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Case Report

SEPSIS AND MULTIPLE ORGAN DYSFUNCTION SYNDROME AS THE FIRST CLINICAL PRESENTATION OF WILSON'S DISEASE: CASE REPORT

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Wilson's disease (WD) is a rare autosomal recessive disorder caused by a mutation in the ATP7B *gene. The evolution of Wilson's disease is the result of the accumulation of copper in affected tissues. In this study, we report on a 30-year-old patient with multiple organ dysfunction syndrome and sepsis. After the necessary investigations and genetic tests, the patient was diagnosed with WD. Unfortunately, the first symptoms appeared at least ten years ago with elevated liver transaminases and amenorrhea. It is possible that if any of the previous physicians had provided a detailed examination, the patient would have reached a diagnosis sooner. The patient received adequate penicillamine treatment and her condition improved. The patient manages to have a healthy child by slightly changing the treatment of Wilson's disease. This case demonstrates that proper examination and collection of anamnesis information can lead to a diagnosis of WD. In addition, we emphasise the importance of targeted testing for elevated transaminases, especially if the patient has amenorrhea at reproductive age. Wilson's disease is not a barrier to carrying a healthy child. Of course, more research is needed to develop the best treatment and disease management plans.*

Keywords: *Wilson's disease, elevated transaminase levels, amenorrhea, pregnancy.*

INTRODUCTION

Wilson disease (WD) is a rare autosomal recessive inherited disorder that was first described by Kinnear Wilson in 1912. Wilson's disease is caused by mutations in the *ATP7B* gene located in the long arm of chromosome 13. The *ATP7B* gene encodes a polypeptide that acts as a copper transport protein. The evolution of Wilson's disease is the result of the accumulation of copper in affected tissues (Zou *et al*., 2021). Clinical symptoms can vary widely, but the symptoms that are detected and appear most often are neuropsychiatric disturbances and liver function complaints. The estimated incidence of WD is 1 per 30 000. The age of the onset of Wilson's disease is variable and most cases occur in individuals between the ages of 5 and 35 (European Association for the Study of the Liver, 2012).

In this study, we report a on a 30-year-old- female patient with multiple organ dysfunction syndrome and sepsis. After the necessary investigations and genetic tests, the patient was diagnosed with WD.

CASE HISTORY

A 30-year-old woman, in August 2015, was placed in an acute care unit in the Department of Gastroenterology due to a clinical diagnosis of acute haemolysis. She reported weakness and was found to have jaundice, febrile fever, headache, and dark urine. Initial investigations showed an elevated leukocyte count (WBCs) 32×10^9/l, total bilirubin 238 μmol/l, direct bilirubin 155 μmol/l, C-reactive protein (CRP) 36 mg/l, AST 125 U/l and ALT 110 U/l. However,

