Structural and functional changes in organs of the abdominal cavity in patients with Wilson’s disease

Abstract. The paper presents the results of the ultrasound diagnosis of 76 patients with neurological forms of hepatocerebral dystrophy, or Wilson’s disease (WD), who were examined and treated at the clinic of the Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine. According to ultrasound diagnosis, all patients had pathological changes in the liver. In 58 % of patients, these changes corresponded to chronic hepatitis, in 42 % — to liver cirrhosis. 32 % of patients had evidence of portal hypertension. A Doppler test showed that background hepatic hemodynamics in patients with neurological forms of hepatocerebral dystrophy was within normal limits, but 82 % of patients had an impaired reciprocal autoregulation of liver microcirculation. It indicates a decrease in the compensatory and adaptive capabilities of the liver. This position is confirmed by the fact that 70 % of such patients have a decrease in the vasoactive function of the endothelium. In general, the indicator for the group was only 8.12 %, with a norm of 10 % or more. Despite the young average age of our patients (29.7 years), only 30 % of them had a normal vasoactive reaction. These were patients under the age of 25 with chronic hepatitis. The degree of endothelial dysfunction was significantly higher in patients with liver cirrhosis compared to those with chronic hepatitis. According to ultrasound elastography, most examined patients with WD (88 %) had increased stiffness of the liver parenchyma. On average, it was 10.62 kPa with a range from 4.74 to 20.69 kPa (norm 0.4—6.0 kPa). Thus, patients with neurological forms of WD who are observed by a neuro-pathologist should undergo an abdominal ultrasound before each course of treatment, but at least 1—2 times a year.

Keywords: Wilson’s disease; liver; ultrasound diagnosis; Doppler examination; haemodynamic changes

Introduction
Hepatocerebral dystrophy, or Wilson’s disease (WD), is a hereditary disease caused by a copper metabolism disorder. Its development is determined by the ATP7B gene, which is located on the long arm of chromosome 13 and encodes a P-type transmembrane ATPase protein. To date, more than 400 mutations of this gene have been registered. This protein incorporates a copper molecule into apo-ceruloplasmin and carries out the release of copper into the liver bile [9].

The liver carries out and regulates metabolic processes that affect almost all types of metabolism. It is the central regulator of copper homeostasis; it stores and excretes this metal. Hepatocytes are the primary site of copper intake and accumulation in the liver. The lysis of copper-overloaded hepatocytes causes an increase in the level of free toxic copper in the blood serum, which leads to the accumulation of copper in the structures of the brain and other target organs. Thus, the preneurological abdominal stage of the disease progresses to the neurological one [2, 8].

At present, there are only a few studies on the ultrasound diagnosis of structural and haemodynamic changes of the liver in patients with WD. These works reflect the results of research conducted mainly on patients with the abdominal form of WD, or in children.
Ultrasound examination of structural and haemodynamic changes in both the brain and the liver is important for the study of neurodegenerative and demyelinating diseases of the nervous system [2].

M.E. Bagaeva (2004) conducted an abdominal ultrasound examination in 40 children with WD, whose average age was 12.6 years. Nineteen of the examinees had liver cirrhosis. The author noted a significant increase in both lobes of the liver with heterogeneity of the parenchyma among patients with chronic hepatitis. In this group, the diameter of the trunk of the portal and splenic veins, as well as the size of the spleen were within the age norm. Among patients with liver cirrhosis, the size of the liver was increased, but less than in individuals with chronic hepatitis. Signs of portal hypertension in this group were manifested in dilatation of the portal vein trunk. In 11 patients with liver cirrhosis, recanalization of the umbilical vein with blood flow through it was detected. In the group with liver cirrhosis, the author noted a significant increase in the size of the spleen [1].

T.P. Rozina (2005) based on an ultrasound examination of 71 patients with an abdominal form of WD found signs of portal hypertension such as enlargement of the portal, splenic and umbilical veins in 76.1 % of cases.

It is also necessary to note the fact that in WD, a liver damage can occur with a minimal degree of activity, and, therefore, be asymptomatic. All this can cause certain diagnostic difficulties. The most informative method of detecting these conditions is a liver puncture biopsy with light and electron microscopic examination, however, the invasive nature of this method significantly limits its use. Even in specialized hepatology departments, it is used in no more than 50 % of patients with WD [5].

Therefore, our work aimed to study the structural and haemodynamic changes of the liver in patients with the neurological stage of WD using a safe, fast and multi-faceted ultrasound method.

Materials and methods

The paper presents the results of an abdominal ultrasound examination in 76 patients with WD (neurological forms of the disease), 32 women and 44 men. During the period of examination in the clinic of the institute, the age range of patients was from 17 to 54 years, with an average of 29.4 ± 5.6 years. In 32 patients, an ultrasound diagnosis was performed in dynamics 6—12 months after treatment.

