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Neuropsychological and differential diagnostic features in patients with acquired non-Wilsonian degeneration on the background of liver cirrhosis

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Abstract: In this article, we reviewed acquired non-Wilsonian hepatocerebral degeneration, which is a rare pathology that develops against the background of cirrhosis of the liver, for this reason, many aspects of this disease are not well understood. Including the nature of neuropsychological disorders, which has a diverse clinical picture. The aim of our study was to describe the neuropsychological symptoms in patients with associated acquired non-Wilsonian hepatocerebral degeneration, with liver cirrhosis. 9 patients with liver cirrhosis were examined, 6 of them with portocaval shunting. A clinical neurological study was performed using the UPDRS scale, cognitive impairment was determined using the MoCA test. The content of iron, copper, and manganese in the hair of patients was determined using neutron activation analysis; MRI of the brain was performed. In conclusion, we can say that The picture of neuropsychological disorders was dominated by cognitive impairments of the type of subcortical dementia, a decrease in spatial-visual and long-term memory, emotional and personality disorders in the form of the dominance of apathetic-abulic syndrome, hallucinatory phenomena, depressive and anxiety disorders, obsessive-compulsive disorders. The content of manganese in the hair was increased, while the content of copper, iron, and selenium remained within the control values. The abnormally high signal was detected on T1-weighted images in the basal ganglia, especially in the globus pallidus and, to a lesser extent, in the putamen, subthalamic nucleus, and substantia nigra, but T2-weighted images showed no changes in the basal ganglia, but hyperintense signal changes were detected on T2 with indefinite boundaries in the supratentorial white matter and in the deep white matter of the cerebellum.

Keywords: Cirrhosis of the liver, liver failure, parkinsonism syndrome, acquired non-Wilsonian hepatocerebral degeneration. Liver cirrhosis, liver failure, Parkinsonism syndrome, acquired non-Wilsonian hepatocerebral degeneration.

In this article, acquired non-Wilsonian hepatocerebral degeneration (ANWHD) was presented, which is a rare pathology that develops against the background of cirrhosis of the liver, for this reason, many aspects of this disease are not well understood. Including the nature of neuropsychological disorders, which has a diverse clinical picture. The aim of our study was to describe the neuropsychological symptoms in patients with ANWHD associated with liver cirrhosis.

The material of our study was 9 patients with (ANWHD) on the background of liver cirrhosis, 6 of them with porto-caval shunting. They underwent a clinical and neurological study using the UPDRS scale, cognitive impairment was determined using the MoCa test. The content of iron, copper and manganese in the hair of patients was determined using neutron activation analysis, MRI of the brain was performed.

The results of our work included, along with the symptoms of Parkinsonism syndrome, choreic hyperkinesias, myoclonuses, and sensory disorders of the "plus symptoms" type. The content of manganese in the hair was increased, while the content of copper, iron and selenium remained within the control values. Abnormally high signal was detected on T1-weighted images in the basal ganglia, especially in the globus pallidus and, to a lesser extent, in the putamen, subthalamic nucleus, and substantia nigra, but T2-weighted images showed no changes in the basal ganglia, but hyperintense signal changes were detected on T2 with indefinite boundaries in the supratentorial white matter and in the deep white matter of the cerebellum. In conclusion, I would like to note that ANWHD is a consequence of manganese intoxication and hyperammonemia, the observed neuropsychological symptoms are associated both with an increased amount of ammonia in the blood and with the accumulation of manganese in the basal ganglia and cholinergic insufficiency.

Parkinson's Syndrome is a manifestation of most neurodegenerative diseases. Such diseases include both Parkinson's disease and progressive supranuclear palsy, multisystem atrophy, corticobasal degeneration, as well as storage diseases such as Wilson's disease, Hallervorden-Spatz's disease and the least known pathology resulting from chronic liver diseases, in particular liver cirrhosis. - manganese parkinsonism.

Manganese parkinsonism, known in foreign literature as acquired non-Wilsonian hepatocerebral degeneration (ANWHD), is the result of damage to the nervous system, and in our opinion the name does not fully reflect the structures involved in the pathological process. So, with this pathology, not only the basal ganglia are involved in the process, but also the cerebellum, spinal cord, and, in some cases, the peripheral nervous system [2,3,4,6,9,10]. For this reason, the clinical picture of the disease is represented not only by the symptoms of Parkinson's syndrome, but also by other symptoms of damage to the basal ganglia - choreoathetosis, myoclonuses, as well as symptoms of damage to the cerebellum (ataxia, intentional tremor) and the spinal cord (lower paraparesis, impaired pelvic functions by the type of incontinence), as well as signs of polyneuropathies [14]. Neuropsychological disorders include apathy, impaired mental and motor functions, memory impairment and deficits in attention and concentration, indicating subcortical dementia, psychotic states, aggression, agitation [8]. There are isolated reports where visual hallucinations are an integral part of the neuropsychological syndrome in ANWHD [15]. In our studies, we also encountered isolated cases of visual hallucinations in patients with ANWHD associated with liver cirrhosis.

