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Wilson – Konovalov Disease: Clinical Cases with Different Manifestations and Outcomes

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Aim: to describe clinical cases of Wilson – Konovalov disease in pediatric patients.
Key points. The first clinical case demonstrates the manifestation of Wilson – Konovalov disease with unexplained mild elevation of aminotransferases at the age of 6 years. Despite the persistent hyperenzymemia, no additional laboratory tests were prescribed. At the age of 10, the patient showed signs of liver failure and neurological symptoms. Laboratory and instrumental examination enabled to diagnose Wilson – Konovalov disease at the stage of liver cirrhosis. The diagnosis was confirmed at the Federal medical center. The diagnosis was delayed and made 4 years after the hyperenzymemia was first revealed. The relief of clinical signs was observed after the orthotopic transplantation of the right lobe of the liver from a living related donor. The patient was under surveillance for 10 years after the transplantation.
The second clinical case shows another variant of the course of the Wilson – Konovalov disease manifested as an acute hepatitis. To clarify the etiology of the disease, the patient was hospitalized. In 2 weeks, the patient developed symptoms of acute liver failure, progressive hemorrhagic syndrome, acute hepatic encephalopathy. Death from fulminant hepatitis occurred in 3 weeks after the disease onset after the disease onset.
Conclusion. Healthcare workers should be aware of clinical signs of Wilson – Konovalov disease. Screening for the disease is recommended for children with an unexplained increase of liver transaminases, acute liver failure, chronic hepatitis and liver cirrhosis.
Keywords: Wilson – Konovalov disease, children, acute liver failure, hyperenzymemia
Conflict of interest: the authors declare no conflict of interest.

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Болезнь Вильсона – Коновалова в практике педиатра: клинические наблюдения с разными вариантами течения и исхода

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Цель исследования: представить клинические наблюдения болезни Вильсона – Коновалова в педиатрической практике.
Основные положения. В первом клиническом случае поражение печени зарегистрировано впервые в возрасте 6 лет в виде незначительного повышения аминотрансфераз в сыворотке крови. Несмотря на сохраняющуюся гиперферментемию, дополнительное обследование не было проведено. В возрасте 10 лет отмечено появление признаков печеночной недостаточности и неврологической симптоматики. Проведенное лабораторно-инструментальное обследование позволило установить диагноз болезни Вильсона – Коновалова на стадии цирроза печени. Болезнь Вильсона – Коновалова была диагностирована через 4 года от момента впервые выявленной гиперферментемии. Регресс клинических симптомов наблюдался после проведения ортотопической трансплантации правой доли печени от живого родственного донора. Наблюдение после трансплантации печени составило 10 лет.
Второй клинический случай демонстрирует другой вариант течения болезни Вильсона – Коновалова с манифестацией в виде острого гепатита, для уточнения этиологии которого пациент был госпитализирован в стационар. Через 2 недели появились симптомы острой печеночной недостаточности, прогрессирующий геморрагический синдром, острая печеночная энцефалопатия. Летальный исход фульминантного гепатита отмечен через 3 недели от момента появления первых симптомов болезни.
Заключение. Практикующим врачам необходимо проявлять настороженность в отношении болезни Вильсона – Коновалова, которая должна быть включена в дифференциальный диагноз у детей с необъяснимым повышением трансаминаз, проявлениями острой печеночной недостаточности, хронического гепатита и цирроза печени.

Ключевые слова: болезнь Вильсона – Коновалова, дети, острая печеночная недостаточность, повышение активности трансаминаз
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Wilson — Konovalov disease (WKD) (hepatolenticular degeneration, hepatocerebral dystrophy) is a rare severe inherited multisystem disease manifesting mainly as hepatic, neurological and psychiatric disorders resulting from excessive copper deposition in organs and tissues [1].

The disease was named after English neurologist Samuel Wilson. In 1912, he published a paper describing the clinical and pathoanatomical describtion of a new disease characterized by nervous system disorders and liver cirrhosis. N.V. Konovalov investigated the clinical course, pathomorphology and pathophysiology of WKD for many years [2].

