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CHRONIC FATIGUE IN PATIENTS WITH CHRONIC VIRAL HEPATITIS

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ABSTRACT

The aim of this prospective observational study was to assess the relationship between chronic fatigue, etiology of disease, age, gender, duration of disease, stage of liver fibrosis and degree of inflammation in patients with chronic viral hepatitis. 233 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 a Fatigue Severity Score Scale (FSS) to confirm the presence of chronic fatigue. A total score of 4 or higher indicates the presence of chronic fatigue. Clinical data included age, gender, etiology of disease, duration of disease, stage of liver fibrosis, serum ALT levels and serum AST levels. Subsequent multiple regression analysis showed that older age ($p < 0.000$), gender (female) ($p < 0.058$) and fibrosis stage ($p < 0.000$) were the variables most closely associated with chronic fatigue. The early identification of chronic fatigue is necessary due to the high risk of progression to the stage of severe cognitive deficit.

1. Introduction

Viral hepatitis plays a significant role in the structure of diseases of the digestive system. It affects the lives of hundreds of millions of people around the world and is a source of steadily progressive morbidity and mortality. Viral hepatitis B (HBV) and viral hepatitis C (HCV) are the most common which tend to chronic infection and are characterized by inflammatory processes in the liver, capable of eventually trasforming into fibrotic and cirrhotic changes[1,2]. According to the latest estimates, more than 257 million people in the world have active HBV infection, and according to some researchers, the number of infected could be as many as 350 million, the estimates for HCV infection are between 71 and 150 million people[3,4].

One of the most severe forms of chronic viral hepatitis is chronic viral hepatitis D (HDV), which can often develop into liver cirrhosis and hepatocellular carcinoma[5]. A necessary condition for the manifestation of pathogenicity in chronic viral hepatitis D is the simultaneous presence of HBV infection[6]. Thus, according to the latest data, worldwide 5% of patients chronically infected with HBV are also infected with chronic viral hepatitis D, which is estimated to be about 20 million people[7].

Cognitive function disorders and neuropsychiatric disorders which do not depend on the severity of liver disease or the rate of replication of HCV infection[8] are present in almost 50% of patients with HCV infection.

In addition, symptoms such as chronic fatigue, sleep disturbance, depression and decreased quality of life are usually associated with neurocognitive changes in patients with non-cirrhotic chronic HCV infection, regardless of the stage of fibrosis, the infecting genotype and in the absence of structural brain damage or signal abnormalities revealed

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through conventional magnetic resonance imaging of the brain[9].

The term «Chronic Fatigue Syndrome» was adopted in Atlanta in 1994. According to the CDC classification, the term includes a set of symptoms, such as feeling unreasonably tired for 6 months or more, prolonged unmotivated subfebrility, headaches, muscle pain, joint pain, sleep disturbance and a state of unmotivated depression. Some patients may complain of a violation of short-term memory and a decrease in the ability to concentrate[10].

In chronic liver diseases chronic fatigue may be one of the important symptoms affecting the quality of life of this group of patients and which has no correlation with the severity of liver disease[11,12]. Thus, with chronic HCV infection in different cohorts the prevalence of chronic fatigue ranges from 20% to 80% of patients[12]. The pathogenesis of fatigue in chronic viral hepatitis remains poorly understood, while there is little progress in the treatment of this debilitating symptom in most cases[13]. It should be noted that patients with cirrhosis, as a rule, have complex multiple organ dysfunction. However, fatigue may also appear in patients with non-cirrhotic liver disease[14]. Infectious agents such as hepatitis C virus are considered as etiological agents of the development of chronic fatigue syndrome, moreover, antiviral treatments used to suppress them are regarded as potential triggers or as contributing causes of the formation of chronic fatigue syndrome[15]. Fatigue is an important clinical finding in patients with chronic hepatitis virus infection.

The aim of our study is to evaluate the presence of chronic fatigue in patients with chronic viral hepatitis.