The age of the patients before the onset of the first symptoms of the disease was on average 22.3 ± 4.3 years with a range from 5 to 45 years. The time from the onset of to the final diagnosis, and, therefore, the beginning of etiopathogenetic therapy with copper-eliminating (chelator) drugs was 2—3 years on average. The diagnosis of WD was made or confirmed in the clinic of the State Institution “Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine” based on a decrease in serum ceruloplasmin below 20 mg/dL, an increase in urinary copper excretion above 100 µg/day and the presence of Kayser-Fleischer rings.

Clinical and neurological examinations of patients showed polymorphic neurological symptoms with the predominance of damage to the extrapyramidal system. Depending on the leading neurological symptoms, according to the classification of N.V. Konovalov (1960), the patients were distributed as follows: most patients (23 (30 %)) had a tremor form of the disease, 18 (24 %) — a tremor-rigid, 13 (17 %) — an arrhythmogenic hyperkinetic, 18 (24 %) — an extrapyramidal-cortical, and 4 (5 %) patients had an abdominal form of WD.

The ultrasound examination was carried out on the ultrasound scanner Ultima PA Expert manufactured by Radmir. In addition to liver size, structure and weight, the duplex mode was used to determine the parameters of background haemodynamics and its changes in response to a standard food load (75 g of glucose). Time-averaged maximum blood flow velocity (TAMAX) in the portal vein, peak systolic (Vs) and end-diastolic (Vd) blood flow velocity, as well as resistance index in the hepatic artery were assessed. In addition, the stiffness of the liver parenchyma was evaluated in the mode of shear wave elastography. In addition to the liver, the gallbladder, spleen and kidneys were examined.

In connection with the available data on the relationship between the functional state of the vascular endothelium and chronic diffuse liver disease, we studied the functional state of the vascular endothelium in patients with WD [7].

The SPSS Statistics application package (version 17.0.1) was used to process research results. Mathematical statistics methods were applied to determine the differences between various samples according to the level of the characteristic, measured both qualitatively and quantitatively. To determine the reliability of the differences between indicators, the following criteria were used: Mann-Whitney U test and Pearson’s chi-squared test.

Results and discussion

The results of the qualitative assessment of hepatic echotexture showed that all patients with the neurological forms of WD have, to varying degrees, pathological changes in the liver. According to the research data, there was a diffuse heterogeneity of the parenchyma due to small and medium focal heterogeneity of small and medium signals varying in echogenicity.

In addition, we measured liver function parameters in the duplex signal mode on an empty stomach and 20 minutes after a food load, Vps and Vd in the superior mesenteric artery and proper hepatic artery, and also determined maximum TAMAX in the portal vein. Fig. 1 presents an ultrasound picture of haemodynamic changes in the hepatic arteries and portal vein before and after the food load.

As can be seen from Table 1, the diameter of the portal vein in the group as a whole was at the upper limit of the norm — 13.42 ± 0.15 mm (with a normal value of up to 14 mm). However, in 32 % of patients, the diameter of the portal vein was significantly larger than normal. Gender comparisons showed that men tended to have a slightly larger diameter than women (13.69 ± 0.18 mm and 12.92 ± 0.44 mm, respectively). There are no significant differences in portal vein diameter depending on the form of the disease.
In the comparison group (patients with hepatic encephalopathy), the diameter of the portal vein was slightly smaller than in patients with WD (12.57 ± 0.28 mm).

Analyzing the data presented in Table 2, it should be noted that in general in the group of patients with WD, the background haemodynamics of the portal vein is at the upper limit of the norm (26.53 ± 0.53 cm/sec with a norm of 18 to 30 cm/sec). Gender analysis showed that there is a tendency to a higher blood flow velocity in the portal vein in women than in men (27.52 ± 1.62 cm/sec and 24.00 ± 0.98 cm/sec, respectively). There were no significant differences in the velocity of blood flow through the portal vein depending on the form of the disease.

Evaluating the changes in hepatic haemodynamics after the food load test, it is noteworthy that in the whole group, there is almost no increase in blood flow velocity per test (27.00 ± 1.04 cm/sec and 26.53 ± 1.10 cm/sec, respectively). Moreover, in 25% of patients, the blood flow velocity not only did not increase but, on the contrary, decreased.

The gender analysis showed that the response of hepatic haemodynamics to food load was significant-
ly (p < 0.05) higher in women than in men (5.75 ± 0.48 cm/sec and 1.44 ± 0.35 cm/sec, respectively). It should be noted that there is no dependence of the change in blood flow velocity in the portal vein under food load on the form of the disease.

In patients in the comparison group, the velocity of blood flow in the portal vein was close to that of patients with WD and averaged 27.04 ± 1.04 cm/sec.

