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Cognitive functions in patients with liver cirrhosis: A tendency to commit more memory errors

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Background: Minimal hepatic encephalopathy (MHE) is the mildest form of hepatic encephalopathy (HE). For diagnostic purposes, 2 alternative batteries of psychometric screening tests are recommended. They differ from each other in terms of the cognitive domains assessed. The research was designed to provide a profile of cognitive functioning in patients with liver cirrhosis, using an assessment that covers a wider range of cognitive functions than the usual screening battery.

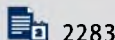
Material/Methods: We examined 138 persons, including 88 with liver cirrhosis and 50 healthy volunteers. The Mini Mental State Examination (MMSE) was used for screening and excluding advanced cognitive impairment. Then, to assess cognitive functions in more detail, the following tests were used: *Auditory Verbal Learning Test (AVLT)*, *Letter and Semantic Fluency Tests (LF and SF)*, *Trail Making Test (TMT A&B)*, *Digit Symbol Test (DST)*, *Block Design Test (BDT)*, and *Mental Rotation Test (MRT)*. The MRT task has not been used in MHE diagnosis so far. Finally, 57 patients and 48 controls took part in the entire study.

Results: Patients with liver cirrhosis commit significantly more errors of intrusions in the AVLT during the delayed free recall trial. Results significantly deviating from the norm in at least 2 tests were found only in 7 cirrhosis patients.

Conclusions: The results do not provide any specific profile of cognitive disturbances in MHE, but suggest that cirrhosis patients have a tendency to commit more memory errors, probably due to subtle impairments of executive function.

Key words: **AVLT • liver cirrhosis • minimal hepatic encephalopathy • MRT • neuropsychological tests**

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Background

Minimal hepatic encephalopathy (MHE) is the mildest form of overt hepatic encephalopathy (HE). Its occurrence is estimated at 30–84% according to different authors and it strongly depends on the diagnostic methods used, as well as the considered population [1–4]. The occurrence of MHE in the Polish population was estimated by Habor et al to be 17.6–31.3% [5]. MHE is a subtle cognitive impairment that can be detected with a neuropsychological assessment [6–7]. Other techniques using neurophysiological or neuroimaging methods can reveal differences in group comparisons; however, individual diagnosis on their basis is currently not possible [8–12]. MHE affects quality of life, as well as specific abilities like driving (it increases the risk of road accidents) [13,14], and can also lead to the development of overt hepatic encephalopathy, which is linked with increased mortality [3,4,15,16]. A study by Hilsabeck et al showed that cognitive disorders can be observed in patients with viral hepatitis C, even when no cirrhosis symptoms are observed. Intensification of cognitive deficits is related to advancement of the liver fibrosis process [17]. From the clinical point of view, it is essential to diagnose MHE as soon as possible in individual cases. This provides an opportunity for immediate commencement of treatment, which, according to numerous studies, significantly improves the prognosis [1,4,18,19].

However, the diagnosis of MHE is difficult, as there are no clear clinical symptoms that can be easily observed during a medical examination. Hence, there are attempts to employ a cognitive assessment in a more detailed way than provided by the Mini Mental State Examination (MMSE) scale. On the other hand, a sufficiently easy method would be preferred in order to avoid having to perform a time consuming and less available neuropsychological examination [6,7].

Currently, use of a Psychometric Hepatic Encephalopathy Score (PHES) is recommended. This consists of 4 paper-pencil tests: Digit Symbol Test (DST), Line Drawing Test (LDT), Serial Dotting Test (SDT), and Trail Making Test (TMT; comprised of parts A and B, but in the MHE literature sometimes referred to as 2 separate number connection tests, which is incorrect) [6,7]. All these tests are performed under time pressure. They require copying of simple graphic symbols or drawing lines from one place to another, or within a defined drawing path. Apart from the TMT, which is a commonly used neuropsychological test, the rest are not widely used in neuropsychological assessment. It is not clear which detailed aspects of cognitive functioning they measure besides psychomotor speed, which depends on attentional, motor, and perceptual efficiency. Moreover, all the information from the individual performance scores is obscured when the single total PHES score is calculated. The sensitivity of PHES is also mediated by age and education level [20].

On the other hand, the Commission on Neuropsychological Assessment of Hepatic Encephalopathy of the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) recommends using a battery other than PHES, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [21]. It is a simplified routine of neuropsychological assessment, which allows for separate examination of the following cognitive domains: immediate memory, visuo-spatial and construction abilities, attention, language, and delayed memory. Among other things, RBANS tasks require figure copying, learning a list of words and later recall of figure and words, picture naming, and choice of correct line orientation that matches the target line. Contrary to the PHES, which is used only in MHE research, the RBANS can also be used in screening for either dementia or cognitive impairments in other diseases [22,23].

