ORIGINAL ARTICLE

Assessment of cognitive impairment in patients with chronic viral hepatitis

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Abstract

Background: Chronic viral hepatitis is a systemic disease characterized by a wide range of extrahepatic manifestations, one of which is cognitive impairment. *Aim and Objectives:* To assess cognitive impairment in patients with chronic viral hepatitis at various stages of liver fibrosis and assess factors affecting cognitive dysfunction. *Material and Methods:* Two hundred thirty three patients with chronic viral hepatitis at the Infectious Diseases Hospital of Shymkent City and the Regional Hepatological Center of Shymkent City were enrolled between March 2021 and January 2022. All patients were surveyed on Montreal Cognitive Assessment (MoCA) to confirm the presence of cognitive impairment. *Results:* Mild cognitive impairment was detected in 12.7% patients with fibrosis stage F_0, at the stage F_1-20.7% of patients, at the stage F_2- 32.5% of patients, at the stage F_3- 36.8% of patients, at the stage F_4-40% of patients. Subsequent multiple regression analysis showed that older age ($p < 0.023$) and duration of the disease ($p < 0.002$) were the variables most closely associated with cognitive impairment. *Conclusion:* The early identification of cognitive impairment in patients with chronic viral hepatitis is necessary due to the high risk of their progression to the stage of severe cognitive deficit.

Keywords: Viral Hepatitis, Neurocognition, Mild Cognitive Impairment, Montreal Cognitive Assessment

Introduction

Viral hepatitis is one of the global socially significant problems worldwide for public health and is characterized as one of the main causes of disability and mortality among the population [1-5]. Viral hepatitis is a systemic disease characterized by a wide range of extrahepatic manifestations caused by a variety of immunological disorders caused by the replication of viruses in the liver and beyond, as well as the direct pathological influence of viral particles [6]. Patients with chronic viral hepatitis may have various neurological manifestations, which range from cognitive impairment to peripheral neuropathy [7-8]. According to various researchers, patients may experience symptoms such as fatigue, depression, attention disorders and verbal thinking. Some authors have found that the prevalence of depression in elderly patients is quite high, and it increases with age [9]. However, in patients with chronic viral hepatitis, depression can be detected at a younger age and these neuropsychiatric manifestations do not have a complete connection with improved liver function or other psychosocial factors [9]. In addition, cognitive impairment may occur in patients with chronic viral hepatitis in the absence of cirrhosis of the liver or liver failure [10]. Therefore, the aim of this study was to assess cognitive impairment in patients with chronic viral hepatitis at various stages of liver fibrosis.

Material and Methods

Study setting and study design

A study was conducted in the Infectious Diseases Hospital of Shymkent City and in the Shymkent Regional Hepatological Center of Shymkent City, Shymkent, Kazakhstan, from March 2021 to January 2022.The research is carried out in accordance with the ethical principles approved by the Experiments Ethics Committee of Kazakh Medical University of Continuing Education (Protocol № 3 of 17.03.2020, Protocol № 3 of 16.03.2021) and Asfendiyarov Kazakh National Medical University (Protocol № 7 of 30.05.2022).

We examined 233 patients with an established diagnosis of chronic viral hepatitis B, chronic viral hepatitis C, chronic viral hepatitis D. The patients were were on inpatient treatment at the Infectious Diseases Hospital of Shymkent City and were approached during their scheduled visit to the at the Shymkent Regional Hepatological Center of Shymkent City between March 2021 and January 2022. The collection of basic information, analysis of demographic, clinical, laboratory, and instrumental data was carried out after receiving written informed consent from the patient.

A total of 233 patients 28.3% (n=66) were residents of Shymkent, 71.6% (n=167) applied from various districts of Turkestan region: Suzak, Sairam, Kazygurt, Arys, Saryagash, Maktaral, Tolebi, Baudibek. All patients with chronic viral hepatitis were distributed by gender: patients 111 (47.6%) were male and 122 (52.4%) were female, whose average age was 47.14 ± 14.1 years. Patients with chronic viral hepatitis had different duration of the disease: from 1 month to 20 years or more. The patients had clinical symptoms and laboratory changes characteristic of different degrees of activity in chronic viral hepatitis. We analyzed patients with the following diseases: chronic viral hepatitis C - 98 (42.1%), chronic viral hepatitis B – 41 (16.7%), chronic viral hepatitis D- 40 (17.1%), liver cirrhosis of HBV etiology- 5 (2.1%), liver cirrhosis of HCV etiology- 33 (14.2%), liver cirrhosis of HBV+ HDV etiology- 18 (7.7%).

