Wilson’s disease — hepatocerebral dystrophy

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Key words: Wilson’s disease (hepatocerebral dystrophy), definition, etiology, pathogenesis, diagnosis, treatment

The main, sometimes decisive importance of the internal causes of diseases are factors of hereditary predisposition and individuality.
I.V. Davydovsky (1887 — 1968) [3].

Definition. Until now, there is no unambiguous definition of Wilson's disease. Here are some of the most successful, as we see it, definitions.

1. Wilson's disease, or hepatocerebral dystrophy, is a rare, genetically determined disease with an out -of-axis osomno-recessive type of inheritance, which is based on a violation of copper exchange with its excessive accumulation, mainly in the liver and in the central nervous system [5].
2. Wilson's disease is a rare hereditary deterministic autosomal recessive disease characterized by excessive accumulation of copper in the liver, brain, kidneys and other organs [12].
3. Wilson's disease, or hepatolenticular degeneration, is a rare, hereditary disease, which is based on a metabolic disorder with its accumulation in target organs: the liver, the brain (chevestex cores, subcortex and cortex), and brown-green pigmentation edge of the cornea and renal damage [7].

In the International Classification of Diseases and Related Health Problems, 10 revision (ICD-10), 1995, Wilson's disease is included under the code (code) E83.0 [12].

Terminology. The term "Wilson's disease" comes from the name of a British neurologist (Samuel Alexander Kinnier Wilson, 1878 — 1937), who described the disease in 1912. However, much earlier its description was presented by two other German scientists: Karl Friedrich Otto Westphal (1833 — 1890) — in the 1883 (Arch. Psychiatr, 1883; 14: 87-134) and Adolf Strumpel (1853 — 1925) — in 1898 (Dtsch., Zschr., Nervenkrankh., 1998; 12: 115-149), in connection with which it was originally called the disease of the Westval — Stryumpel [20]. The reason for this discrepancy was that, first, the Westval — Strumpel disease and Wilson's disease was considered as two separate diseases, and only in 1920, Spielmayer and Hall have proved that the disease of the Westval — Stryumpel is

only one of the variants (forms) of Wilson's disease. Later it was possible to establish that the first description of this disease was presented even earlier — in 1854 (Frerichs) [20].

In our country it is still often referred to as Wilson's *disease, "Wilson's disease — Konovalova"* (NV Konovalov, 1900 — 1966 — Russian neurologist). This is due to the fact that in the post-war years (1949 — 1953) in the USSR, the official authorities initiated another loud political campaign under the slogans of *"fighting cosmopolitanism"* and*"admiration for foreigners ",* which in medical science resulted in a search, whatever became the priority of domestic authors in various fields of medicine. It was at that time there were no sufficient scientific evidence *"double" eponymous terms* of many clinical symptoms and disease: symptoms Shchetkina — Blumberg, Grekov — Ortner, Vinogradov -Duroziez e s, St. George's — Musso and many others. One of them became the term *"Wilson — Konovalov's disease",* which is not used anywhere in the world. We believe that aninternationally recognized term, Wilson's disease, should be used [13].

Synonyms. In the medical literature, many other names of Wilson's disease can be found: the Westval — Strympel — Wilson disease — hepatolenticular degeneration (degeneration hepatolenticularis); Wilson disease — hepatocerebral dystrophy (dystrophia hepatocerebralis); neurohepatic degeneration, etc. However, the most commonly usedeponymic term is Wilson's disease [20].

Prevalence. Most authors indicate that the frequency of Wilson's disease is 1: 100 thousand of the population, is a rare disease [2]. The disease usually manifests at the age of 8 — 18 years, and sometimes even earlier, but in cases when in the initial stage it proceeds latently or malosymptomatically, it is diagnosed in older age groups, often already with the formation of cirrhosis of the liver. Wilson's disease is more common in men than in women [2].