she had a reduced erythrocyte count (RBC) 1.3 × 10^{12}/l, prothrombin 24.14 % and haemoglobin 4.8 g/dl, and urine tests showed a urinary tract infection. The patient's blood pressure (BP) was reduced to 105/60 mmHg, pulse 64×/min, and respiratory rate 14×/min. She had multiple subcutaneous haematomas after falling from a scooter a week ago. In examination, the patient complained of pain in the lower abdomen that radiates upwards, multiple loss of consciousness, and oedema on ankles. The patient denied having any chronic illnesses. The patient was also consulted by a neurologist. The conclusion of the neurologist was hand tremors and facial spasticity; the patient answered questions slowly but correctly. During the day, the patient's condition worsened (BP 90/46 mm/Hg; pulse 60×/min; SpO_2 – 91%;) and she was transferred to a sepsis and toxicology clinic. The patient was prescribed torasemide (20 mg for 1 day), silymarinum (for nine days in hospital), also intravenously (IV) ceftriaxone (2,0 mg + sodium chloride 0.9% 200 ml for five days), short-term corticosteroids and fresh frozen plasma transfusion (for four days). Positive dynamics was observed during therapeutic treatment. Ultrasound (USG) examination showed that kidney inflammation could not be ruled out, there was a slight lymphadenopathy, but other structures were unchanged. Urine tests showed elevated erythrocyte count (139/µl), leukocyte count (42/µl) and PH, but negative urine culture. Analysis shows that there were liver and renal impairments which was consistent with multiple organ dysfunction syndrome (MODS) caused by sepsis. Additional investigations revealed that antinuclear antibodies (ANA), extractable nuclear antigen (ENA), double-stranded DNA (anti-dsDNA), anti-Leptospira antibodies, antibodies to syphilis bacteria and haemoculture of aerobic, anti-HIV-1, HBsAg, HCV Ab and anaerobic flora were negative. Computer tomography (CT) demonstrated fluid collection in the gallbladder, subhepatic with distribution through the right lateral canal to pelvis. Magnetic resonance imaging (MRI) revealed a hydrothorax on the right side of the lung. Thoracentesis was performed, and an inoculation was also carried out that showed negative DNS assay on mycobacterium tuberculosis (Mtb). A council was called to clarify the cause of chronic liver damage. The medical history showed that signs of liver dysfunction had been present for approximately ten years, as there had been elevated transaminase levels in blood tests. This might suggest Wilson's disease. The patient was prescribed a 24-hour urine copper test and genetic tests. The copper content was elevated (810 µg/24 h) in the daily urine, and the level of ceruloplasmin (0.159 g/l) was reduced. Ophthalmologists did not observe the Keysner ring characteristic of WD, but the patient had primary amenorrhea for approximately ten years. The patient uses hormonal contraception at that time. The patient was discharged from the hospital for further outpatient treatment. Also, outpatient genetic testing was prescribed. After genetic testing and 24-hour urine copper test, the patient was diagnosed with Wilson's disease.

Second time in hospital (a month after the first hospitalisation). During consultation with the doctor for infection and hepatology, the patient was required to go to hospital for treatment for the second time, due to fever, increased jaundice in the dynamics, significant fatigue, dark urine, and vomiting.

Two weeks before this hospitalisation, the patient began receiving 500 mg of penicillamine per day as a prescribed starting dose, which was later increased to 1000 mg per day. While in therapy, the patient developed nausea, vomiting, and fever.

In the course of the hospital treatment, the patient received USG of the abdomen to test for gallstone disease, signs of kidney parenchyma damage and signs of liver parenchyma damage, as well as EHO, that is without significant pathological indication.

The patient was hospitalised for five days, and during this time the condition improved, jaundice decreased, body temperature returned to a normal level, still periodic headache detected, and the patient was released in a stable state. The recommendation was to continue penicillamine 1000 mg medication daily, spreading the dose in four parts within one day, one hour before eating. To determine dynamics, it was necessary to conduct USG or magnetic resonance imaging (MRI) on abdomen and MRI on the brain. In ten days, the patient was given a full blood test, and bilirubin, prothrombin, INR and urine tests. The patient avoided copper-containing food and had regular appointments with an infectologist-hepatologist.

Further development of the disease. The check-up at three months revealed increased copper content (1330 µg/24 h) in daily urine. Therefore, the dose of penicillamine was increased to 1250 mg per day (1 tablet five times a day). Ten months after starting treatment, in 2016, the menstrual cycle resumed. The patient experienced periodic headaches, memory problems, and arm tremors during the entire time. A neurologist made a diagnosis of hand tremor and impaired fine motor skills of hand. Magnetic resonance imaging (MRI) showed non-specific foci in the right hemisphere of the brain, but no specific therapy was applied. Also, after the last check in March of 2022, the patient complained of increased tremor under stress. The patient also noted depression and recurrent headaches. Dynamic testing indicated copper decreases in daily urine under the therapy used — penicillamine 1250 mg per day (see Fig. 1).

