ANNOTATION

of PhD thesis Polukchi Tatyana Vasiliyevna on the topic **«Cognitive disorders in patients with chronic viral hepatitis»**, submitted for the degree of Doctor of Philosophy (PhD) in the specialty 8D10103 – «Medicine»

Relevance of the research topic.

Diseases of the digestive system in recent years occupy a special place in modern healthcare, which constitute one of the five groups of nosologies that have a significant impact on the structure of world disability and mortality (Nersesov A.V. et. al., 2019). An increase in the number of patients, especially those of working age, infected with chronic viral hepatitis (CVH), patients with metabolic disorders, alcoholism, and injecting drug users leads to an increase in the overall incidence of chronic liver diseases (CLD) (Lanini S. et. al., 2019).

Viral hepatitis (VH) plays a significant role in the structure of CLD, which is characterized by one of the world's most important socially significant problems. HCV is one of the most important causes of the immediate increase in morbidity and mortality, and also has a significant impact on the lives and activities of hundreds of millions of people. The largest number of cases of total hepatitis occurs in viral hepatitis B (HBV) and viral hepatitis C (HCV), with a long course of which fibrosis and cirrhosis of the liver may occur (Conde I. et. al., 2017). At last count more than 350 million cases of active HBV infection have been reported worldwide-infection, and more than 150 million people are affected by viral hepatitis C (Carvalho-Louro et. al., 2020). According to the latest data, worldwide, 5% of patients with chronic HBVinfection are infected with chronic viral hepatitis D, of which 20 million have co-infection with HIV (Komas N.P. et. al., 2018).

According to current hypotheses, the number of people with advanced stages of liver disease and the number of deaths from them are expected to increase in the coming years. However, there may also be a slight decrease in the incidence of CVH, due to significant progress in the quality of diagnosis and treatment (Wedemeyer H. et al., 2014).

CVH B and CVH C are characterized as systemic diseases with a wide range of extrahepatic manifestations due to various immunological disorders. The cause of these disorders is the replication of viruses both in the liver tissues and beyond, although direct exposure to viral agents may also play a direct role. Numerous extrahepatic manifestations can serve as indicators of the presence of viruses and play a major role in the clinical picture of the disease (Baikova T. A. et al., 2013).

In the modern literature, the definition of «CHASM» is often used, meaning systemic phenomena caused directly by HCV-infection. These systemic manifestations include a wide range of diseases, such as thyroiditis, atherosclerosis, glomerulonephritis and nervous diseases (Sherman A. C. et al., 2015).

Often, extrahepatic events have the ability to outstrip the clinical symptoms that occur with the lesion itself and the liver, which subsequently requires the use of

additional methods of diagnosis and therapy. In addition, they significantly change the treatment strategy and prognosis of the disease (Bedelbaeva G. G., 2012). One of the main extrahepatic manifestations in patients with CVH includes disorders of the central and peripheral nervous systems that develop at different times after infection. These disorders are caused by both direct neurotoxic effects of viral particles on brain cells, and indirect effects caused by the influence of viruses on the immune system or as a result of the antiviral therapy (AVT) (Pawełczyk A. et. al., 2016).

According to various researchers, cognitive disorders and psychoemotional disorders are observed in almost half of patients with CVH, regardless of the severity and degree of disease activity, viral replication. Moreover, such manifestations as chronic fatigue, sleep disorders, anxiety-depressive disorders, and a deterioration in the quality of life associated with health in patients with CVH can occur even with non-cirrhotic chronic HCV infection, regardless of the stage of AF, the infecting genotype, in the absence of significant structural brain damage detected by magnetic resonance imaging (MRI), resonance imaging (Monaco S. et. al., 2015). There are also differences in cognitive disorders when infected with a particular hepatitis virus, for example, depressive disorders are less often detected in patients with HBV who are on antiviral therapy using interferon compared to patients with HCV. This fact proves the direct role of viral particles themselves in the formation of neuropsychic disorders (Ferenci, P et. al., 2015). Based on this, it is of great interest to study the formation of cognitive impairments in patients with CVH, cirrhosis of viral etiology, as well as their role in disability and mortality in the population.