2. Material and methods

Study design and subjects

The current study was conducted at the Infectious Diseases Hospital of Shymkent City and the Regional Hepatological Center of Shymkent City between March 2021 and January 2022. The study protocol was approved by the Local Ethics Committee of the Asfendiyarov Kazakh National Medical University. All participants gave written informed consent before study entry. The study involved 233 patients with chronic viral hepatitis, who were on inpatient treatment at the Infectious Diseases Hospital of Shymkent City and were approached during their scheduled visit to the Shymkent Regional Hepatological Center of Shymkent City. Inclusion criteria were: patients aged over 18 years with an established diagnosis of chronic viral hepatitis B, chronic viral hepatitis C or chronic viral hepatitis D. Exclusion criteria were: patients under the age of 18, pregnant patients, or patients with , cancer, pacemaker, HIV infection, obesity, acute forms of viral hepatitis and/or a history of mental disorders. The patients had different disease durations: from 1 month to 30 years. The patients had clinical symptoms and laboratory changes corresponding to different degrees of activity in chronic viral hepatitis. Chronic hepatitis B, chronic hepatitis C and chronic hepatitis D diagnosis was confirmed based on criteria published by the European Association for the study of the liver [16,17]. Liver fibrosis was staged using indirect ultrasound elastography (or elastometry) «FibroScan» (Echosens, Paris, France) with subsequent interpretation of the results according to EASL-ALEH Clinical Practice Guidelines[18].

Assessment and Quantitation of Fatigue

Chronic fatigue was assessed using the Fatigue Severity Score Scale[19], which was translated into Russian. It is a self-report, generic instrument, which includes 9 items (questions) that evaluate the severity of fatigue. Grading of each item ranges from 1 to 7, where 1 indicates strong disagreement and 7 strong agreement, and the final score represents the mean value of the 9 items. The total score was calculated: a score of 4 or higher indicates the presence of chronic fatigue.

Statistical analyses

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). One-way analysis of variance (ANOVA), chi-square test, Pearson correlation analysis and univariate and multivariate logistic regression analysis were used to analyze the data. All the p-values were two-tailed. Data were considered to be statistically significant at $p < 0.05$. Quantitative variables are expressed as mean±standard deviation.

Ethics statement

Written informed consent was obtained from the patients for publication of this article.

3. Results

Baseline characteristics of the enrolled patients

The baseline characteristics of the 233 patients are presented in Table 1.

The patients were distributed by gender: male - 111 patients (47,6%), female - 122 patients (52,4%). 66 people (28.3%) were residents of Shymkent, 167 people (71.6%) were residents of various districts of Turkestan region. There were 111 men and 122 women, with a mean age of 47,14±14,1. The patients had different disease durations: from 1 month to 29 years. According to the structure, we studied patients with the following nosologies: chronic viral hepatitis B – 44 patients (18,9%), chronic viral hepatitis C- 132 patients (56,7 %), chronic viral hepatitis D - 57 patients (24,4%), The patients were also distributed according to the stages of fibrosis: F_0- 47 patients (20,2%), F_1 - 52 patients (22,7%), F_2 - 40 patients (17,2%), F_3 - 38 patients (16,3%), F_4 - 56 patients (23,6%).

Characteristics		Patients with chronic viral hepatities (n = 233)	
		n	%
Gender	Male	111	47.6
	Female	122	52.4
Age	18-19	4	1.7
	20-29	25	10.7
	30-39	50	21.5
	40-49	52	22.3
	50-59	38	16.3
	60-69	59	25.3
	70-79	5	2.2
Nosological structure of patients with chronic viral hepatitis	Chronic viral hepatitis B	44	18.9
	Chronic viral hepatitis C	132	56.7
	Chronic viral hepatitis D	57	24.4
Duration of the disease	<1 year	28	12.1
	1-5 years	109	46.7
	6-10 years	73	31.3
	11-20 years	19	8.2
	>20 years	4	1.7
Distribution of patients with chronic viral hepatitis by fibrosis stages	F_0	47	20.2
	F_1	53	22.7
	F_2	40	17.2
	F_3	38	16.3
	F_4	55	23.6

Table 1. Baseline characteristics of the enrolled patients

One hundred and twenty patients (51,5%) presented abnormal ALT/AST rates at the time of the assessment. There were statistically significant differences in age, gender and duration of the disease, but no statistical differences were found in fibrosis indicators or inflammation grade between three types of infection. The patients' clinical and demographic characteristics are shown in Table 2.