Five years after Wilson's disease was diagnosed, the patient became pregnant for the first time. Pregnancy occurred while the patient had therapy with penicillamine at a dose of 1250 mg per day. Several councils took place to discuss further doses of penicillamine. Consilium recommendations were to reduce the dose of penicillamine during the second trimester of pregnancy to 1000 mg per day and during the third trimester of pregnancy to 750 mg per day. After childbirth it was recommended to continue with the initial penicillamine dose of 1250 mg per day.

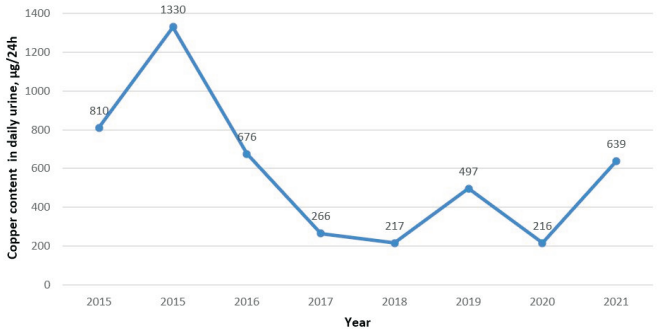

Fig. 1. Copper content in daily urine

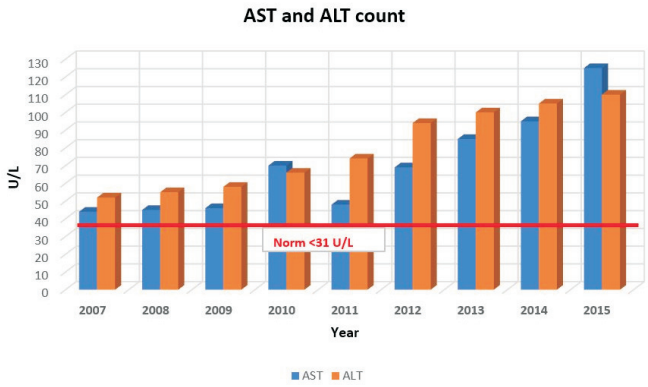

Fig. 2. Changes in transaminase level

*AST, aspartate transaminase; ALT, alanine transaminase

The patient gave birth to a healthy boy, and she had physiological vaginal delivery without any complications. The newborn weighed 4.3 kg and was 53 cm long. Other studies found that newborns born to women with Wilson's disease usually have lower birth weight (Yu *et al*., 2019).

Breastfeeding was not recommended because of possible negative effects of penicillamine on the newborn (Yu *et al*., 2019). Presently, the five-year-old boy is healthy, and has not yet been examined for Wilson's disease.

DISCUSSION

In the case of WD, copper excretion with bile is defective, which leads to copper accumulation, most likely in the liver and the brain. Thus, the most common symptoms occur in these areas. WD symptomatic manifestation usually occurs between ages of 5 and 35 years. In this case, the patient was 30 years old. 95 percent of WD patients have Kayser–Fleischer ring (copper deposition in the Descemet membrane of the cornea) with or without neurologic symptoms (European Association for the Study of the Liver, 2012). Unfortunately, the ophthalmologist did not find a Kayser–Fleischer ring in our patient, but she had neurologic symptoms such as hand tremor and dysarthria, which occurs in 50% of cases. Also, mood changes occur in 25% of WD patients. Our patient had mood fluctuation and neurological symptoms. The patient suffered from changes in mood in all years, but more markedly in recent years. Also, hand tremor became stronger, especially when the patient was nervous. This occurs because copper accumulation causes damage to the basal ganglia in the central nervous system, and hence also headaches become common. This mechanism is thought to be similar to that seen in neurodegenerative disease (Ferenci *et al*., 2015; Litwin *et al*., 2018). Our patient is currently undergoing psychotherapy.