Etiology and pathogenesis. Among the etiological factors of Wilson's disease it is advisable to distinguish between external and internal factors. At various times as possible vneshnesre pa etiological factors figured infection — bacterial and viral and microbial intoxication, however, to prove infectious origin of Wilson's disease and failed. [14]

Now it is established that the main significance in the origin of Wilson's disease belongs to heredity — genetic factors.

Wilson's disease is a hereditary — deterministic disease with an autosomal recessive type of inheritance, which is based on a violation of excretion of copper (Cu) from the liver with bile and its excessive accumulation in organs and tissues, especially in the liver and brain (in chevish-like nuclei, in the subcortex and in the cortex) is a kind of*"inherent error of copper exchange"* [5, 10, 14, 16, 19].

The gene of Wilson's disease is located on the long arm of chromosome 13. It encodes the structure copper transporting ATPase P-type (ATP7B), localized in the m Tranfer network apparatus Gaulle ji and mitochondrial membranes, and also

on the membrane of hepatocytes kananikulyarnoy [1, 10, 14, 18, 25]. Important in functional terms are: 1) 6copper-binding domains; 2) the domain released by the hydrolysis of ATP, which participates in energy transcription and 3) the ATP-binding domain.

The gene of Wilson's disease is often subjected to mutations (about 100 of them are known), of which the most important mutation is H 1069 Q [10].

Within days with food daily in the human body enters 2 — 5 mg of copper, which is being absorbed in the intestine, transported via the portal vein to the liver, r de Gaulleconnected in the apparatus with ji *ceruloplasmin* — a special whey protein from the a — globulin fraction belonging to the group of metalloproteins, which contains copper and has the properties of an oxidative enzyme. It is synthesized in the liver and regulates the transport of copper in the human body. Then copper is excreted into the intestine along with bile. In Wilson's disease copper absorption in the intestine increases (up to 1.2 — 1.7 mg/day), and its excretion in the bile, on the contrary — is reduced (up to 0.6 mg/day), which is due to a sharp reduction or complete absence of gene of Wilson's disease. In this case, copper in an increased amount is deposited in the bloodstream, in the liver tissue, the brain, the cornea of the eye, the kidneys and other organs. Thus, the content of copper in the ganglions of the brain increases by 10 times.

The increased concentration of copper in organs and tissues causes blockade of sulfhydryl (SH) groups of a number of enzymes, disrupting metabolic processes in the liver and causing intoxication, and also causes energy starvation of the brain [7, 28].

Copper serves as an activator of insulin, causing the disorder of carbohydrate metabolism — *hyperinsulinism*.

In addition, *copper is a pro-oxidant,* so its excessive accumulation in hepatocytes is manifested in increased generation of products of free radical lipid oxidation (CPO L), a decrease in the content of antioxidants and glutathione stores in the liver, which leads to cytolysis (necrosis) of hepatocytes. In this case, copper is released from the liver cells, accumulating in increased amounts in the blood stream, and deposited in the target organs [10, 16, 25].

In a special study, the family (hereditary) nature of Wilson's disease was noted in 80 cases out of 175 examined families of patients. It was established that the full Concordantnost sickness Wilson identical twins. The high penetrance of the Wilson disease gene was also proven [7, 16].

Carriers of the pathological allele are *heterozygotes expected to* be 1% of healthy individuals — they reveal abnormalities of copper metabolism. In ze Tero zygote parents born 25% of patients with Wilson's disease, 25% of healthy children and 50% — heterozygous whose genotype is like a parent.

Clinical picture. The clinical picture of Wilson's disease differs polymorphism. Most often (in 40 -65% of cases), the disease debuts with a liver

lesion that develops at the age of 5-18 years; less often (in 30%) — with neurological and psychiatric disorders. Significantly less likely the onset of the disease with hemolytic crisis and hemolytic anemia (Kegaraform). The course of the disease can be fulminant and slowly progressing.

