent of astrocytic degradation is proportional to the degree of hepatic encephalopathy^{1,2}.

Hepatic encephalopathy is characterized by a wide spectrum of neuropsychological disturbances, ranging from sleep disorders, changes in personality, degradation of cognitive functions, and neural and motor functions³⁻⁵. The HE stage in which a certain number

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Received November 25, 2009, accepted October 25, 2011

of patients show no symptoms of HE but will have pathologic findings on neurocognitive tests is called minimal hepatic encephalopathy (mHE). This stage is of clinical significance because the disturbances can greatly affect the quality of life of these patients, and is also of prognostic value for the development of overt HE⁶⁻⁹.

The aim of this study was to diagnose mHE in patients with decompensated liver cirrhosis using neuropsychological and neurophysiological tests.

Patients and Methods

This clinical study was conducted at University Department of Infectious Diseases, Vojvodina Clinical Center during the 2004-2006 period and included 60 patients aged 40-65. Patients were divided into two groups: experimental group and control group.

Experimental group comprised of patients with decompensated liver cirrhosis but with no symptoms of overt HE and with normal neurological findings. Control group consisted of inpatients with normal liver functions as well as other laboratory, clinical and neurological findings, matched to experimental group according to age and gender.

Exclusion criteria were illiteracy, active variceal bleeding, bacterial infection, renal insufficiency, active alcohol abuse (abuse in the past 6 months), drug abuse (benzodiazepines, antidepressants, anticonvulsants, psychostimulative drugs), mini mental test score lower than 25, and diagnosis of overt HE by a neurologist.

Neuropsychological testing

Testing was performed in collaboration with a psychologist from the University Department of Neurology. Patients were first given a quick test measuring their general cognitive status (Mini Mental Score, MMS), and then the two tests specific for changes in mHE, Trail Making Test – Part A and Symbol Digit Test.

Trail Making Test – Part A (TMT-A) evaluates attention and concentration, visual perception and visual-motor coordination¹⁰. The result is time in seconds, so the higher test results mean lower performance.

Symbol Digit Test (SDT) is a test of cognitive functions, mainly attention, but measures coordina-

tion and manual skills. The results are independent of IQ levels, memory and learning skills¹¹. The result is the number of well-matched digits and symbols, so the higher the score, the better the performance.

Patients received detailed instructions for all tests.

Neurophysiological testing

Electroencephalography (EEG) was performed in all patients. Testing was conducted at Department of Physiology, Medical Faculty, University of Novi Sad. A standard EEG was implemented, which included registering basic electro-cortical activity, reactions to intermittent photo stimulation and hyperventilation, and blinking rate.

Results

The study included 60 patients divided into two groups of 30 patients. The average age of participants was 58 (49-65) years, with a male to female ratio of 2:1 and with an average of 11 years of schooling. The groups were similar in age, gender and schooling, as set in the study design.

Because the study was carried out at University Department of Infectious Diseases, in the experimental group patients liver cirrhosis was mostly due to chronic viral infections. Out of 30 patients, 43% had chronic hepatitis B infection, 50% had chronic hepatitis C viral infection, and only 7% had alcoholic liver disease. The number of decompensations before the actual hospitalization ranged from 0 to 4. Only two of 30 patients had never had an episode of decompensation in their history. Four experimental group patients had previous episodes of overt HE.

Taking into account the toxic effect of ammonia on the central nervous system, ammonemia was assessed in all patients. In the experimental group, 70% of patients had normal levels of ammonia, range 7-30 $\mu\text{mol/L}$.

Based on the findings of total bilirubin, serum albumin levels and prothrombin time, as well as on the presence of ascites, the experimental group patients were divided into Child-Pugh B (53%) or C (47%) groups.

The MMS measuring basic cognitive status showed a statistically significant difference between the two groups of patients ($P < 0.001$). Still, patients in both groups had a score 25 or above, as it was one of the inclusion criteria (Fig. 1).

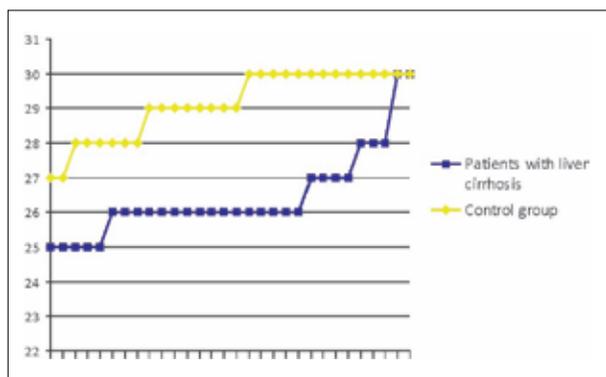


Fig. 1. Performance of patients on the Mini Mental Score.

The TMT-A results were also significantly different between the two groups (Student's *t*-test, $t=4.39$, $P<0.005$). Using the formula $X_{\text{control group}} + 2 \text{SD}$, the upper limit for completing the test was set at 60.78 seconds. Longer reaction time was recorded in 60% of the experimental group patients (Fig. 2).