The aim of the dissertation research is to determine the clinical and neurological characteristics of fibrosis in patients with chronic viral hepatitis at various stages of liver fibrosis.

Research objectives.

1. To study the incidence of chronic viral hepatitis in the city of Shymkent and Turkestan region.

2.To determine the characteristics of neurological status and cognitive functions in patients with chronic viral hepatitis at various stages of liver fibrosis.

3. To assess the pathological fatigue syndrome in patients with chronic viral hepatitis at various stages of liver fibrosis.

4. Evaluate the quality of life according to the EQ-5D quality of life questionnaire (EUROQUAL) in patients with chronic viral hepatitis at various stages of liver fibrosis.

5. To study the correlation of neurological disorders and changes in cognitive functions with the activity of clinical and biochemical manifestations, etiology, and stage of fibrosis.

6. To develop an algorithm for the diagnosis of cognitive impairment in patients with chronic viral hepatitis at various stages of liver fibrosis.

Methods

According to the progress of the current dissertation study, all patients underwent a detailed examination, which resulted in verification of the diagnosis of a or established exclusion criteria.

The second step of the study was a general clinical examination, which includes the collection of complaints, clinical indicators and anamnesis data. In the course of collecting anamnestic data, complaints from the hepatobiliary system were carefully detailed and possible causative factors of CVH were studied, such as surgical interventions, invasive medical and non-medical procedures, past blood transfusions, tissue and organ transplants, parenteral use of injectable forms of drugs, promiscuous sexual relations, professional contact with biological environments.

The next necessary step was to study the general condition of the patient, during which the clinical symptoms of dyspeptic syndrome were determined - a decrease in appetite, pain and heaviness in the epigastrium, the presence of nausea, vomiting. Other important symptoms have been identified, such as the presence of general weakness, malaise, irritability, headache, and reduced performance.

Physical examination consisted of examination, palpation, percussion, and auscultation of patients. To determine the intensity of jaundice, existing teleangiectasias and traces of scratching, the skin was examined and the mucous membranes were visible. Edema on the lower extremities, an increase in the volume of the abdomen due to fluid, dilated veins on the anterior wall of the abdomen were recorded, and the size of the liver and spleen was determined during palpation and percussion.

A neurological status study was conducted, including the patient's mental status, cranial nerve function, motor system, muscle strength, gait, statics, coordination of movements, surface and deep sensitivity, reflexes, and the autonomic nervous system.

Neuropsychological examination methods: The examination included testing using a number of scales and tests. Since there is currently no generally accepted set of neuropsychological tests for the diagnosis of mild cognitive dysfunction, we chose formalized screening methods with a quantitative assessment of the results obtained, which allow us to assess the main cognitive functions (memory, attention, speech, visual-spatial functions and regulation of voluntary activity). The Montreal Cognitive Function Assessment Scale (MoCA), the Fatigue Severity Score, the Visual-Analog Fatigue Scale, the Beck and Hamilton Scale, the Hospital Anxiety and Depression Scale (HADS), and the EQ-5D Quality of Life Questionnaire (EUROQUAL).

Object and subject of research:

This work is based on the analysis of 233 patients with chronic viral hepatitis, who were characterized by neurological status and cognitive functions, assessment of pathological fatigue syndrome, assessment of quality of life according to the quality of life questionnaire EQ-5D (EUROQUAL) on the basis of the hepatology Center of the Regional Clinical Hospital and the City Infectious Diseases Hospital of Shymkent for the period from 2019 to 2022.

This study was approved by the local ethics Committee of the S. D. Asfendiyarov Kazakh National Medical University (Minutes of the LEC meeting №7 (123) of 30.05.202.05.2022).

The study was conducted in accordance with the international rules of «Good clinical practice» (National Institute on Drug, Abuse, 2017), as well as in accordance with the principles of the Helsinki Declaration.

Inclusion criteria:

-patients with chronic viral hepatitis, cirrhosis of the liver of viral etiology aged over 18 years.

Exclusion criteria:

-patients under the age of 18; patients with pregnancy; patients with hepatocellular carcinoma (HCC) and other oncological diseases; patients with a pacemaker; patients with obesity; patients with acute forms of viral hepatitis; patients with a history of mental disorders; patients with intoxication with psychotropic drugs; patients with alcoholism.