Abdominal Wilson's disease can manifest fulminant liver failure, acute and chronic hepatitis with the outcome of liver cirrhosis, portal hypertension and characterized edematous ascites syndrome, and bleeding from varicose veins extended GOVERNMENTAL esophagus and stomach. In 1%, the onset of the disease is possible with kidney damage that occurs with the proximal tubular dysfunction (Fanconi syndrome), increased excretion of calcium in the urine, with hyperphosphaturia and a violation of itsacidification, which contributes to the development of urolithiasis and nephrocalcinosis; IgA -n efropatii or chronic glo merulonefrita. Sometimes there is an endocrine dysfunction with symptoms of hypogonadism (oligo o- and amenorrhea, infertility, hirsutism signs) [1, 2, 4, 5, 8, 12, 14, 21, 25].

Fulminant hepatic failure occurs with rapidly progressive jaundice, acute liver insufficiency, encephalopathy, moderate splenomegaly minutes, vnutrisosudi stym hemolysis followed by hemolytic anemia (up to 50 g/l or less); thrombocytopenic purpura with severe hemorrhagic syndrome; Hyperbilir with kunemia due to conjugated andunconjugated fractions at low alkaline phosphatase levels and a significant increase in free copper in blood serum, which is the main cause of hemolytic crisis and in nutritional haemolysis (in 15% of patients). In this case, hemoglobinuria is observed and the development of acute renal failure is possible, and the ratio *"alkaline phosphatase: bilirubin"* is reduced to 2.0/100% [9].

In a short time fulminant liver failure leads to a fatal outcome, which can be prevented only by urgent liver transplantation [1, 14, 19]. As provoking factors for the development of fulminant hepatic insufficiency, acute viral hepatitis with viral replication in the liver and herpesvirus type VI, affecting the liver tissue [22, 17, 31] can occur.Chronic hepatitis in Wilson's disease is characterized by high activity, the expression of th jaundice and necrosis Comrade hepatocyte, as evidenced by a significant increase of serum enzymes cytolysis (AST and ALT), enzymes, cholestasis (alkaline phosphatase, γ — GTP, LAP), hypergammaglobulinemia and rapid transformation in cirrhosis of the liver with its characteristic portal hypertension, ascites and peripheral edema [1, 2, 14, 25, 27, 30]. Histologically, the presence of microvezicular fatty degeneration andcoagulation necrosis of hepatocytes are determined [7].

In relatively rare cases in the initial period of Wilson's disease there is a latent or low-symptom current with an "erased" clinical symptom, manifested by mild jaundice, asthenic syndrome, moderate deviation from the norm of functional

liver samples (ASAT and ALAT, APF, etc.). In these cases, the disease can be diagnosed only at the stage of the formed cirrhosis [2].

Extrahepatic lesions in Wilson's disease are manifested primarily neurological and psychiatric disorders.

They develop usually later — at the age of 20 — 30 years and are manifested by extrapyramidal disorders: *"fluttering tremor" of* outstretched hands and the whole body, which increases with emotional strains and anxious condition of patients; hypomia *("Masklike"* face); hypersalivation; monotonous, as it were complicated speech, muscular rigidity and choreoatetotic torsion-spastic hyperkineses in the form of *"beating wings"*, change in voice and dysphonia [1, 4, 7, 14, 19]. In severe disease Wilson discloses Guillain-Barre syndrome (Gillain — Barre) syndrome: a circumferential polyradiculoneuropathy tetraparesis [9, 24].

Mental disorders in Wilson's disease are manifested by changes in the emotional sphere and behavior of patients; epilep tiformnymi seizures; schizophreniform-likesymptoms; gradual decrease in intelligence [1, 2, 4, 14, 29].

Very characteristic of eye damage in Wilson's disease, — the appearance of the corneal *"copper ring" Kaiser — Fleischer* (Kayser — Fleischer): green-yellow-brownish staining on the border of the sclera and cornea. Less common is cataract in the form of *"sunflower"* [9].