The SDT also showed a difference in cognitive function between patients with and without decompensated liver cirrhosis (Student's *t*-test, $t=6.99$, $P<0.001$). This time, a different formula was used to determine the smallest number of symbols that needed to be remembered ($X_{\text{control group}} - 2\text{SD}$). The limit was set at 12.64 symbols and only nine (30%) patients in the experimental group had a result better than that (Fig. 3).

All patients in the experimental group had changes in EEG findings, which were defined as minor or median. Minor changes in EEG were recorded in 53.3% of patients, while 46.7% had median changes in terms of cortical dysfunction.

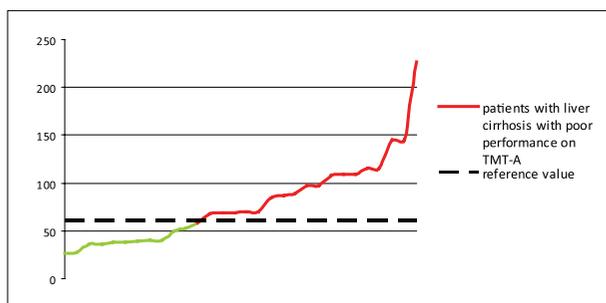


Fig. 2. Performance of patients with decompensated liver cirrhosis on the Trail Making Test – Part A.

Minimal HE is defined as a pathologic finding on one EEG and at least one pathologic result on a neuropsychological test. Our study showed that 80% of patients with decompensated liver cirrhosis had signs of mHE. Half of the experimental group patients had a result outside the set reference values on one test and one-third of patients had results outside the set reference values on both tests. The SDT more frequently defined patients with mHE.

Discussion

Considering that in mHE, there is development of cognitive brain dysfunctions, neuropsychological tests should be aimed at recognizing changes in visual perception, attention and concentration. The most sensitive and specific tests out of the entire battery of tests used in previous researches are the TMT-A and SDT¹²⁻¹⁴. As patient age and education can influence performance on these tests^{15,16}, the experimental and control groups were similar as defined in the study. Normal values for both tests are determined by the control group results: $X + 2 \text{SD}$ for TMT-A and $X - 2 \text{SD}$ for SDT^{17,18}.

According to the literature, the Child-Pugh score can also influence performance on the neuropsychological tests^{15,17}. In this study, patients in Child-Pugh class B had significantly better results than class C patients (37.5% pathologic results in class B compared to 85.6% in class C).

In this study, the percentage of results outside the reference values on neuropsychological tests was higher than in previous studies. According to this study, 80% of patients had poor performance on one test and 50% performed poorly on both tests. Similar studies

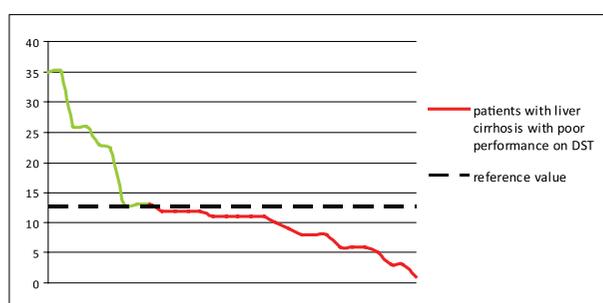


Fig. 3. Performance of patients with decompensated liver cirrhosis on the Symbol Digit Test.

recorded low performance in 25% to 52% of patients with liver cirrhosis^{15,17}. A possible explanation could lie in the fact that patients in our experimental group were older and had a more advanced liver damage.

All our patients with decompensated liver cirrhosis had diffuse slowing of brain waves, which is characteristic of metabolic encephalopathies. These EEG findings can be expected when mHE is present¹⁹. Around half of our patients had medium EEG changes and these patients also had pathologic findings on both tests as well as more advanced liver damage (78.6% belonged to Child-Pugh class C). The level of EEG changes correlated with the level of liver damage as well as with test results.

In our study, 80% (n=24) of patients had mHE. As much as 92.86% of the Child-Pugh class C patients had mHE. The percentage of patients with mHE in Child-Pugh class B was 68.75%. According to the literature, 30% to 84% of patients with chronic liver disease had mHE. The large diversity of the results is a consequence of different definitions of mHE and diagnostic tools used to identify mHE^{13,14,20-22}.

In their study, Quero *et al.*¹⁴ used TMT, SDT and EEG, as we did in our study. Their study involved 137 patients aged 17 to 77 (average age 49), which means that adjustment in the results had to be made according to age groups. After adjustments, mHE was found in 23% of patients, with most of the patients belonging to the Child-Pugh class C¹⁴. Almost the same methods were used by Groeneweg *et al.*¹³ and Hartmann *et al.*²⁰ in 2000. The percentage of mHE in these studies was 22% and 27%, respectively^{13,20}. Another very similar study was carried out by Yoo *et al.*, however, they found a much higher frequency of mHE, 42.4% (28 of 66 patients)²¹.