These 2 methods differ in terms of the range of the examined cognitive functions. The PHES score depends to a greater extent on psychomotor speed. The RBANS score, on the other hand, depends on efficiency in other domains. However, although RBANS assesses a wider range of abilities, it does not allow for measuring executive functions, but the PHES includes the TMT test, which does measure them. Hence, the 2 methods can detect a decrease in cognitive functioning in different groups of patients, which in consequence leads to inconsistent MHE diagnosis.

In the present study, a different way of assessing cognitive functions in patients with liver cirrhosis was used. It was expected that this would enable quantification of the abilities that are also covered by either PHES or RBANS. In addition to typical scores defined on the basis of performance time or number of correct responses, the number of errors was also considered. In typical neuropsychological assessment, when cognitive impairments are suspected it is of key importance to examine the number and type of errors committed, instead of global performance. However, this information is rarely taken into account during the examination of patients with liver cirrhosis. The aim of the study was to determine a profile of cognitive functioning in patients with liver cirrhosis and to determine the usability of typical clinical tests in the diagnosis of MHE.

Material and Methods

We examined 138 subjects, including 88 patients with liver cirrhosis being treated in the outpatient clinic of the Department of Gastroenterology, Hepatology and Infectious Diseases, Jagiellonian University Medical College Hospital and 50 healthy volunteers, matched according to demographic data. All participants signed written informed consent forms after receiving detailed information regarding the study. The procedure was compliant with the directives of the Helsinki Declaration (1975; 6th

revision, 2008) and was approved by the Bioethics Committee of Jagiellonian University (approval no. K/PBW/000340).

Criteria used for exclusion were: neurological, psychiatric or other serious diseases unrelated to hepatic insufficiency; any symptoms of brain lesions or peripheral nervous system disorders found during the neurological examination; regular intake of anticonvulsants, psychoactive drugs or narcotics reported during the inquiry; and symptoms of overt hepatic encephalopathy, stage 1 or more in West Haven criteria and score on the MMSE [24] of less than 27. Finally, 57 patients and 48 controls took part in the entire study.

Liver cirrhosis was diagnosed on the basis of medical documentation, biochemical tests, USG, CT, and MRI examination of the abdominal cavity. A liver biopsy was performed in 16 patients. The stage of hepatic insufficiency was assessed using the Child-Pugh scale. The etiology of liver cirrhosis in the patient group was viral hepatitis B or C.

The following examinations were performed: medical history inquiry, biochemical tests, and neurological and neuropsychological tests. According to recommendations for routine neuropsychological assessment [6,7], the following tests were used: the Digit Symbol Test (DST) [25], the Block Design Test (BDT) [25], and TMT [22,26]. The battery also includes: the Letter Fluency (LF) and the Semantic Fluency (SF) tests [22,26], the Auditory Verbal Learning Test (AVLT) [27], and the computerized version of the Mental Rotation Test (MRT) [28]. The MRT has not been used until now in MHE diagnosis. These tests measure attention and psychomotor speed (DST, TMT A), executive functions (TMT B, LF), language (SF), episodic memory (AVLT), and visuo-spatial abilities with the influence of constructional abilities (BDT) and without them (MRT). It was assumed that MHE would be diagnosed when the subject scored 2 standard deviations (SD) below the mean of the control group in at least 2 tests.

Statistical analysis

Due to violated normality assumption in the data distributions, results were analyzed using the non-parametric Mann-Whitney U test (neuropsychological data) and Kruskal-Wallis test (liver cirrhosis etiology). To avoid type-I errors (false positive) related to multiple comparisons, p-levels obtained in single analysis were corrected using the FDR (false discovery rate) procedure. The co-variation between the biochemical and neuropsychological data was analyzed with Spearman's rho correlation.

Results

Demographic data in both groups are shown in Table 1. The MMSE scores did not reveal significant differences between

Table 1. Demographic data.

	Clinical group N=57		Control group N=48	
Age (SD)	40.91	(10.87)	40	(13.21)
Men (N%)	29	(50.88%)	23	(47.92%)
Education (N%)				
<12 years of education	14	(24.56%)	8	(16.67%)
12 years of education	22	(38.60%)	18	(37.50%)
16 years of education	21	(36.84%)	22	(45.83%)

SD – standard deviation; N – sample size.

Table 2. Results of biochemical tests (SD values in brackets).