233 people with chronic viral hepatitis passed the selection criteria,233 people with chronic viral hepatitis and cirrhosis of the liver of viral etiology passed the selection criteria, among which 66 people (28.3%) were residents of Shymkent, 167 people (71.6%) applied from various districts of the Turkestan region: Suzak, Sairam, Kazygurt, Arys, Saryagash, Maktaral, Tolebi, Baydibek, etc.

Scientific novelty of the study.

1. For the first time in the Turkestan region, the characteristics of neurological status and cognitive functions in patients with chronic viral hepatitis at various stages of liver fibrosis were studied.

2. We evaluated the pathological fatigue syndrome in patients with chronic viral hepatitis at various stages of liver fibrosis.

3. The quality of life was assessed in patients with chronic viral hepatitis at various stages of liver fibrosis.

4. The correlation of neurological disorders and changes in cognitive functions with the activity of clinical and biochemical manifestations, etiology, and stage of fibrosis was studied.

5. The algorithm has been developed for the diagnosis of cognitive disorders in patients with chronic viral hepatitis at various stages of fibrosis, allowing for early therapeutic measures.

The main provisions of the work submitted by the author for defense:

1. In the Turkestan region and Shymkent in recent years (the period 2011-2022), a complex epidemiological situation has developed for chronic viral hepatitis with an increase in the incidence of chronic viral hepatitis B, C, D.

2. In patients with CVH, there is an increase in neurological manifestations with an increase in the degree of liver fibrosis. The most common neurological disorders at various stages of fibrosis are headache, sleep disorder, emotional lability, impaired concentration, memory impairment, paresthesia.

3. Patients with CVH have a syndrome of pathological fatigue, which has a close relationship with age, female sex, fibrosis stage, degree of hyperfermentemia and an indicator of viremia.

4. Health-related quality of life (HRQoL) in patients with chronic viral hepatitis is reduced and correlates with age, female sex, degree of liver fibrosis, ALT level, viral load.

5. Cognitive impairments in patients with chronic viral hepatitis are detected at all stages of liver fibrosis and are significantly associated with age and duration of the disease.

6. The developed algorithm for detecting cognitive dysfunctions at early stages in patients with chronic viral hepatitis of the disease will allow for timely correction of treatment and improve the quality of life of patients and prognosis.

Practical significance.

1. This study allows us to identify the frequency and severity of cognitive impairment, pathological fatigue syndrome in patients with chronic viral hepatitis, which can be an indication for timely treatment measures aimed at improving the quality of life in this category of patients.

2. Quality of life was assessed in patients with chronic viral hepatitis at various stages of liver fibrosis.

3. Clinical, biochemical, and neurological disorders in patients at various stages of liver fibrosis were compared.

4. An algorithm of diagnostics and recommendations for reducing cognitive impairment in patients with chronic viral hepatitis at various stages of liver fibrosis has been developed, which can be used to improve the diagnosis of cognitive impairment in patients with chronic viral hepatitis.

Personal contribution of the author:

For 3 years, the author was directly involved in the diagnosis and detection of cognitive disorders in patients with chronic viral hepatitis who are being treated in the City Infectious Diseases Hospital of Shymkent and the Hepatology Center of the Regional Clinical Hospital of Shymkent

As part of the dissertation, the author conducted clinical examinations (examination of patients, collection of anamnesis, screening, assessment of higher mental functions, assessment of neurological status).

We conducted a literature search for a given problem, database collection, primary processing of the material, statistical analysis, interpretation of the results obtained with the development of an algorithm for diagnosing cognitive disorders.

Conclusions.

1. For the period from 2011 to 2022, an increase in the incidence of chronic viral hepatitis has been established in the Turkestan region and the city of Shymkent: for HCV B by 1.9 times, for HCV C - by 2.6 times, for HCV D - by 3.9 times.