The patient had an elevated transaminase level in blood for approximately ten years (Fig. 2). She had already previously visited specialists regarding the elevated transaminase level, but this was investigated in detail until the patient was hospitalised with acute haemolysis. The typical symptoms like jaundice, hand tremors, loss of consciousness, and haemolytic anaemia occurred only shortly before hospitalisation. Thus, if the previous practitioners had paid attention to the elevated transaminase, the patient might not have been hospitalised. She might even have been diagnosed and treated sooner. Therefore, we want to emphasise the importance of targeted testing for elevated transaminase, if no other explanation for the increase in transaminases is found. However, it should be noted that aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels vary in WD. At first, AST and ALT are elevated in asymptomatic patients, but in later stages, a decrease of liver enzyme decrease as cirrhosis appears. Also, there might be a rapid fall during haemolytic anaemia (coombs-negative) (Cho *et al*., 2011; Hayashi *et al*., 2019).

There are three, most recently issued, clinical practice guidelines on Wilson disease: the American Association for the Study of Liver Diseases (AASLD) in 2008, the European Association for the Study of the Liver (EASL) in 2012 and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2018 (Palumbo and Schilsky, 2019). In this paper, we will compare the European and American guidelines for clinical practice in the adult treatment of Wilson's disease. Both guidelines suggest that treatment of symptomatic patients should be initiated with a chelating agent (D-penicillamine or trientine), but both state that trientine might be better tolerated. Both medications promote copper excretion with urine. However, AASLD and EASL guidelines propose that for presymptomatic patients the first line treatment should be with zinc or chelating agent (D-penicillamine or trientine). Also, these medications are recommended as maintenance therapy. Combination with zinc and chelator in AASLD guidelines is proposed as decompensated cirrhosis therapy. However. in the EASL guidelines, zinc alone is considered as a first line therapy in neurological patients. The AASLD guidelines propose that there is a need for dose-reduction of chelator therapy in the case of a surgical procedure because of potential concern for wound healing. Both guidelines also note the importance of a low copper diet combined with medical treatment during the first year. The AASLD and EASL guidelines introduced two possible additional medications — tetrathiomolybdate and vitamin E (Roberts and Schilsky, 2008; European Association for the Study of the Liver, 2012). Fabregues *et al*. (2020) reported

that ammonium tetrathiomolybdate could be the initial treatment of WD patients with neurological symptoms, as it was found to reduce symptoms for all included patients. The concern worldwide is that chelators may induce further neurological deterioration in some treated WD patients, in such patients the symptoms were improved as ammonium tetrathiomolybdate treatment was started (Fabregues *et al*. 2020). It was also noted that there have been a limited number of studies on tetrathiomolybdate treatment for WD. Even the studies were conducted by one researcher — G. J. Brewer (Fabregues *et al*., 2020). Kalita *et al*. (2019) showed that vitamin E and C improved clinical outcomes and oxidative stress for WD patients with neurological symptoms who used zinc with or without chelating therapy. It has been proven that vitamin E has antioxidant properties (Kalita *et al*., 2019). However, there are only a few studies on vitamin E as a treatment for WD. Therefore, more studies are needed in this field to fully understand the impact of tetrathiomolybdate and vitamin E treatment.

In our case the patient complained about amenorrhea for almost ten years, the patient could not become pregnant and the gynaecologist did not have any explanation for this. Problems with the menstrual cycle were resolved only after the patient was diagnosed with WD and received therapy. The first time when amenorrhea appeared in our patient's medical history was when she was only 24 years old. The gynecologist sent her for blood tests. Her first blood tests results were: AST 46 U/l and ALT was 58 U/l, LH, FSH, and TSH were within the normal range and blood tests did not show any other changes. The patient was treated with Gestodenum/Ethinylestradiolum but menstruation did not occur. She went back to the gynaecologist a few months later, and the doctor repeated blood tests: AST 70 U/l, ALT 66 U/l, and the patient also had lymphocytosis and neutropenia. A diagnosis was made of dysfunction of ovaries and hypogonadotropic primary amenorrhea, and therapy was changed to Remens and Cyklobiol. After the patient was diagnosed with Wilson's disease and treated with penicillamine, her menstrual cycle came back to normal. Other studies also described that changes in menstrual cycle like oligomenorrhea or amenorrhea and ovarian dysfunction are common manifestations of Wilson's disease (Woimant *et al*., 2018).