Li *et al.* conducted a large study in 409 cirrhotic patients using TMT and SDT, where the prevalence of mHE was found to be 29%. In this study, the diagnosis of mHE required a pathologic finding on at least one of two neuropsychological tests. The percentage of mHE was highest in the Child-Pugh class C²². Several similar studies in fewer patients were done using only TNT and SDT, and the frequency of patients with mHE was identical²³⁻²⁵.

Das *et al.*²⁶ used a battery of 9 neuropsychological tests (including TMT and SDT) in 165 patients with liver cirrhosis and identified mHE in 62.4% of

patients. Minimal HE was more frequent in patients with a Child-Pugh score over 6. In Japan, Kato *et al.* tested 292 patients using a battery of 8 tests and found mHE in 58.2% of patients²⁷.

Citro *et al.* conducted a study in 77 patients, 59.1% of them having pathologic TMT result, thus fulfilling the criteria for a cognitive deficit most probably caused by mHE²⁸.

Sharma *et al.* used three neuropsychological tests, P300 evoked potentials and CCF (critical flicker frequency), and identified 53% of patients having mHE. In this study, as many as 83% of patients had pathologic findings on neuropsychological tests and the results were mostly dependent on the extent of liver damage²⁹.

Saxena *et al.* investigated the presence of cognitive deficits and extrapyramidal symptoms in patients with liver cirrhosis. For mHE diagnosis, they required a pathologic finding on one test, P300 evoked potentials or EEG. Thirty-five of 75 patients (47%) fulfilled the diagnostic criteria¹².

Certainly, there is a significant difference in the outcomes of studies focusing on mHE. Obviously, liver damage but also the methods used will greatly determine the frequency of patients with mHE.

In conclusion, current diagnostic methods allow for identifying functional disturbances before the onset of symptoms. Behavioral changes, avoidance of predisposing factors or timely treatment can help postpone or even avoid clinical forms of decompensated liver cirrhosis.

At present, there is no consensus on routine testing for mHE. Recent recommendations are mostly focused on testing and treating patients who do have symptoms like poor memory, lack of concentration, difficulties in performing everyday activities, or for patients who are at an increased professional risk of accidents (i.e. drivers)²⁷.

In case of identifying mHE, there is a definite need to prevent development of HE. The importance of its early diagnosis also lies in the improvement of the quality of life and work capacity of these patients, as there are consequences of this minor but still evident cognitive and neurological disorder.

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Sažetak

MINIMALNA JETRENA ENCEFALOPATIJA U BOLESNIKA S DEKOMPENZIRANOM JETRENOM CIROZOM

D. Marić, B. Klasnja, D. Filipović, S. Brkić, M. Ružić i V. Bugarski

Minimalna jetrena encefalopatija (mHE) obilježena je minimalnim nespecifičnim promjenama u moždanim funkcijama, koje se mogu otkriti samo neuropsihološkim ili neurofiziološkim testovima, ali koje ipak remete svakodnevni život bolesnika. Ranim prepoznavanjem ovih poremećaja mogla bi se spriječiti njihova progresija ili pak odgoditi razvoj bolesti u pravu jetrenu encefalopatiju. Cilj ove studije bio je dijagnosticirati mHE u bolesnika s dekompenziranom jetrenom cirozom. U studiju je bilo uključeno 60 bolesnika u dobi od 40-65 godina koji su podijeljeni u dvije skupine: eksperimentalnu i kontrolnu skupinu. Bolesnici u eksperimentalnoj skupini dalje su podijeljeni u Child-Pughove skupine A, B ili C: Child-Pugh B 53% i Child-Pugh C 47%. Bolesnici su ispitani pomoću tri neuropsihološka testa: Mini Mental Score za brzu procjenu kognitivnog statusa i dva specifična testa za promjene u mHE: Trail Making Test – Part A (TMT-A) i Symbol Digit Test (SDT). Elektroencefalogram je napravljen kod svih bolesnika. Granice za završetak testa postavljene su pomoću formule $X_{\text{control group}} + 2 \text{ SD}$ za TMT-A i $X_{\text{control group}} - 2 \text{ SD}$ za SDT. Sva tri testa iskazala su statistički značajno različite rezultate između dviju skupina. Svi bolesnici s cirozom imali su stanovite promjene u EEG. Studija je pokazala kako 80% bolesnika s cirozom ima znakove mHE. Child-Pughov zbir utjecao je na uspjeh u neuropsihološkim testovima. DST je bio brži u otkrivanju bolesnika s mHE. Naši rezultati ukazuju na učestalost mHE, kao i na važnost rane dijagnoze u prevenciji progresije mHE u pravu jetrenu encefalopatiju.

Ključne riječi: *Jetrena encefalopatija; Psihomotorički poremećaji; Neuropsihološki testovi; Elektroencefalografija*