In some cases there is *damage to the kidneys*, occurring micro o and gross hematuria, about teinuriey, aminoaciduria, Glu kozuriey, edema syndrome, increased creatininein serum, as well as the proximal renal dysfunction — Fanconi syndrome (1% of cases). Furthermore, there may g iperu rikozuriya prone to nephrolithiasis; nephrotic and edematic syndromes; chronic glomerulonephritis [1, 2, 8, 14].

Joint damage at bo existing illness Wilson proceed with the art ralgiey, dysarthria, flexion contracture, changes in the spine, knee joints; osteoporosis and osteomalacia.

Often there is a defeat of the blood system: acute intraspecific hemolysis, hemolytic anemia, which develops after the hemolytic crisis [21].

In some patients with Wilson's disease, there are *signs of hypogonadism*, manifested by disorders of the menstrual cycle, amenorrhea, infertility [4].

Skin syndrome manifests itself as vasculitis, cutaneous, vascular and thrombocytopenic purpura [4, 8].

Wilson's disease can be complicated by intercurrent infections

Classification. There is no universally recognized international classification of Wilson's disease. We have developed a clinical classification of this disease, which is presented below [12].

Clinical classification of Wilson's disease

I. Latent (or malosymptomatic) stage.
II. Stage of clinical manifestations (Figure 1).

1. *Lesions of the liver*, acute and chronic hepatitis; cirrhosis of the liver; fulminant liver failure.
2. *Neurological disorders:* a) early — monotonous, difficult speech; hypersalivation; ataxia; violation of coordination of movements; b) late — extrapyramidal disorders;muscle rigidity; epileptiform n ripadki; tremor; hypomia; gi perkinezy; dysphonia.
3. *Mental disorders:* emotional disorders; behavior change; epileptiform seizures; schizophreniform symptomatology.
4. *Eye defeat:* Kaiser — Fleischer ring; cataract.
5. *Kidney* damage: micro- o- and macrohematuria, proteinuria, aminoaciduria, hypercalciuria, hyperphosphaturia, glucosuria; nephrolithiasis; Fanconi's syndrome;nephrotic syndrome; chronic glomerulonephritis.
6. *Defeat of the joints:* arthralgia; osteoporosis and osteomalacia; flexion contracture.
7. *Defeat of the blood system:* acute intravascular hemolysis; hemolytic anemia.
8. *Lesion of the skin:* vasculitis; cutaneous, vascular and thrombocytopenic purpura.

III. The terminal stage [12].

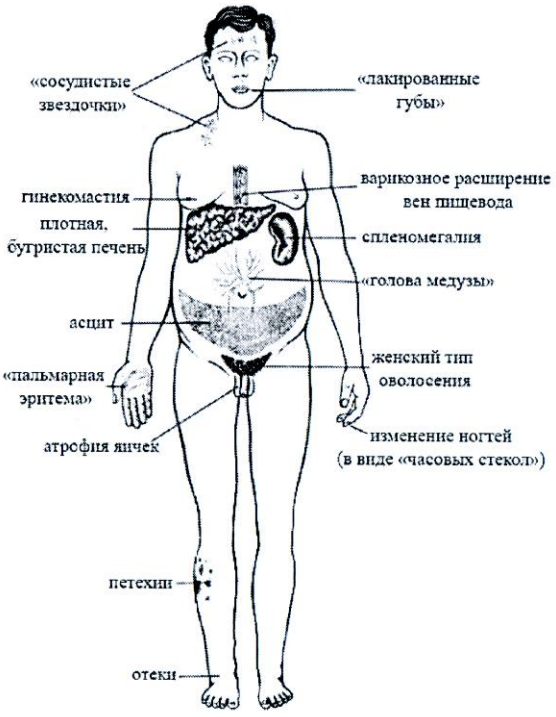

Fig. 1. Clinical manifestations of Wilson's disease.

Diagnostics. Numerous "masks" of Wilson's disease and (in a small part of cases) an asymptomatic course of the initial stage of the disease make it difficult to diagnose it in time.

The most frequent and reliable sign of Wilson's disease is the presence of the Kaiser — Fleischer ring on the cornea of the eye (determined in 90% of cases and can be considered a pathognomonic symptom): examination using a slit lamp.