Characteristic		Total (N = 233)	Chronic viral hepatitis B (N = 44)	Chronic viral hepatitis C (N = 132)	Chronic viral hepatitis D (N = 57)	p-value
Age (years)	Range (Min-Max) Mean ± SD	18-75 47.1±14.1	18-69 39.4±13.9	20-75 50.9±13.9	19-69 44.3±11.8	0.000*
Sex (N, %)	Male	111 (47.6%)	30 (68.1%)	60 (45.5%)	21 (36.8%)	0.012**
	Female	122 (52.4%)	14 (31.9%)	72 (54.5%)	36 (63.2%)	
Duration of the disease	Range Mean ± SD	5.5±4.6	5.4±4.7	5.0±4.0	6.8±5.7	0.049*
Fibrosis (kPa)	Median Mean ± SD	10.7±7.9	8.4±4.2	11.0±9.0	12.0±6.9	0.069*
Serum ALT levels	Mean ± SD	56.1±49.4	52.9±54.3	61.5±52.6	46.0±34.5	0.129*
Serum AST levels	Mean ± SD	49.5±41.3	43.8±42.8	53.2±45.6	45.2±27.1	0.284*

** One-way analysis of variance (ANOVA)*

Table 2. Clinical and demographic patients' characteristics in accordance with chronic viral hepatitis

Table 3 presents the results of the analyses performed to assess factors associated with summary scores (FSS) for chronic fatigue separately in three types of infection. As shown in this table, the presence of chronic fatigue was associated with an older age (p <0.047), female gender (p <0.030) and disease duration (p <0.029).

Variable	Chronic viral hepatitis B (N = 44) FSS*		Chronic viral hepatitis C (N = 132) FSS*		Chronic viral hepatitis D (N = 57) FSS*	
	Sig. (2-tailed)	p-value	Sig. (2-tailed)	p-value	Sig. (2-tailed)	p-value
Age	0.808	0.047	0.000	0.680	0.000	0.601
Gender Male-1 Female-2	0.316	0.155	0.239	0.103	0.827	0.030
Duration of the disease	0.651	0.70	0.746	0.029	0.025	0.296
Fibrosis	0.000	0.540	0.000	0.375	0.004	0.380
Serum ALT levels	0.021	0.348	0.002	0.271	0.062	0.248
Serum AST levels	0.043	0.348	0.002	0.262	0.041	0.272

Summary score of the Fatigue Severity Score Scale. Pearson correlation.

Table 3. Clinical parameters associated with the presence of chronic fatigue in patients with chronic viral hepatitis

Table 4 demonstrates the results of the univariate and multivariate analyses performed in the entire sample to assess factors associated with chronic fatigue in patients with chronic viral hepatitis. As shown in this table, Fatigue Severity Score (FSS) was associated with age (p <0.000), fibrosis stage (p <0.060), serum AST levels (p <0.050). Subsequent multiple regression analysis with FSS as dependent variable and major demographic characteristics as independent variables and the statistically significant variables based on the previous multivariate analyses showed that older age (p <0.000), gender (female) (p <0.058), fibrosis stage (p <0.000) were the variables most closely associated with chronic fatigue.

Variable	Chronic viral hepatitis B (N = 44) FSS*				Chronic viral hepatitis C (N = 132) FSS*				Chronic viral hepatitis D (N = 57) FSS*			
	Univariate Analyses p-value	Multiple Regression Analysis beta	p-value	Regression Coefficient (95% CI)	Univariate Analyses p-value	Multiple Regression Analysis beta	p-value	Regression Coefficient (95% CI)	Univariate Analyses p-value	Multiple Regression Analysis beta	p-value	Regression Coefficient (95% CI)
Age	0.348	0.365	0.008	(−0.09, 0.06)	0.000	0.636	0.000	(−0.00 0, 0.051)	0.010	0.509	0.000	(0.053, 0.070)
Gender Male-1 Female-2	0.316	0.079	0.578	(−0.11, 0.578)	0.239	0.112	0.058	(−0.09, 0.542)	0.827	0.049	0.647	(−0.04 ,0.575)
Duration of the disease	0.680	0.020	0.879	(−1.046, 0.229)	0.235	-0.920	0.359	(−1.04 6, 0.229)	0.400	0.142	0.186	(−1.032, 0.225)
Fibrosis	0.397	0.372	0.019	(0.30, 0.67)	0.060	0.255	0.000	(-0.27, 0.33)	0.122	0.274	0.017	(-0.17, 0.38)
Serum ALT levels	0.235	0.226	0.823	(0.000, 0.12)	0.550	0.205	0.123	(0.000, 0.15)	0.099	0.212	0.221	(0.000, 0.19)
Serum AST levels	0.535	0.260	0.769	(-0.09, 0.06)	0.050	-0.056	0.675	(-0.07, 0.08)	0.806	-0.082	0.653	(-0.02, 0.07)
Regression Statistics R Square Adjusted = 0.473					Regression Statistics R Square Adjusted = 0.579				Regression Statistics R Square Adjusted = 0.484			