2. Neurological manifestations detected in 49.4% of cases, disorders of the peripheral nervous system in 43%, cognitive disorders in 35.2% increased with an increase in the degree of liver fibrosis. Of the most frequent neurological disorders

at various degrees of liver fibrosis, headache was found in 46.3%, paresthesia in 43.8%, sleep disorder in 41.6%, memory impairment in 37.8%, impaired concentration in 33%, emotional lability in 30% of cases.

3. Pathological fatigue syndrome in patients with fibrosis degree F_0 was found in 6.4% of cases, with F_1 - in 22.7% of patients, with F_2 - in 32.5% of patients, with F_3 - in 47.4% of patients, in 65.5% of patients with F_4, in general in the study population - in 35.1% of cases.

4. A decrease in health-related quality of life (HRQoL) was found in patients with chronic viral hepatitis, directly proportional to the increase in the degree of liver fibrosis. There was a correlation with age (patients older than 50 years) ($p < 0.000$), female sex ($p < 0.014$), stage of liver fibrosis (stage F1 and higher) ($p < 0.008$), high viral load ($p < 0.006$).

5. Cognitive disorders in the form of anxiety and depression are correlated with age (patients older than 50 years) ($p < 0.001$), high level of viral load ($p < 0.000$) in accordance with the type of pathogen of HCV.

6. The developed algorithm for detecting cognitive dysfunctions in the early stages of the disease in patients with chronic viral hepatitis will allow for timely correction of treatment and improve the quality of life of patients and prognosis.

Implementation of work results. The theoretical provisions and practical results of this dissertation are used in the educational process and research work of the bases of the Department of Infectious Diseases and Dermatovenereology of the South Kazakhstan Medical Academy, as well as introduced into the practical activities of the City Infectious Diseases Hospital of Shymkent.

Testing the results.

The main provisions and results of the dissertation work were reported and discussed at:

1. International Scientific and practical Conference «Modern aspects of Medicine and Pharmacy: Education, Science and practice», dedicated to the 40th anniversary of the establishment of the South Kazakhstan Medical Academy, Shymkent, 11-12 October, 2019. (Oral report and abstract);

2. Scientific and practical conference with international participation «Modern innovative approaches to the diagnosis, treatment and prevention of infectious and parasitic diseases» Tashkent, 18th October, 2019. (Oral report);

3. I International Book Edition of the Commonwealth of Independent States «Best Young Scientist-2020» (Nur-Sultan, 13-17 March, 2020) (Oral report and article);

4. International Student Scientific Conference «IV Interdisciplinary Scientific Forum (Moscow, 2020), International Congress on Infectious Diseases (19th ICID), Kuala Lumpur, September 10-14, 2020. (Poster report);

5. International Congress «COVID-19: Pandemic of the XXI century», Ufa, November 13-14, 2020 (Oral report);

6.International Scientific conference and Practical Conference «Brain Diseases: The Challenge of the XXI Century» Shymkent, November 13-14, 2020. (oral report and article);

7. VII Internationaloй Scientific Conference of young scientists and students «Prospects for the development of biology, medicine and pharmacy», Shymkent, 10-11 December, 2020. (Oral report and abstract);

8. Russian Scientific and Practical online Conference "Managed and other socially significant infections: diagnosis, treatment and prevention" Moscow, February 03-04, 2021. (Oral report);

9.Republican interdisciplinary scientific conference «COVID-19 pandemic: current problems and solutions» for residents, undergraduates, doctoral students, dedicatedяto the 30th anniversary of Independence of the Republic of Kazakhstan, Almaty, February 12, 2021. (Oral report and article);

10. International Congress «IMED 2021. Many voices. One health». 4-6 November 4-6 2021, 2021 (Poster report);

11. International scientific and practical conference of young scientists dedicated to the 30th anniversary of independence of the Republic of Uzbekistan «Immunology and genetics: Modern achievements». Tashkent,5 September 1-5, 2021 (Oral report);

12. II Kazakhstan congress «Infectious diseases in the context of globalization: challenges and solutions». Nur-Sultan, October 6-7, 2021 (Poster report);

13. VII Central Asianoй Gastroenterological Week-2021. Almaty, October 7-9, 2021. (Poster report);

14. VIII International Scientific Conference of young scientists and students «Prospects for the development of biology, medicine and pharmacy», Shymkent, 9-10 December, 2021. (Oral report);

15. International Scientific and Practical Conference «COVID-19 and other topical infections in Central Asia», Shymkent, 23-24 June 23-24, 202.22г. (Oral report).