Purpose of the study. Description of neuropsychological symptoms in patients with ANWHD associated with liver cirrhosis.

Materials and methods of research. 9 patients with cirrhosis of the liver with a disease duration of more than 5 years were examined. In order to identify the etiology of cirrhosis of the liver, the history of the disease was analyzed, the surface antigen of hepatitis B, antibodies to the hepatitis C virus were determined by ELISA. An ultrasound examination of the liver (routine ultrasound, fibroelastography) was performed to confirm the diagnosis of liver cirrhosis. To assess the functional reserve of the liver, the Child-Pugh scale was used, based on the assessment of biochemical and clinical parameters. The International Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS UPDRS) was used to determine the severity of symptoms in Parkinson's disease. Cognitive impairment was determined using the MoCa test

In order to determine the level of macro- and microelements in the body, hair was analyzed for elemental composition by neutron activation analysis. A visual analysis was carried out, the changes detected on the magnetic resonance tomogram (device with a power of 1.5 Tesla) - the presence of structural changes in the substance of the brain was taken into account. All patients gave informed consent to the study prior to the study.

Research results. Of all patients, 7 (77.8%) were men, and the mean age was 46.9±3.75 years (range 38 to 67 years). The duration of the disease was more than 5 years - an average of 7.3 ± 0.8 g. The etiology of liver cirrhosis was as follows: 1 (11.1%) secondary biliary cirrhosis, 3 (33.3%) alcoholic cirrhosis, 2 (22.2%) hepatitis C virus-associated cirrhosis, 1 (11.1%) cirrhosis of the liver associated with hepatitis B virus, and 2 (22.2%) patients with cirrhosis of unknown etiology. 4 (44.4%) patients were assigned to group B, and 5 (55.6%) to group C according to the Child-Pugh scale, that is, all patients were with decompensated cirrhosis. 6 (66.7%) patients had a porto-caval shunt (Table 1).

Table 1. Distribution of patients according to common characteristics

№ patient	Gender	Age, years	Duration, years	Etiology	Child-Pugh scale	The presence of a shunt
1	M	38	5	AC	B	Sh
2	M	36	7	BC	B	-
3	M	42	5	HepB	C	Sh
4	M	58	6	AC	C	Sh
5	M	48	9	HepC	C	-
6	M	47	10	CC	B	Sh
7	M	39	5	HepC	C	-
8	F	69	11	AC	C	Sh
9	F	45	8	CC	B	Sh

Note: M-male, F-female, AC-alcoholic cirrhosis, BC-biliary cirrhosis, CC-cryptogenic cirrhosis.

In the neurological status of patients with signs of Parkinson's syndrome, other symptoms were also noted, indicating signs of damage to the basal ganglia. Thus, dystonia, myoclonus, choreic hyperkinesis, cerebellar symptoms (ataxia, adiadochokinesis, gait disturbances) not characteristic of Parkinson's syndrome were detected in patients with ANWHD. Patients did not have pelvic organ dysfunction,

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acheirokinesis, and motor fluctuations. It should also be noted that motor disorders were not leveled when taking levodopa preparations. Sensory disturbances in patients were presented in the form of burning in the distal extremities (3; 33.3%) and itching (2; 22.2%).

Table 2. Neurological symptoms in patients

	№ patient								
	1	2	3	4	5	6	7	8	9
Rigidity	+	+	++	+	-	+	+	-	++
Tremor	+++	+++	++	++	+++	++	++	+++	++
Hypomimia	+	+	+	+	+	+	+	+	+
Bradilalia	-	-	-	-	-	-	-	-	-
Dysphagia	+	+	+	++	+	++	+	+	++
Acheirokinesis	-	-	-	-	-	-	-	-	-
Slowness in daily life	+	+	+	++	++	++	++	+	++
Dystonia	++	++	++	+	+++	++	+	+++	+
Myoclonus	+	++	+	++	+	+	+	++	+++
Chorea	+	+	+	++	++	+	+	+	++
Urinary and fecal incontinence	-	-	-	-	-	-	-	-	-
Sensory disturbances	++	++	++	+	+++	++	+	+++	+
Depression	+++	+	++	++	+	+	+	+	+
Anxiety	+	+	+	+	+	+	+	+	+
Aggression	+++	++	++	++	++	++	+	++	+++
OKR	+	+	-	-	+	+	+	-	+
Sleep disorder	+	+	-	-	+	+	+	++	+
Cognitive disorders	+++	++	++	+++	+	++	+++	+++	++
Hallucinations	++	-	-	++	-	-	-	++	-
Motor fluctuations	-	-	-	-	-	-	-	-	-
Response to levodopa therapy	-	-	-	-	-	-	-	-	-

+++ - pronounced signs, ++ - signs of moderate severity, + - mild signs, - no sign.