Table 4. Univariate and multivariate logistic regression analysis of factors associated with the presence of chronic fatigue in patients with chronic viral hepatitis (N=233)

4. Discussion

Several studies have studied chronic fatigue syndrome in patients with chronic hepatitis, however, data are particularly scarce, most studies evaluated the quality of life of such patients[20,21,22,23,24]. Considering the limitations of the existing literature, this study aimed to cross-sectionally assess patients with chronic viral hepatitis for chronic fatigue.

To evaluate chronic fatigue, the patients were assessed using the Fatigue Severity Score Scale to establish the presence and severity of this syndrome. In the existing literature, there are studies in which chronic fatigue has been assessed based on the specified questionnaire.

The demographic profile of the study sample is similar to a number of previous studies that evaluated HCV patients from Canada, but their study had differences in gender distribution, so their sample included a larger number of men [25]. Therefore, it can be said that the socio-demographic profile of the participants in this study is comparable to existing studies. Our analysis, conducted to detect chronic fatigue in patients with chronic viral hepatitis C, showed the presence of clinically significant fatigue, which is consistent with the conclusions of the previous study.

Similar to the results of a study conducted in Germany, our data suggest a significant association of fatigue with the degree of fibrosis[26]. Data from other researchers show that chronic fatigue in patients with chronic viral hepatitis in most cases manifests itself as central fatigue, which really correlates with traditional markers of activity or with the severity of the disease[20,27].

In this study, multivariate analyses showed that older age (p <0.047), gender (female) (p <0.030), and disease duration (p <0.029) were the variables most closely associated with chronic fatigue. Such findings are congruent with the literature, which finds strong associations between chronic fatigue and age, fibrosis indicators and inflammation grade in patients with chronic viral hepatitis[28,29].

A recent content analysis revealed that the overall level of cognitive impairment and chronic fatigue syndrome in chronic viral hepatitis correlated significantly with age[26]. It has also been found that emotional and psychosocial problems associated with fatigue in patients with chronic viral hepatitis may be more common than physical problems. Despite its clinical significance, fatigue in chronic viral hepatitis is poorly understood and therefore invariably underestimated.

The researchers note that a cognitive-behavioral approach can be used to understand chronic fatigue syndrome in chronic viral hepatitis. In addition, the studies did not consider the relationship of chronic fatigue with various stages of fibrosis in patients with chronic viral hepatitis.

Taking into account these limitations of the existing literature, this study was aimed at assessing the chronic fatigue of patients with chronic viral hepatitis.

The limitations of the study are, first of all, that the presence of chronic fatigue was the only dimension of symptom examined in relation patients with chronic viral hepatitis. This study only evaluated the relationship of fatigue and selected variables of gender, age, disease duration, fibrosis indicators and inflammation grade. Additional study of the phenomenon should include depressive symptoms, which are independently associated with several aspects of HRQOL in patients with chronic viral hepatitis in different stages of liver fibrosis.

5. Conclusions

The current investigation shows the main predictors of chronic fatigue in patients with chronic viral hepatitis. Our results demonstrate that most patients with chronic viral hepatitis have indicators of chronic fatigue, regardless of the etiology.

Chronic fatigue is one of the most frequent and disabling complaints and is an early extrahepatic manifestation of cognitive disorders in patients with chronic viral hepatitis in the absence of pronounced somatic symptoms and with an asymptomatic course. The early identification of chronic fatigue is necessary due to the high risk of progression to the stage of severe cognitive deficit. The use of the main predictors helps to improve the diagnosis of chronic fatigue in patients with chronic viral hepatitis, which may be an indication for timely therapeutic measures aimed at improving the quality of life in this category of patients.

In future, especially in low-income Countries, the only strategy to reduce the impact of chronic viral hepatitis should be primary prevention such as universal vaccination campaign against hepatitis B in newborns [30,31].

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