WKD is a hereditary pathology with an autosomal recessive mode of inheritance and high allelic heterogeneity. The basis of the WKD is a mutation of *ATP7B* gene on chromosome 13, which encodes the transmembrane protein ATPase-7B, which is responsible for excretion of copper into bile ducts and its incorporation into ceruloplasmin [3, 4]. Abnormalities in copper ATPase trafficking result in decrease of copper binding to ceruloplasmin and decrease of circulating ceruloplasmin level, since apoceruloplasmin (ceruloplasmin lacking copper) has a shorter elimination half-life compared to copper-containing ceruloplasmin.

At an early age, introduction of copper-containing food into child's diet leads to progressive accumulation of copper in the liver, and then in the brain, kidneys and cornea. Copper accumulation leads to oxidative tissue damage and cell apoptosis. Thus, WKD, initially a liver disease, becomes a multisystem disease with damage of various organs [5, 6].

The diagnosis of WKD is an important, but extremely difficult task for practitioners. According to clinical observations, the diagnosis of WKD is usually delayed by at least 4–15 years to the stage of neurological symptoms and/or liver cirrhosis [2, 7]. On the one hand, the late diagnosis of WKD is associated with the absence of symptoms for many years. The patients under 5 years rarely show any symptoms. The age of the disease manifestation usually varies from 3 to 74 years (mean age is 13.2 years). On the other hand, the diagnosis is complicated by nonspecific and polymorphistic symptoms, a wide range of phenotypic manifestations, a variety of clinical forms, and the severity of clinical signs. All of the above suggests the need to exclude the disease (WKD) in every patient with signs of liver damage [1, 2, 8]. One of the clinical cases described in the article demonstrates untimely diagnosis of hepatic form of WKD in a patient with long-term isolated thrombocytopenia. Another clinical case shows WKD occurring under the clinical mask of amenorrhea and a mild increase of alanine aminotransferase [7, 9].

Recent studies have expanded the understanding of the WKD clinical phenotype, which appears as a multisystem disease involving not only the liver, but also the central nervous system and the musculoskeletal system [10]. Due to mental disorders, many patients with WKD have behavioral problems, which significantly worsen their adherence to treatment.

Most often, a periodic moderate increase of serum transaminase activity is the first laboratory manifestation of WKD, and a mild increase in liver size is the first clinical manifestation [7]. The diagnosis of WKD includes assessment of clinical symptoms, instrumental examination, laboratory data and the results of molecular genetic testing. Scoring system (the Leipzig score) developed at the 8th International Meeting on Wilson's disease enables to standardize diagnosis and objectively assess the patients with WKD [1, 8, 11]. The Leipzig score includes specific clinical features such as the presence or absence of Kayser — Fleischer rings, Coombs-negative hemolytic anemia, neuropsychiatric manifestation and/or MRI abnormalities, serum ceruloplasmin levels, staining for copper on liver tissue, 24-hour urinary copper excretion (spontaneous or after penicillamine challenge) and genetic analysis for *ATP7B* mutations [1, 8]. Serum coper assessment also has a high diagnostic value [12].

The Leipzig score implies a comprehensive assessment of all the parameters, while the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines incorporate the Leipzig score into a broader, stepwise approach to diagnosis of WKD, which can be used in daily clinical practice [13]. The first step consists of clinical evaluation (hepatosplenomegaly, ascites and Kayser — Fleischer rings), liver

function tests and assessment of copper metabolism (ceruloplasmin, 24-hour urinary copper). The second step includes molecular genetic testing. One mutation is considered sufficient to diagnose WKD in the presence of clinical signs, whereas 2 mutations are required in an asymptomatic patient. Liver biopsy for copper quantification is the third and final diagnostic step [13]. Whole genome sequencing is now available for verification of the WKD [6].

Treatment of patients with WKD is selected individually, taking into account the severity of organ disorders and includes diet, pharmacological and non-pharmacological therapy. It is recommended to avoid copper-rich foods. Medications promoting copper excretion (d-penicillamine, which remains the standard treatment of WKD, trientine), as well as zinc, which inhibits copper absorption in the intestine, are prescribed lifelong in adequate doses. With high patient compliance, a positive effect of the treatment is observed in 6 to 12 months [2, 5].

Zinc salts (preferably zinc acetate), given their safety profile, can be administered to children with WKD diagnosed by family screening, and also as maintenance therapy after after initial decoppering by enterosorbents, as long as serum transaminase levels remain normal. Children with severe liver injury should be preferably treated with the medications promoting copper excretion [5].