Some authors point to the "triad" of diagnostic features: 1) the Kaiser — Fleischer ring; 2) jaundice; 3) hemolytic anemia [1, 5, 7, 10].

Severe hemolytic anemia develops as a result of necrosis of hepatocytes depositing copper, which, when released, induces hemolysis of red blood cells [30].

Diagnostic value also has a *family history — the* presence of a similar disease in blood relatives of the first degree of kinship. In a genetic study, a mutation of the ATP7B gene responsible for the development of Wilson's disease can be determined [18].

Important diagnostic significance is characteristic of neuropsychic disorders and the development of fulminant liver failure.

Laboratory tests allow to establish: 1) reduction in the serum ceruloplasmin (35 -65%) in 95% of patients — -200 to 0 mg/L (at a rate of 355 ± 100 mg/l); 2) an increase in the content of free copper in the blood (up to 300 μg/l and more) and in liver biopsy samples (with the coloring of orsein and rhodanin) — more than 250 mg/g dry weight (at a rate <50 mg/g); 3) in liver biopsies, in addition, the presence of *lipofuscin*, fatty liver dystrophy, fibrosis and cirrhosis can be determined; 4) the level of alkaline phosphatase (APF), as a rule, is reduced, despite the presence of jaundice; moderately increased the content of cytolysis enzymes: more ASA than ALT.

Isolation of copper in urine before treatment with D — penicillamine is most often (in 65% of patients) reduced (by 50% or more), and with the systematic administration of D — penicillamine, urinary excretion increases up to 50 times! (norm: <50 mg/day) — *Hyperpruria*.

Instrumental diagnostics. Magnetic resonance imaging (MR-T) reveals changes in the basal nuclei of the brain.

In scintigraphic study, biopsies of liver with radioactive copper which is absorbed by the hepatic tissue at 2 and 24 h after intravenous administration of the radionuclide liver radioactivity ratio is 0.2 — 0.3 (at a rate of 1.4 — 9.0).

It is advisable for all patients to consult a psychoneurologist.

Differential diagnosis should be carried out with hepatotereal syndromes in viral and other liver diseases; with multiple sclerosis; encephalitis; trembling paralysis (Parkinson's disease).

Treatment. Therapeutic measures Wilson's disease are aimed primarily at preventing irreversible changes in organs and tissues by vozdeyst Via congenital defects secretion copper [6].

When determining the diagnosis of Wilson's disease, treatment should be given immediately. It should be ensured that the level of free copper in the blood

serum does not rise above 20 μg/dl during treatment. *Treatment should be continuous and lifelong, as it is an incurable disease.*

Therapeutic diet (Diet No. 5 according to MI Pevzner) with increased protein content. It is necessary to exclude from the food ration copper-containing products: crustaceans (crabs, crabs, etc.), lamb, chicken and duck meat, fish, legumes, nuts, prunes, cocoa, chocolate, honey, pepper [7].

Pharmacotherapy. The main drug for the treatment of Wilson's disease is still (for more than 50 years!) Is *D — ne niacillamine in an individually selected dose* — in the range of 1.5 to 4 g/day; the optimal dose is 0.9 — 1.2 g/day [7, 14, 10, 1, 25].

Treatment D — penicillamine — is a pathogenetic therapy that helps to remove excess copper from the body.

With long-term treatment of D — penicillamine, various *side effects are* possible: development of a nephrotic syndrome; syndrome Goodpasture; interstices ceiling elements glomerulonephritis; agra nulocytosis; thrombus on — and lymphopenia; fibrosing alveolitis (due to a violation of collagen synthesis); lupus-like syndrome; aplastic anemia; optic neuritis; follicular conjunctivitis; pemphigus; aphthous stomatitis; cutaneous erythema; deep ulcers of the lower leg, furunculosis, etc. [7, 11, 26, 27].

Despite such an extensive list of side effects, most patients suffer long-term treatment with D — penicillamine is quite satisfactory.