When analysing blood flow velocity in the hepatic artery before and after a standard food load, it should be noted that in the group of patients with WD, there is a slight decrease in it after loading. If the blood flow before the load was 55.45 ± 1.04 cm/sec, then 20 minutes after the test, it became 51.77 ± 1.12 cm/sec.

Reactivity to food load in women was significantly higher than in men. If in men after the load the speed changed from 54.33 ± 1.12 cm/sec to 52.42 ± 0.97 cm/sec, then in women this difference was significantly greater, from 56.68 ± 1.25 cm/sec to 48.10 ± 1.05 cm/sec.

We did not observe any significant differences in blood flow velocity and responsiveness to food load depending on the form of the disease.

Also noteworthy is the fact that the velocity in the hepatic artery in patients with WD is higher than that in the portal vein (55.45 ± 1.15 cm/sec and 26.53 ± 0.98 cm/sec, respectively).

The hepatic artery resistance index did not react to the standard load and remained at the level of 0.68. In women, the resistance index was slightly lower than in men: 0.66 and 0.69, respectively). There were no significant differences in relation to different forms of WD.

In the superior mesenteric artery, the blood flow velocity was 121.13 ± 2.83 cm/sec. In men, it was lower than in women: 116.29 ± 2.36 cm/sec and 126.94 ± 3.02 cm/sec, respectively. The highest blood flow velocity through the mesenteric arteries was in patients with the abdominal form of the disease (130.20 ± 3.18 cm/sec).

### Table 1. The diameter of the portal vein depending on the gender and the form of WD, mm (M ± m)

<table>
<thead>
<tr>
<th>Gender and form of WD</th>
<th>The diameter of the portal vein</th>
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<tbody>
<tr>
<td></td>
<td>Average</td>
</tr>
<tr>
<td>Men + women</td>
<td>13.42 ± 0.15</td>
</tr>
<tr>
<td>Men</td>
<td>13.69 ± 0.18</td>
</tr>
<tr>
<td>Women</td>
<td>12.92 ± 0.44</td>
</tr>
<tr>
<td>Tremor</td>
<td>13.82 ± 0.28</td>
</tr>
<tr>
<td>Tremor-rigid</td>
<td>12.78 ± 0.10*</td>
</tr>
<tr>
<td>Arrhythmogenic hyperkinetic</td>
<td>13.45 ± 0.33</td>
</tr>
<tr>
<td>Extrapyramidal-cortical</td>
<td>13.80 ± 0.36</td>
</tr>
<tr>
<td>Abdominal</td>
<td>12.82 ± 0.18*</td>
</tr>
</tbody>
</table>

Notes: here and in Table 2: M ± m is the mean value of the parameter and its standard deviation; * — differences with the group of patients with tremor form of the disease are significant (p < 0.05); ** — differences with the group of men are significant (p < 0.05).

### Table 2. The velocity of blood flow in the portal vein before and after a standard food load depending on the gender and form of WD, cm/sec (M ± m)

<table>
<thead>
<tr>
<th>Gender and form of WD</th>
<th>The velocity of blood flow in the portal vein</th>
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<tbody>
<tr>
<td></td>
<td>Average</td>
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<td></td>
<td>Background</td>
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<tr>
<td>Men + women</td>
<td>26.53 ± 0.53</td>
</tr>
<tr>
<td>Men</td>
<td>24.00 ± 0.98*</td>
</tr>
<tr>
<td>Women</td>
<td>27.52 ± 1.62**</td>
</tr>
<tr>
<td>Tremor</td>
<td>25.80 ± 1.06</td>
</tr>
<tr>
<td>Tremor-rigid</td>
<td>26.60 ± 1.17</td>
</tr>
<tr>
<td>Arrhythmogenic hyperkinetic</td>
<td>23.30 ± 1.23</td>
</tr>
<tr>
<td>Extrapyramidal-cortical</td>
<td>–</td>
</tr>
<tr>
<td>Abdominal</td>
<td>28.30 ± 1.18</td>
</tr>
</tbody>
</table>
The blood flow velocity in the superior mesenteric artery increased significantly (p < 0.05) after standard food load: 121.13 ± 2.83 cm/sec and 160.10 ± 3.40 cm/sec, respectively. This increase was significantly greater in men (42.8 cm/sec) than in women (36.46 cm/sec). The greatest increase in blood flow velocity through the mesenteric arteries was in a patient with an abdominal form of the disease (46.8 cm/sec).

The resistance index of the superior mesenteric artery after food load decreased from 0.81 to 0.76. In women, it was more significant (from 0.80 to 0.73) than in men (from 0.82 to 0.79). The greatest decrease in the superior mesenteric artery resistance index was noted in patients with the abdominal form of the disease (from 0.80 to 0.70).