There is a concern that low-copper diet and zinc excess from zinc treatment could interfere with the child's development. Therefore, in asymptomatic young children it would be reasonable to maintain a normal diet and defer treatment till the child is 18 months old [10].

The disease can progress quickly. Liver transplantation (LT) is indicated in cases of decompensated cirrhosis or acute liver failure (ALF) [8].

Clinical case 1

A clinical case presented to raise awareness among health-care workers on the diagnosis of WKD in patients with hepatomegaly and mild hyperenzymemia.

Patient S., 10 years old, was hospitalized to the Regional Pediatric Hospital with edema syndrome, liver enlargement and hyperenzimemia. A hereditary history is not burdened. The increased aminotransferase levels (ALT 306 U/l, AST 122 U/l) were first revealed at the age of 6 years during examination for tubulointerstitial nephritis. During the subsequent four years, transaminases remained within the range of 40–100 U/l. No additional laboratory tests were prescribed.

On admission, a physical examination showed edema of the bilateral lower extremities, scrotal swelling, signs of ascites and liver enlargement (+2 cm below the right costal margin). Laboratory findings: anemia (Hb 93 g/l), thrombocytopenia (108×10^9/l), hypoproteinemia (56 g/l), hypoalbuminemia (26 g/l), low prothrombin index (39.5 %), mildly increased aminotransferase levels (ALT 61 U/l, AST 129 U/l) and bilirubin level (22 mcmol/l), increased urine copper – 0.163 μg/ml (reference range: 0.007–0.100 μg/ml). WKD was suspected.

Administration of albumin and veroshpiron reduces the severity of ascites, the abdominal circumference decreased from 86 to 70 cm. Despite this, the patient's condition deteriorated with development of fetor hepaticus, spider veins on the lower extremities, tremor and anisocoria over the course of a month. Slit lamp examination of eye did not reveal Kayser – Fleischer rings. Serum bilirubin level increased to 43 mcmol/l (direct bilirubin – 13,5 mcmol/l). Liver elastometry showed fibrosis stage F4 (23.4 kPa). Based on clinical, laboratory, and instrumental findings, a clinical diagnosis of WKD with liver cirrhosis was suspected. The patient was transferred to a Federal medical center, where the diagnosis was confirmed. The patient was placed on the liver transplant waiting list and examined according to the related liver transplantation program.

An orthotopic transplantation of the right lobe of the liver from a living related donor was performed in the Russian Research Center of Surgery named after B.V. Petrovsky. A three-component protocol of immunosuppression therapy was individually selected for the patient (tacrolimus, mycophenolate mofetil, corticosteroids).

At present, the patient is 21 years old, he is studying to be an auto mechanic, and he drives a car. Good well-being is preserved. The patient has no neurological disorders. He is constantly receiving tacrolimus, 7 mg.

Thus, the clinical case demonstrates a typical onset of WKD as a mild increase of transaminase levels, which was revealed by chance at the age of 6 years. No further examination to investigate the cause of the hyperenzymemia was performed. It should be noted that according to ESPGHAN guidelines, the diagnosis of WKD should be excluded in children under 1 year of age with any signs of liver disease or asymptomatic elevation of serum transaminases [5].

The interval between the first manifestations of the disease and the diagnosis is usually varying from 6 months to 3 years [12, 14], in the

presented case the interval was longer and constituted 4 years from the first episode of hyperfermentemia. The symptoms of the disease appeared at the age of 10 years at the stage of liver cirrhosis. A. Poujois and F. Woimant analysed medical recors of 107 patients with WKD in a hepatology center and revealed that two thirds of them had cirrhosis at the time of diagnosis [12].

Noteworthy, the patient had tubulointerstitial nephritis, which was diagnosed at the age of 6 years. Renal tubular dysfunction could be an extrahepatic manifestation of WKD, as mentioned by P. Socha et al. [5]. Extrahepatic manifestations of WKD in children may include nephrolithiasis, nephrocalcinosis, secondary IgA nephropathy, cardiomyopathy, arrhythmia, hypoparathyreosis, pancreatitis, skin lipomas, osteoporosis, and arthropathy [15].

Hepatic encephalopathy in children with WKD, decompensated cirrhosis and liver failure, could not be quickly treated by medications that promote copper excretion, these patients require liver transplantation [5], which was performed in the case presented above. The liver transplantation in patients with WKD is aimed to relieve the liver failure and metabolic defect.