The patients were divided into stages of liver fibrosis. Thus, F_0 included patients 47 (20.2%), F_1 - patients 52 (22.7%), F_2 - patients 40 (17.2%), F_3 - patients 38 (16.3%), F_4 - examined patients 56 (23.6%). Confirmation of the diagnosis of chronic hepatitis B, chronic hepatitis C and chronic hepatitis D was carried out according to the criteria published by the European Association for the study of the liver [11-12]. The diagnosis of the stage of liver fibrosis was established using indirect ultrasound elastography (or elastometry) "FibroScan" (Echosens, Paris, France) with further interpretation of the results according to the recommendations of EASL-ALEH [13].

Montreal Cognitive Assessment (MoCA)

The presence of cognitive impairment was detected by interviewing the patient on the MoCA, according to which various cognitive areas were evaluated, including attention and its concentration, visual-constructive and executive skills, memory, speech, abstract thinking, counting and orientation. The norm of parameter was the number of points in the range from 26 to 30 (30 points-the maximum possible points), parameter in the range from 22 to 25 points indicate the presence of mild cognitive impairment, less than 22 points - severe cognitive impairment [14].

Statistical analysis

Data were analyzed using the statistical software SPSS (version 22.0, SPSS Inc., Chicago, IL, USA) for Windows. Summary statistics for all variables were calculated. Normal distribution of data was evaluated by analytical methods (Kolmogorov-Smirnov test). Kruskal-Wallis test, Mann–Whitney U test and multiple regression analysis were used to analyze the data. All the p-values were two-tailed. Data were considered to be statistically significant with at $p < 0.05$. Quantitative variables are expressed as mean ± standard deviation.

Results

Patients were distributed by the number of points scored, so the average number of points on the MoCA in patients at the stage F_0 is 28 ± 1.0 in patients at the stage F_1 is 25 ± 1.9, at the stage F_2 is 25 ± 1.0, at the stage F_3 is 24 ± 1.0, at the stage F_4 is 23.58 ± 1.0 (Table 1).

Patients 84 (36%) had low indicators obtained by applying the MoCA scale. Thus, at the stage F_0 6 (12.7%) patients scored below 26 points, at the stage F_1 - 13 (24.47%) patients, at the stage F_2 - 15 (37.5%) patients, at the stage F_3 - 18 (47.3%) patients, at the stage F_4 - 26 (50.1%) patients. Mild cognitive impairment was detected in 12.7% patients with fibrosis stage F_0, at the stage F_1 - 20.7% of patients, at the stage F_2 - 32.5% of patients, at the stage F_3- 36.8% of patients, at the stage F_4 - 40% of patients. Severe cognitive impairment had 3.77% patients at the stage F_1, 5% of patients at the stage F_2, 10.5% patients at the stage F_3 and 14.5% patients at the stage F_4 (Figure 1).

Thus, 35% of patients at the stage F_0, 37% of patients at the stage F_1, 40% of patients at the stage F_2, 42% of patients at the stage F_3, 45% of patients at the stage F_4 had difficulties with performing tests for visual-constructive and executive skills. With delayed playback (after 5 minutes), 23% of patients at stage F_0, 32% of patients at stage F_1, 41% of patients at stage F_2, 45% of patients at stage F_3, 52% of patients at stage F_4 had difficulty remembering 2 or more words. When assessing attention, errors were noted in 21% of patients at stage F_0, in 24% of patients at stage F_1, in 32% of patients at stage F_2, in 45% of patients at stage F_3, in 51% of patients at stage F_4.

When analyzing abstract thinking tasks, errors were recorded when performing tasks in 18% of patients at the stage F_0, in 25% of patients at the stage F_1, 28% of patients at the stage F_2, 29% of patients at the stage F_3, and in 44% of patients at the stage F_4. Disorientation in time and space was detected in 2% of patients at stage F_3, in 4% of patients at stage F_4, however, errors were associated with the current date. Thus, in patients with chronic

Table 1: Average MoCA score in patients with chronic viral hepatitis

Characteristic	Total number (n = 233)	F_0 (n = 47)	F_1 (n = 53)	F_2 (n = 40)	F_3 (n = 38)	F_4 (n = 55)
MoCA	25 ± 1.04	28 ± 1.0	25 ± 1.9	25 ± 1.0	24 ± 1.0	23.58 ± 1.0