	Clinical group N=57		Control group N=48		p
Platelets, μ L [norm: 125–340]	193.25	(80.63)	225.96	(59.58)	0.15
INR [norm: 0.91–1.2]	1.07	(0.18)	1.01	(0.08)	0.04*
AST, U/L [norm 10–40]	58.95	(44.5)	25.44	(12.81)	<0.01*
ALT, U/L [norm: 10–41]	95.69	(109.64)	32.52	(23.23)	<0.01*
AP, U/L [norm: 91–258]	232.73	(158.15)	147.38	(82.29)	<0.01*
GGTP, U/L [norm: 5–61]	179.45	(234.25)	37.44	(45.96)	<0.01*
Bilirubin, μ mol/L [norm: 0–17.1]	17.68	(14.12)	12.69	(6.84)	0.04*
Albumin, g/L [norm: 35–50]	45.36	(4.43)	47.10	(4.28)	0.12
Ammonia, μ mol/L [norm: 9–33]	40.31	(28.69)	22.17	(7.07)	<0.01*
Child-Pugh, (N%)					
A	36	(63.15%)			
B	21	(36.84%)			

SD – standard deviation. Asterisks indicate a significant difference between groups. N – sample size; p – significance level (Mann-Whitney U-test).

the patient and the control group (29.03; SD 1.38 vs. 29.80; SD 0.50). Therefore, the cognitive abilities measured by this test were equal in both groups.

Significant differences between the groups were found in complete blood count for AST, ALT, AP, GGTP, ammonia ($p < 0.01$), INR, and bilirubin level ($p < 0.05$). In the clinical group, a decreased number of thrombocytes and a decreased level of albumin were observed, but did not reach statistical significance. The results of the biochemical tests are shown in Table 2.

Table 3. Results of neuropsychological tests (SD values in brackets).

	Clinical group N=57		Control group N=48		p	FDR-p
AVLT 1 correct responses	6.39	(1.61)	6.96	(1.97)	0.13	0.19
AVLT 2 correct responses	9.09	(2.33)	9.44	(2.41)	0.72	0.99
AVLT 3 correct responses	10.58	(2.34)	11.33	(2.09)	0.15	0.19
AVLT 4 correct responses	11.26	(2.18)	12.00	(2.18)	0.06	0.17
AVLT 5 correct responses	11.77	(2.36)	12.54	(2.12)	0.06	0.17
AVLT 1-5 total correct responses	49.09	(9.31)	52.27	(9.42)	0.11	0.18
AVLT 1-5 total perseverations	2.63	(3.41)	2.77	(2.52)	0.27	0.29
AVLT 1-5 total intrusions	1.07	(2.54)	0.35	(0.89)	0.26	0.28
AVLT delayed recall - correct responses	10.87	(2.8)	11.83	(2.82)	0.09	0.18
AVLT delayed recall - intrusions	0.59	(0.81)	0.23	(0.59)	0.006	0.05*
DST points	50.26	(12.42)	54.08	(11.71)	0.18	0.21
TMT A time (s)	29.07	(12)	28.13	(8.93)	0.81	0.99
TMT A errors	0.16	(0.37)	0.15	(0.41)	0.67	0.99
TMT B time (s)	73.96	(41.02)	70.60	(39.52)	0.99	0.99
TMT B errors	0.33	(1.11)	0.50	(0.88)	0.12	0.19
LF correct responses	16.21	(5.36)	17.06	(4.77)	0.32	0.38
SF correct responses	22.79	(5.83)	22.65	(6.77)	0.68	0.99
BDT points	30.89	(8.27)	32.63	(8.29)	0.31	0.38
MRT correct responses	23.84	(4.01)	23.81	(4.86)	0.77	0.99
MRT errors	7.98	(3.92)	8.85	(5.82)	0.79	0.99

SD – standard deviation; AVLT – Auditory Verbal Learning Test; DST – Digit Symbol Test; TMT – Trail Making Test; LF – letter fluency; SF – Semantic Fluency; BDT – Block Design Test; MRT – Mental Rotation Test. Asterisks indicate significant differences between groups. N – sample size; p – significance level (Mann-Whitney U-test); FDR-p – FDR corrected significance level.

Neither biochemical nor neuropsychological differences were observed in relation to the various etiologies of liver cirrhosis in the clinical group. No correlations were found between biochemical and neuropsychological scores in any of the groups.

Neuropsychological test scores are shown in Table 3. As can be seen, more intrusions were found in the clinical group (0.59; SD 0.81) than in the control group (0.23; SD 0.59) in the AVLT delayed free recall trial ($p < 0.01$).

The criterion of deviating more than 2 SD on at least 2 tests was fulfilled in 7 (12.3%) liver cirrhosis patients. However, more patients revealed such deviation on 1 of the tests only. This does not satisfy the MHE criteria, although it shows some selective cognitive impairments. The data are presented in Table 4.