Orthotopic liver transplantation is the standard treatment of severe WKD with liver failure and decompensated cirrhosis showing good results with the patients' survival rate of 83 % in 5 years, 80 % in 10 years after the procedure [1]. Liver transplantation promotes restoration of *ATP7B* gene function and leads to normalization of transaminase and copper levels [10].

In presented clinical case, liver transplantation was performed at the age 11 years. The authors of a systematic review on liver transplantation in children with WKD indicated that the average age of liver transplantation in these patients was 12.6 years [16]. Since liver transplantation eliminates the metabolic defect, no medications promoting copper excretion or inhibiting intestinal absorption of copper are required after transplantation [16].

Clinical case 2

The second clinical case demonstrates ат unfavorable course of WKD. Clinical manifestations of liver damage in WKD can range from asymptomatic cases to liver cirrhosis and ALF. The nature of the WKD diversity is not entirely clear. A combination of genetic, epigenetic, hormonal and environmental factors can probably play an important role [14, 17].

Patient L., 8 years old, the third child in the family, one of the twins. The diasease started acutely with upper abdominal pain, weakness, loss appetite. On the second day of the illness, the parents noticed dark color of the urine. On fourth day, the patients' eyes became yellow and he developed repeated vomiting. The parents first sought health care for their child on the sixth day of illness. He was examined by a pediatrician, who prescribed laboratory testing. On the seventh day, the patient was urgently admitted to the infectious disease department of the City Hospital with complains on weakness, nausea, and pain in the right subcostal area.

On admission, the patient appeared toxic but alert, the skin and eyes were yellow. Laboratory findings: hyperbilirubinemia (310 mcmol/l), direct bilirubin — 217 mcmol/l, hyperenzymemia (ALT 224 U/l, AST 473 U/l). Infusion therapy for detoxification (crystalloids), ursodeoxycholic acid and lactulose were prescribed. Despite this, the patient's condition deteriorated with development of severe intoxication, hemorrhagic rash. On the 10th day of illness, he was transferred to the intensive care unit, the severity depended on symptoms of intoxication (lethargy, adynamia, loss of appetite) without hemodynamic and respiratory disorders. The level of consciousness based on the Glasgow coma scale was 15 points. On admission to the intensive care unit, skin and eyes were yellow, ecchymosis were revealed in the injection site, liver was enlarged (+4 cm below the right costal margin), the texture of the liver on palpation was soft. Laboratory findings: hyperlactatemia (7.15 mmol/l); pH 7.456.

In several days, the patient's condition worsened: jaundice increased (total bilirubin — 440 mcmol/l, direct — 216 mcmol/l), hyperenzymemia (ALT 607 units/l, AST 479 units/l), hypocoagulation (Quick prothrombin — less than 3 %, INR — 19.20 (0.97–1.30), antithrombin III 16 % (96–126%), signs of hepatic encephalopathy, sopor, Glasgow coma scale consciousness level 9–10 points, liver size decreased.

Detoxification and pathogenetic therapy, including amino acids formulations for parenteral nutrition, prothromplex and antithrombin III, were continued. On the 15th day of the disease, the patient's condition became extremely severe, consciousness level oppressed to coma stage 1 (Glasgow Coma Scale of 8–9 points). Tracheal intubation was performed and artificial lung ventilation (ALV) was started. Microcirculation disorders were observed (capillary refill time — 4 sec), blood pressure dropped to 90/33 mmHg. Dopamine infusion was given. Hemorrhagic syndrome became more severe.

A telemedical consultation with the Shumakov Scientific Research Center of Transplantology and Artificial Organs was conducted. It was noted that

the patient was non-transportable. Urgent search for kelated donors of the liver fragment was recommended.

To clarify the nature of fulminant hepatitis with ALF, the patient was examined for serological markers of viral hepatitis A, B, C and other hepatotropic viruses (cytomegalovirus, Epstein — Barr virus, herpes viruses type 1, 2, 6). No serological markers were found. Autoimmune hepatitis and alpha-1 antitrypsin deficiency were excluded (alpha-1 antitrypsin level was normal). There was no evidence of acute poisoning with heavy metals or medications (based on anamnesis and laboratory tests results). Serum ceruloplasmin level was decreased — 19.5 mg/dl (20–60 mg/dl), daily copper excretion with urine was elevated — 97 mcg/day (3–50 mcg/day). The diagnosis of WKD was suspected.