Values were expressed in Mean ± SD

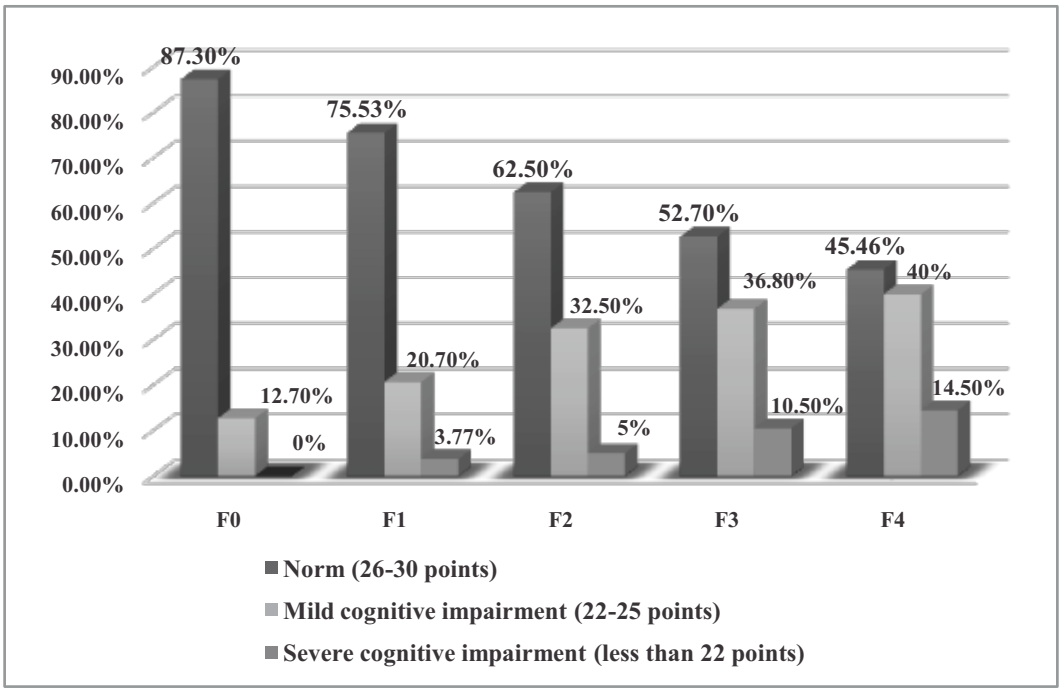

Figure 1: MoCA test results in patients with chronic viral hepatitis at various stages of Fibrosis

viral hepatitis there was a tendency for cognitive impairment to increase with an increase in the stage of fibrosis. The most frequent violations of cognitive functions at various stages of fibrosis were: impaired concentration, memory impairment.

Table 2 presents the results of an analysis conducted to assess the factors affecting the total the MoCA scores in assessing cognitive impairment in patients with chronic viral hepatitis. The conducted correlation analysis showed that the demographic factor (age) It was significantly associated with a decrease in MoCA ($p < 0.000$), so patients older than 50 years reported a greater decrease in MoCA than in the other study groups. Another significant predictor of a decrease in MoCA was the stage of liver fibrosis ($p < 0.001$), so starting from the stage of liver fibrosis above F_1, there was a significant decrease in total MoCA scores. Gender ($p > 0.925$), etiology of the disease ($p > 0.925$), duration of the disease ($p > 0.595$) were not associated with MoCA. We also analyzed the possible impact of clinical characteristics associated with chronic viral hepatitis on the reduction of MoCA using the Mann–Whitney U test. As shown in Table 2, none of the markers of liver disease was associated with a decrease in MoCA. Gender ($p > 0.925$), etiology of the disease ($p > 0.925$), duration of the disease ($p > 0.595$) were not associated with MoCA.

The conducted multiple regression analysis demonstrated that age and duration of the disease were variables significantly associated with cognitive impairment in patients with chronic viral hepatitis. Thus, stepwise analysis of multiple linear regression with significant variables showed that age ($p < 0.023$) and disease duration ($p < 0.002$) are the most significant predictors of a decrease in MoCA. The multiple correlation coefficient (r) was 0.106, and the adjusted r^2 was 0.082 ($F = 38.964$, $p < 0.001$) (Table 3).