Cognitive impairment observed in patients had the character of subcortical dementia. The degree of cognitive impairment was severe in 4 (44.4%) cases, moderate in 4 (44.4%) cases and in 1 (11.1%) mild case. There was a decrease in memory, both working and spatial-visual and long-term memory, violations of recognition processes were less pronounced. Emotional and personality disorders prevailed in the form of dominance of apathic-abulic syndrome (3; 33.3%), a decrease in initiative, both motor and mental, often in patients it was possible to observe dissomnic disorders, or increased drowsiness was noted (2; 22.2%), or dyssomnia (5; 55.6%) at night without any neurological manifestations, only in 2 (22.2%) patients we did not detect sleep disorders. In 3 (33.3%) patients with ANWHD as a result of alcoholic liver cirrhosis, true animalistic visual hallucinations were observed. So, 1 (11.1%) patient "saw" lizards, the other 2 (22.2%) "saw" spiders. In addition to the above disorders, depressive disorders were observed to a greater degree of mild severity, anxiety disorders were also characteristic of patients with ANWHD, obsessive-compulsive disorders (OCD) were observed in 5 (55.6%)

cases, which were manifested mainly by obsessive thoughts (3; 33 .3%) and obsessive actions (2; 22.2%).

It should be noted that patients who experienced visual hallucinations did not take centrally acting cholinomimetics, while patients without visual hallucinations took choline alfoscerate preparations.

In patients with ANWHD, we noted an increase in the content of manganese in the hair, while the content of copper, iron and selenium remained within the control values.

In 8 (88.9%) patients, T1-weighted images showed an abnormally high signal in the basal ganglia, especially in the globus pallidus and, to a lesser extent, in the putamen, subthalamic nucleus, and substantia nigra. Although 5 (55.6%) of these patients had normal T2-weighted signal in the basal ganglia, 1 (11.1%) patient had high signal and 1 (11.1%) patient had low signal T2 in the basal ganglia. In addition, 3 (33.3%) of these patients had hyperintense T2 signal changes with indefinite boundaries in the supratentorial white matter, and 1 (11.1%) of them also had increased T2 signal in the deep white matter of the cerebellum. .

Discussion. The first comprehensive study of neuropsychiatric manifestations in liver damage was carried out by Sherlock et al. in 1954. [thirteen]. The authors described the clinical picture of 18 patients with liver disease and neurological signs. In all subjects, impaired consciousness was accompanied by loss of facial expressions and speech disorders, along with a disorder of the motor system, represented by asterixis, tremor, increased tendon reflexes, increased muscle tone and atactic gait, visual disturbances in patients with hepatic insufficiency are vividly described. Observed visual agnosia, macropsia, distortion and lengthening of images, spatial disorientation and the predominance of visual hallucinations. Auditory, tactile, olfactory and gustatory hallucinations have been reported in rare cases. The mood of the patients fluctuated, while varying degrees of personality change were observed in all patients, even at an early stage of the disease [8]. Visual hallucinations in patients with Parkinson's disease are a common complication with a prevalence range of 8% to 40% and a risk factor for dementia and higher mortality [1,5]. The data of the authors suggest that visual hallucinations may be the result of impaired processing of visual stimuli associated with degenerative processes in the cholinergic pedunculopontine nucleus [5,11,12,16]. The main characteristic of cognitive impairment in Parkinson's patients with visual hallucinations appears to be associated with widespread cholinergic dysfunction. Non-demented patients with Parkinson's disease have mild cholinergic dysfunction, and patients with dementia associated with Parkinson's disease have severe cholinergic deficits in various areas of the cerebral cortex [7].

Conclusions. Parkinsonism syndrome due to impaired liver function is a unique form of acquired hepatocerebral degeneration and is a consequence of manganese intoxication, and in addition to the clinical manifestations of parkinsonism syndrome, it is characterized by other extrapyramidal symptoms, sensory and cognitive and mental disorders.

The observed neuropsychological symptoms in acquired non-Wilsonian hepatocerebral degeneration are most likely associated with both elevated blood

ammonia levels and accumulation of manganese in the basal ganglia and cholinergic insufficiency.

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