On the 20th day of the disease, abdominal ultrasound revealed ascitic fluid up to 3070 ml. Laparocentesis was performed, removing 600 ml of the transudate, drainage was placed in the peritoneal cavity. The renal function decreased — GFR 55.7 ml/min, hemorrhagic syndrome progressed to widespread ecchymoses, oral mucosal bleeding, transient microhematuria. On the 22nd day of the disease, the patient developed asystole, resuscitation measures had no effect, the patient died.

The clinical case is characterized by an acute onset, rapid progression and fulminant course. According to the meta-analysis performed by S.M. Vandriel et al. ALF could be the first manifestation of WKD. The WKD was diagnosed in 3 % of all ALF cases. WKD manifested as ARF is usually fatal requires emergency liver transplantation. The favorable outcome was observed in only 11 % presented in the meta-analysis [18].

Understanding of the ARF nature is challenging. It is hardly possible to distinguish WKD with ARF from ARF of other causes. Laboratory markers indicating impaired copper metabolism can be both false-positive and false-negative, the sensitivity of biochemical diagnostic ratios in children is low. Thus, the sensitivity of the ratio of alkaline phosphatase to total bilirubin (in WKD is less than 4.0, in our observation it was 2.4) and AST/ALT (in WKD is more than 2.2, in our observation — 2.1) is only 71 % [18]. Nevertheless, an almost twofold increase in daily copper excretion with urine is suggestive of WKD with ARF in a patient.

According to a meta-analysis that included a large cohort of children (256 individuals, 52 studies), the median age of manifestation of ARF in WKD was 13.4 years. The percentage of girls was higher than boys in most of cases, 60 % of boys were postpubertal, whereas in our clinical case the patient was prepubertal. The main predictors of fatal outcome in WKD with ALF are the combination of hepatic encephalopathy with coagulopathy. The international normalized ratio (INR) is a marker of this condition [18]. In the presented clinical case we noticed a progressing coagulopathy with high INR level (19.20, ref.: 0.97–1.30). Patients with WKD and ALF with INR > 2.0 had more than 7 times higher odds of death [18].

Signs of hepatic encephalopathy in the presented clinical case were present on the 14th day of illness as an impaired consciousness (9–10 points according to Glasgow coma scale). The patients with WKD accompanied by hepatic encephalopathy are usually 100 % fatal [18]. Therapeutic strategies in favorable outcomes include the use of extracorporeal treatment methods, including plasmapheresis combined with D-penicillamine, and the molecular adsorbent recirculating system (MARS). Survival of patients with WKB and ARF after the liver transplantation ranges from 80 to 90 %, which is significantly higher compared to conservative therapy [18].

In our case, the rapid progression of the disease, the fulminant course of ARF, the impossibility of transporting a patient in an extremely severe condition to the transplantation center did not allow performing a liver transplantation to prevent an unfavorable outcome.

Conclusion

Early diagnosis and therapy of WKD generally increases the chances for favorable outcome. Undoubtedly, raise of healthcare workers'awareness on WKD is required to prevent severe organ damage and lethal outcomes in children. Early diagnosis of WKD is the key to timely therapy and a favorable prognosis.

Taking into account the gradual onset of the disease, the absence of specific symptoms, and the relative rarity of the disease, the timely diagnosis of WKD is challenging. This leads to the diagnosis of WKD at the stage of liver cirrhosis and marked neurological disorders, which significantly worsens the prognosis of the disease. The analysis of WKD clinical cases can be of interest to practitioners willing to update their knowledge on this problem. The clinical cases with confirmed and probable diagnosis WKD presented in the article demonstrate variability of the clinical course and outcomes of the disease.

Early diagnosis and treatment are crucial to prevent disease progression and the development

of cirrhosis or liver failure. Practitioners need to consider the peculiarities of the manifestation and the course of the disease. Thus, screening for WKD should be performed in children over 1-year-old with unexplained increase of serum transaminases, signs of ALF, chronic hepatitis, liver cirrhosis, neurological disorders of unknown etiology, Coombs-negative hemolytic anemia [1].

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