Table 2: Correlation of cognitive impairment

Variables	MoCA *		
	n	Mean ± SD	*p*
Age (years) *			
18-19	4	28.0 ± 1.5	
20-29	25	27.6 ± 1.6	
30-39	50	27.4 ± 2.1	
40-49	52	26.8 ± 2.3	0.000*
50-59	38	24.7 ± 3.4	
60-69	59	24.1 ± 3.4	
70-79	5	24.0 ± 3.2	
Gender**			
Male	111	26.1 ± 2.5	0.925
Female	122	25.7 ± 3.5	
Disease *			
Chronic viral hepatitis B	44	26.3 ± 2.7	
Chronic viral hepatitis C	132	26.3 ± 2.7	0.106
Chronic viral hepatitis D	57	24.9 ± 3.6	
Duration of the disease *			
Up to 1 year	28	26.6 ± 2.7	
>1 to 5 years	109	26.0 ± 3.1	
6-10 years	73	25.7 ± 3.1	0.595
11-20 years	19	25.5 ± 3.4	
More 20 years	4	23.5 ± 5.2	
Fibrosis (kPa) *			
F_0	47	28.0 ± 1.0	
F_1	53	25.0 ± 1.9	
F_2	40	25.0 ± 1.0	0.001*
F_3	38	24.0 ± 1.0	
F_4	55	23.5 ± 1.0	
Serum ALT levels **			
Norm	34	26.4 ± 2.9	0.333
Excessive	199	25.8 ± 3.1	
Serum AST levels **			
Norm	47	26.5 ± 3.0	0.084
Excessive	186	25.8 ± 3.1	
Viral load**			
Low	131	26.1 ± 3.0	0.445
High	102	25.7 ± 3.2	

** Kruskal — Wallis test ** Mann–Whitney U test*

Table 3: Multiple regression analysis of factors affecting cognitive impairment in patients with chronic viral hepatitis at different stages of fibrosis (n=233)

Parameter	Multiple regression analysis	
	beta	*p*
Age	-0.472	0.023*
Gender	-0.113	0.414
Duration of the disease	0.539	0.002*
Form of chronic viral hepatitis	0.063	0.731
Stage of fibrosis	-0.163	0.507
Serum ALT levels	0.011	0.896
Serum AST levels	-0.104	0.223
Viral load	-0.059	0.373

Regression Statistics r^2 Adjusted = 0.106

Discussion

Studies devoted to the study of cognitive impairment in patients with chronic viral hepatitis are limited. As far as we know, our study is the first to study the prevalence of cognitive impairment and factors affecting cognitive function in patients with chronic viral hepatitis. The complexity and limitations of the study lies in the fact that at the moment there are no specific neuropsychological instruments for assessing cognitive dysfunction in this category of patients. There are studies in the literature devoted to the study of cognitive deficits in patients with chronic viral hepatitis, but they focus on chronic viral hepatitis C. In addition, they indicate the heterogeneity of the sample of patients and indicate a different degree of mixed factors [8, 10, 15, 16].

According to some authors, it has been noted that gender can have an impact on cognitive impairment [16]. However, in our study, it was not found that more severe cognitive dysfunction is registered in female patients compared with male.

In another study conducted, it was found that patients with cirrhosis have significant cognitive impairment compared to patients without it, while it is noted that functional liver tests and clinical parameters in patients have no correlation with their cognitive functions [17]. However, this study studied cognitive impairment in patients at the terminal stages of the disease and did not take into account the stage of liver fibrosis.

Viral hepatitis can lead to a decrease in cognitive functions. However, the mechanisms leading to their decrease are unknown [18]. According to the results of studies by other authors, cognitive impairments can be observed in patients with chronic viral hepatitis even in the early stages of the disease and do not depend on the stage of fibrosis [18-20]. In our study, cognitive impairment was also recorded in the early stages of the disease. However, the results of other authors demonstrate convincing evidence that cognitive dysfunction can be observed in patients with chronic viral hepatitis with a mild form of the disease [21]. In other studies by Córdoba *et al*. and by Amendola-Pires *et al*., in patients with chronic viral hepatitis with an increase in the degree of fibrosis, further significant cognitive impairment is noted, in particular in patients with decompensated cirrhosis of the liver [22-23]. The data of our study are consistent with the results of the previous study and prove this fact.

In the study of Bar *et al*., the influence of virology on the severity of cognitive impairment was studied, so according to their research, it was found that a high level of viral load significantly affects the level of neurocognitive disorders in patients with chronic viral hepatitis. However, our study showed that the level of viral load is not a predictor of cognitive decline [24]. Similar results were obtained in the Dirks *et al*. study, which showed that cognitive impairments are detected regardless of viremia [25].

In our study, 36% of patients were found to have cognitive impairment in patients with chronic viral hepatitis, but Fortini *et al*. found a 23.7% prevalence of cognitive impairment in patients, which is likely due to the use of other more sophisticated tools for neuropsychological assessment [26]. According to the authors, the age and duration of viral hepatitis infection are the main clinical determinants of cognitive dysfunction [7]. Our study also demonstrates similar results.

Conclusion

This study suggests that the examination of cognitive disorders in patients with chronic viral hepatitis, which provides for the complex application of clinical and laboratory indicators and the results of neuropsychological tests, allows to diagnose cognitive disorders at an early stage, to make timely correction of treatment, to carry out dynamic control of the therapy.

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