According to ultrasound elastography, most patients with WD (88 %) had increased liver parenchymal stiffness. On average, it was 10.62 kPa with a range from 4.74 to 20.69 kPa (norm 0.4—6.0 kPa).

Currently, much attention is paid to changes in intrahepatic haemodynamics and functional capacity of the endothelium in patients with chronic liver diseases. Dysfunction and damage to the endothelium are obligatory characteristics of the pathogenesis of diffuse chronic liver diseases [6].

However, there are only a few studies on this problem in patients with WD [1, 4].

Our study of the functional state of the vascular endothelium showed that patients with WD have a significant decrease in the vasoactive function of the endothelium. As a whole, the indicator for the group was only 8.12 %, with a norm of 10 % or more. Despite the young average age of our patients (29.4 ± 5.6 years), only 30 % had a normal vasoactive reaction. This included patients under the age of 25 with chronic hepatitis. The degree of endothelial dysfunction was significantly higher in patients with liver cirrhosis compared to those with chronic hepatitis.

In addition to structural changes in the liver and spleen, 78 % of patients had various pathological changes in the gallbladder (dilatation, diffuse-polypoid cholesterolosis of the gallbladder, thickening and thinning of the walls).

Among the extrahepatic manifestations of WD, kidney damage is relatively rare, but it can determine the clinical picture of the disease and complicate the timely diagnosis.

According to our data, echo signs of diffuse changes in the pyramidal sections of the renal parenchyma were detected in 27 (36 %) patients. Our data on the renal involvement in WD indicate a significantly lower its incidence than reported in the literature. This discrepancy is related to the fact that other authors report the frequency of renal damage in patients with the abdominal form of the disease.

In the dynamics of 6–12 months, 32 patients with hepatocerebral dystrophy were re-examined. In 21 (65.63 %) of them, the ultrasound findings were without significant dynamics. In 6 (18.75 %) patients, after the courses of treatment, there was an improvement in some ultrasound parameters: in 2 cases, the size of the liver and spleen reduced, in 3 patients, the degree of portal vein dilation decreased, and one patient had a reduction in the stiffness of the liver parenchyma.

During the treatment, patients with WD showed slight fluctuations in various hemodynamic parameters of the liver. However, none of the group’s parameters obtained before and after the course of treatment had any significant differences. And the patients, as a rule, continued to focus on discomfort in their neurological functions in their complaints.

Conclusions

All patients with neurological forms of WD have pathological changes in the liver according to ultrasound diagnosis. In 58 % of cases, these changes correspond to chronic hepatitis, and in 42 % — to liver cirrhosis.

In 32 % of patients with WD in the neurological phase, evidence of portal hypertension was noted.

A Doppler study showed that the background hepatic haemodynamics in patients with neurological forms of WD is within normal limits. However, after food load most patients have impaired reciprocal autoregulation of liver microcirculation. It indicates a decrease in their compensatory and adaptive capabilities. This position is confirmed by the fact that 70 % of these patients have a decrease in the vasoactive function of the endothelium.

In patients with the neurological stage of WD, in addition to cerebral and liver pathology, structural changes in the kidney parenchyma are noted quite often (36 %).

Despite the structural changes in the liver, spleen, and kidneys in patients with neurological phase of WD detected by the ultrasound, pathological processes in them during this period proceed with a minimal degree of activity and are asymptomatic. It is evidenced by both laboratory data and minimal complaints from patients about the dysfunction of these organs.

Patients with neurological forms of WD who were observed by a neurologist should undergo an abdominal ultrasound before each course of treatment, but at least 1–2 times a year.

References


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Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

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Особливості структурних та функціональних змін органів черевної порожнини при хворобі Вільсона

Резюме. У статті наведено результати ультразвукової діагностики 76 осіб із неврологічними формами гепатоцеребральної дистрофії, або хвороби Вільсона (ХВ), яких обстежували та лікували в клініці Інституту неврології, психіатрії та наркології НАМН України. За даними ультразвукової діагностики, у всіх пацієнтів спостерігалися патологічні зміни в печінці. У 58 % випадків вони відповідали хронічному гепатиту, у 42 % — цирозу печінки. Ознаки портальної гіпертензії мали 32 % хворих. Допплерометрія показала, що фонова печінкова гемодинаміка в пацієнтів із неврологічними формами гепатоцеребральної дистрофії була в межах норми, але у 82 % із них спостерігається порушення реципрокної автоматичної регуляції мікроциркуляції органа. Це свідчить про зменшення компенсаторно-адаптивних можливостей печінки. Таке положення підтверджується тим, що 70 % цих хворих мають зниження вазоактивної функції ендотелію. Загалом по групі показник становив лише 8,12 % при нормі 10 % і більше. Не-