P. Ferenci [10], as an alternative to D — penicillamine, suggests the *treatment with* trientin (trientin), which also contributes to the removal of excess copper from the patient's body; *a dose of* 1, 0 — 1.5 g/day. According to him, the effectiveness of trientine in Wilson's disease is not inferior to D — penicillamine, but it has fewer side effects.

D — Penicillamine, like trientine, is a copper — chelating compound.

A valuable method of treatment of Wilson's disease (especially in case of D — penicillamine intolerance) is the *use of zinc* (sulfate or acetate) *preparations.* Zinc competes with copper for binding to a carrier protein on the erythrocyte membrane and thereby blocks the transport of copper, which is excreted with feces along with desquamated epitheliocytes. *Dose:* 75 — 200 mg/day 3 times a day for 30 minutes before meals, long. This is an inexpensive, safe and sufficiently effective method of treatment [1, 7, 14].

With the development of fulminant liver failure — the most terrible symptoms of Wilson's disease — is used plaz maferez, albumin dialysis, hemofiltration, peritoneal dialysis, and in their inefficiency arises a need for urgent orthotopic allotransplantation liver [1, 5, 7, 14, 15, 19].

Adjuvant (accessory) therapy. Several authors have considered warranted designation patients with Wilson's disease *unitiola,* which contains two sulfhydryl (SH) group and the enzyme is able to restore function GOVERNMENTAL liver

systems has detoxicating activity [5, 7]. *Dose unithiol:* 5-10 ml 5% solution intramuscularly daily or every other day, 25 — 30 days.

The foreign preparation *"BAL — British antilyuizit "* (dimercaprol-2,3-dimercap topropanol) is close to the unitiol by the mechanism of action to unithiol, but it is more toxic [7]. It is administered intramuscularly *at a dose of* 1.25 — 2.5 mg/kg 2 times a day for 20 days; several courses are held with a break of 20 days.

When liver disease in patients with Wilson's disease justified application *Hepa-Merz* (L-ornitina-L-aspartate), especially in the presence hepatodepressive (gepatoprivnogo) syndrome, *in a dose of* 500 mg/day in 500 ml saline, i.v. drip (4 — 8 kap/min).

Undoubtedly useful is the intake of antioxidants: *vitamin E* (a-to- coffee-acetate): 10% oily solution, 1 ml (100 mg) inside 1 capillary, for 2 to 3 months.

More effective combined antioxidant — *antioxidant capsules,* which comprises a selenium (15 mg), ascorbic acid (100 mg), and tocopherol acetate (30 mg) and P-carotene (20 mg). It is taken orally 1 cc/day after meals for 2 — 3 months.

When ascites, and peripheral edema prescribe diuretics: spironolactone *(Al s dakton, veroshpiron)* 100 — 200 mg of 2 — 3 times/day or *amiloride hydrochloride* 5 — 10 mg/day — up to complete elimination of ascites and edema. Use also *furosemide* (lasix) 40 mg orally 1 time/day intramuscularly or intravenously slowly struyno: 20 — 60 mg 1 time/day.

Wilson's disease is incurable, but with timely and continuous (lifelong) treatment, the patients' well-being remains stable for many years, and they preserve their lives for a long time.

With ineffectiveness of drug treatment, the only method of saving their lives is liver transplantation.

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Wilson's disease — hepatocerebral dystrophy

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Key words: Wilson's disease (hepatocerebral dystrophy), definition, etiology, pathogenesis, diagnosis, treatment

The article presents a detailed review of modern ideas on Wilson's disease — hepatocerebral dystrophy. The definition, terminology, history of the study of the disease are stated. Special attention is paid to the analysis of the pathogenesis of hepatocerebral dystrophy, including the genetic basis of its development, the violation of copper metabolism. The clinical picture is thoroughly described,

taking into account the characteristics of liver lesion and extrahepatic manifestations, diagnostics, classification. Particular attention is paid to the means of pathogenetic and symptomatic treatment.