16. International Conference of Young Scientists «Infectious Diseases: Interdisciplinary problems in the post-covid period», Astana, 17th February, 2023. (Oral report).

Reliability of the results of the work: The basis for the scientific provisions, conclusions, and recommendations presented in the dissertation study were the materials of the statistical departments of the regional health department of the Turkestan region, stationary maps, and conclusions of indirect ultrasound elastometry, the results of which were processed using modern methods of statistical processing. The validity of the obtained results is justified by the consistency of theoretical and experimental positions, logical conclusions, as well as publications of the main research data.

Related publications:

Based on the materials of the dissertation, the author published 16 papers, including: 5 articles-in journals recommended by the Committee for Control in the Field of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan; in an international peer-reviewed scientific journal with an impact factor according to JCR (indexed in the Web of science Core Collection, Science Citation Index Expanded, CiteScore percentile not less than 25 in the Scopus database) - 1, 11 abstracts are presented at international conferences abroad.

1. Chronic fatigue in patients with chronic viral hepatitis. Polukchi, T. V., Abuova, G.N., Zhankalova, Z. M., Kasymova, T. V. EuroMediterranean Biomedical Journal. 2022,17 (19) 84-88. DOI: 10.3269/1970-5492.2022.17.19 (article in the journal Scopus-44th percentile, Q3).

2. Polukchi Tatyana Vasiliyevna, Slavko Yelena Alekseevna. Assessment of cognitive impairment in patients with chronic viral hepatitis // Journal of Krishna Institute of Medical Sciences University. – 2023. – Vol. 12, Iss. 2. – P. 65-73. (article in the journal Scopus-36 th percentile, Q3).

3. Polukchi Tatyana Vasiliyevna, Abuova Gulzhan Narkenovna, Slavko Yelena Alekseevna. The Neuropsychiatric Aspect of the Chronic Viral Hepatitis // Prague Medical Report. – 2023. – Vol. 124, Iss. 2. – P. 94-107.(article in the journal Scopus-32 th percentile, Q3).

4. Quality of life assessment in chronic viral hepatitis. Tatyana Polukchi, Zulfiya Zhankalova, Gulzhan Abuova, Akhmedova Muborakhon. J CLIN MED KAZ 2022; 19(3):19-23. DOI: https://doi.org/10.23950/jcmk/12149.

5. Polukchi, T. V., Slavko, E. A., and Abuova, G. N., Modern concepts of the role of chronic viral hepatitis in the development of cognitive disorders, Nauka i Zdravookhranenie. 2021. 4 (Vol. 23), pp. 58-65. doi 10.34689/SH.2021.23.4.006.

6. Polukchi T. V., Slavko E. A., Abuova G. N., Kasymova T. V. Cognitive disorders in patients with chronic viral hepatitis in the Turkestan region. 2022. 2 (Vol. 24). pp. 71-77.doi 10.34689/SH.2022.24.2.009.

7. Polukchi T. V., Slavko E. A., Abuova G. N., Kasymova T. V. Anxiety and depressive disorders in chronic viral hepatitis. Literature review / / Science and Healthcare. 2022. 4 (Vol. 24), pp. 206-215. doi 10.34689/SH.2022.24.4.025.

8. T. V. Polukchi, G. N. Abuova, E. A. Slavko, Z. M. Zhankalova. Anxiety and depression in patients with chronic viral hepatitis/ / Pharmacy of Kazakhstan. 2022. Vol. 4. pp. 84-90. DOI 10.53511/PHARMKAZ.2022.21.41.014.

One author's certificate «Methodology for detecting cognitive impairments in patients with chronic viral rhepatitis» was obtained. No. 20871 of 14th October, 2021.

Structure and scope of the dissertation: The dissertation is presented on 112 pages, consists of an introduction, three chapters, conclusion, conclusions, practical recommendations and a list of references, including 209 sources, including 45 domestic and 164 foreign authors. The thesis contains 27 tables, 11 diagrams, 3 figures, and 5 appendices.