CONCLUSION

This case demonstrates that proper examination of the patient and collection of anamnesis information leads to diagnosis. Thus, if other practitioners had paid attention to the elevated transaminase level and amenorrhea, the patient might not have been hospitalised, and been diagnosed and treated sooner. We emphasise the importance of targeted testing for elevated transaminase level, especially if the patient has amenorrhea at reproductive age. This case is a good example that with proper treatment of Wilson's disease, the patient's menstrual cycle returns after as little as ten months. The patient managed to carry a healthy child on the background of Wilson's therapy in 2020. However, the patient retains the neurological symptoms and headaches associated with Wilson's disease. Of course, further research is needed to develop the best disease management and treatment plan.

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SEPSE UN MULTIORGĀNU DISFUNKCIJAS SINDROMS KĀ VILSONA SLIMĪBAS PIRMĀ KLĪNISKĀ IZPAUSME: KLĪNISKAIS GADĪJUMS

Vilsona slimība ir autosomāli recesīva slimība, ko izraisa mutācija *ATP7B* gēnā, šīs slimības attīstība ir saistīta ar vara uzkrāšanos dažādos orgānos. Šajā pētījumā mēs ziņojam par 30 gadus vecu pacienti, kura nonāca uzņemšanas nodaļā ar multiorgānu disfunkciju un sepsi. Pēc padziļinātiem izmeklējumiem, ģenētiskajām pārbaudēm un vairākiem konsīlijiem pacientei tika noteikta diagnoze — Vilsona slimība. Diemžēl izrādījās, ka pirmie simptomi bija parādījušies jau vismaz desmit gadus atpakaļ, kas bija vērojami laboratorās izmaiņās kā paaugstināts aknu transamināžu līmenis un klīniskas izpausmēs, piemēram, amenorejā. Iespējams, ja, parādoties pirmajiem simptomiem, paciente būtu mērķtiecīgi izmeklēta, tad diagnoze būtu noteikta ātrāk un slimība nebūtu nonākusi līdz smagai stadijai. Pacientes veselības stāvoklis uzlabojās, kad viņai tika uzsākta Vilsona slimības ārstēšana ar penicilamīnu. Saņemot penicilamīna terapiju, pacientei atrisinājās arī menstruālā cikla traucējumi. Neraugoties uz Vilsona slimības diagnozi un terapiju, pacientei iestājās grūtniecība, kas noritēja bez nopietniem sarežģījumiem, un piedzima veselīgs bērns. Šis gadījums parāda, ka mērķtiecīga un pareiza izmeklēšana, kā arī precīza anamnēzes ievākšana noved pie pareizās diagnozes — Vilsona slimība. Mēs vēlamies uzsvērt, cik svarīgi ir mērķtiecīgi pārbaudīt ilgstoši paaugstinātu transamināžu līmeni, it īpaši, ja pacientei ir sūdzības par amenoreju reproduktīvā vecumā. Vilsona slimība nav šķērslis veselīga bērna iznēsāšanai. Šajā gadījumā grūtniecības laikā pencilamīna terapija tika nedaudz samazināta, pēc dzemdībām atjaunota sākotnējā deva. Ir nepieciešami vairāki pētījumi par Vilsona slimības diagnostiku un klīniskajām manifestācijām, lai uzlabotu kolēģu zināšanas par šo slimību un nodrošinātu pēc iespējas laicīgāku un kvalitatīvāku pacientu ārstēšanu.