Discussion

The only statistical difference between the clinical and the control group was found in the intrusions level in the AVLT delayed free recall. Intrusions can be interpreted as difficulty in distinguishing whether information currently present in the mind is a kind of recollection related to the task or an association not related to the task itself, which is called source monitoring [26]. In the cognitive model of intrusions it is assumed that they can result from natural processes organizing encoding and retrieval [29]. According to this model, all information that is temporarily stored in the short-term memory (STM) activates semantically or phonetically related information in the long-term memory (LTM). During the encoding phase, relevant task-related information can activate content from the LTM, which is not directly related to the task, and

Table 4. Psychometric tests in which single subjects scored below 2SD from the mean.

	Clinical group N=57	Control group N=48	P
AVLT 1 correct responses	1 (1.75%)	0 (0.0%)	0.36
AVLT 5 correct responses	3 (5.26%)	3 (6.25%)	–
AVLT 7 delayed recall – correct responses	4 (7.02%)	2 (4.17%)	0.49
LF correct responses	4 (7.02%)	2 (4.17%)	0.53
TMT A time (s)	4 (7.02%)	2 (4.17%)	0.53
TMT B time (s)	5 (8.77%)	3 (6.25%)	0.63
DST points	4 (7.02%)	1 (2.08%)	0.24
BDT points	3 (5.26%)	2 (4.17%)	0.79

SD – standard deviation; AVLT – Auditory Verbal Learning Test; LF – Letter Fluency; TMT A – Trail Making Test A; TMT B – Trail Making Test B; WAIS-R – Wechsler Adult Intelligence Scale-Revised; DST – Digit Symbol Test; BDT – Block Design Test; N – sample size; p – significance level (chi-square).

both can be encoded together. Retrieval in this model is described as activation of information in the LTM related to the retrieval cue. One recalled piece of information helps in the recall of another (e.g., one word from the list helps in the recall of the next word). Even when the information has been encoded properly, the retrieved information can activate content in LTM that is non-related to the task. Clinical data show that basic functions such as organizing and controlling information processing in memory can be assigned to the executive functions cognitive domain.

A high amount of intrusions in tests based on learning a list of words (such as AVLT) can be observed in frontal lesions [26] and in dementia, including Alzheimer's disease (AD) [30]. AD impairs episodic memory at its early stages; this is the main reason for decreased AVLT performance. However, the relationship between intrusions in free recall trials and efficiency of the frontal lobes in AD has been proved [31]. An increase of intrusions was also found, to a lesser extent, in a group of schizophrenia patients with executive function disorders compared to those with schizophrenia but without executive impairments [32]. Similarly, the same effect was found in children with either Tourette syndrome or ADHD compared to a control group, even when executive functions tests did not show any changes [33]. Similar results were obtained in our study, where the measures of executive functions (TMT B, fluency tests) did not show an apparent decrease in performance. This suggests that the number of intrusions in AVLT is a very sensitive indicator in both mild and severe cognitive disorders and

is related to other kinds of executive functions than those examined with the TMT B or fluency tests.

No significant differences were found in AVLT measures of short-term memory span (the first trial), learning process (sum of tests 1–5), or general index of encoding and retrieval (correct answers in delayed free recall trial), which suggests that the 2 groups do not differ in episodic memory, although some near-significant subtle differences were observed. Ortiz et al. [34] described episodic memory impairment measured with AVLT in MHE patients with subsequent improvement after liver transplantation. However, the number of errors was not considered in this study. It can be assumed that a larger sample would make our near-significant AVLT effects stronger, which is in line with the suggestion of specific memory impairments in MHE.

The tests in which the cirrhosis patients scored 2 SD below the mean were most often related to executive functions (TMT B and LF), to psychomotor speed (TMT A and DST), and to memory (AVLT). Executive dysfunction and bradyphrenia are symptoms of a subcortical profile of cognitive impairment, which is sometimes described in MHE patients [35]. However, there were only a few patients diagnosed with MHE according to the criteria used in our study. This does not allow us to reach conclusions about the specific profile of cognitive impairments. Recommendations for MHE diagnosis suggesting the use of neuropsychological tests (e.g., BDT, DST, or TMT) or screening batteries (e.g., PHES or RBANS) are designed for quantitative assessment. In such a case, the number of failed tests is taken into account, but not their specific kind. This is not theoretically satisfying, but in light of the obtained results, no further directions for clinical practice can be provided unless future research reveals more reliable data on the cognitive profile of MHE.

Conclusions

Among the many neuropsychological tests used in this study, only one showed significant differences in performance. It was found that patients with liver cirrhosis have a tendency to commit significantly more errors of intrusions in the AVLT test during the delayed free recall trial, but they perform relatively well in other kinds of tasks. Although no MHE-specific profile of cognitive deficits could be identified, our findings suggest that cirrhosis patients have a tendency to commit more memory errors. This was interpreted as a possible effect of subtle impairments of executive function.

Conflict of interests

The authors declare that they have no conflict of interests.

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