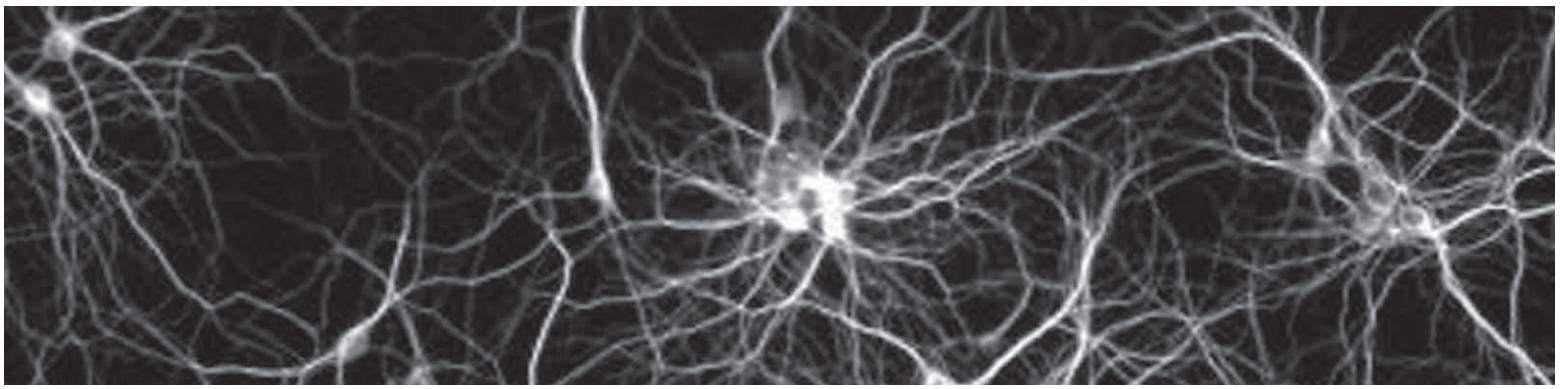

Wilson's disease: importance of early recognition and genetic testing of family members

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ABSTRACT – *Objectives:* Wilson's disease (WD) is a rare autosomal recessive hereditary disorder of copper metabolism with an effective treatment available if diagnosed in the early stages, preferably before symptoms show. However, due to sometimes unspecific signs and symptoms, diagnosis is only possible with a high index of clinical suspicion. Therefore, for early recognition of asymptomatic patients, genetic testing of family members is extremely important. In addition, the aim of this article is to emphasize the role and importance of multidisciplinary approach in the diagnosis and treatment of WD. *Case description and results:* We present a patient with WD that was accidentally detected after routine ophthalmologic examination following head injury. Owing to efforts invested by different members of our multidisciplinary team for WD, a genetic mutation was determined, pathologic parameters of copper metabolism were examined and appropriate therapy was introduced. Genetic testing was also carried out in the patient's daughter, his sister and her son. The patient's 5-year-old nephew was found to be a homozygote for the mutation. He was referred to pediatric hepatologist. *Conclusion:* The nephew was the youngest asymptomatic person diagnosed with WD from establishment of our multidisciplinary team. This dramatically improved the outcome of this boy and is certainly going to increase his overall quality of life.

Key words: Wilson's disease, copper, genetic testing

INTRODUCTION

Wilson's disease (WD) or hepatolenticular degeneration is a rare autosomal recessive disorder of copper metabolism (1,2). It was first described by Samuel Alexander Kinnier Wilson in 1912 (3).

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Mutation of the ATP7B gene on chromosome 13 (13q14.3) results in disturbance of copper metabolism with consequent accumulation of copper in the liver and extrahepatic tissues such as brain and corneal Kayser-Fleischer (KF) ring. WD may be presented with hepatologic, neurologic and psychiatric symptoms or their combination. However, many other symptoms may be present, for example hematologic, such as hemolytic anemia, leukopenia, thrombocytopenia, etc. (4,5).

Diagnostic algorithm for WD includes complete blood count, kidney tests (proteinuria, creatinine clearance), ceruloplasmin, copper in serum, copper in 24-hour urine and copper in 24-hour urine after d-penicillamine challenge, biomicroscopy (KF ring), brain magnetic resonance imaging (MRI), and in doubtful cases liver biopsy with copper concentration *per* gram of dry liver tissue and histopathologic analysis of liver tissue. However, genetic testing is needed in some cases to confirm the diagnosis (3,4).

In therapy of WD we use copper chelators (d-penicillamine, trientine, tetrathiomolybdate) and zinc salts (2). Zinc salts are first-line therapy in asymptomatic and pregnant patients (6).

About 400 mutations are known, including missense and nonsense mutations, deletions and insertions. The most common mutation in Caucasians is H1069Q located on exon 14 of WD gene. Therefore, routine genetic testing applies to this one as the most frequent mutation. If the patient with clinical suspicion of WD is not homozygous for this mutation, then complete sequencing of the gene is indicated (7,8).

Ceruloplasmin is a serum copper transporting protein the concentration of which is decreased in most WD patients. However, the clinical value of this test could be limited because a decreased ceruloplasmin level may be present in 1% of controls, 10% of individuals heterozygous for WD mutation, as well as in malabsorption and chronic liver failure (8). Therefore, diagnosing WD may be difficult and complete diagnostic algorithm is needed in some patients. In this scenario, genetic testing may be very important not just for the patient but also for his/her family members.

CASE REPORT

A 37-year-old male was admitted to emergency unit following a head trauma after an accident while playing football. He was examined by a surgeon and then by an ophthalmologist, who detected KF rings in the patient. The patient's records were looked into and no KF rings were detectable during previous ophthalmolgic exams, one year before diagnosing WD. Following this finding, the patient was referred to gastroenterologist and neurologist in the subspecialist outpatient unit for movement disorders as there was a high suspicion of WD. Available tests were performed and the following significant results were obtained: serum copper 11.8 mmol/L (12.2-25.1), ceruloplasmin 0.06 g/L (0.20-0.60), copper in 24-hour urine 4.58 mmol/dU (<1.7). In addition, fine bilateral postural hand tremor was recorded during neurologic exam. Following initial examination, he was hospitalized in the specialized Unit for Heredodegenerative Disorders.

Medical history revealed that the patient had been hospitalized in a psychiatric department at the age of 25 due to a psychotic episode. He was successfully treated with fluphenazine and biperiden. He also suffered from chronic bronchitis. He was a worker in metal industry, in regular contact with copper. His family history showed that his mother suffered from liver cirrhosis.

Next, more detailed tests were performed. MRI showed slightly enlarged cerebellomedullary cistern, bilateral microvascular ischemic lesions predominantly in the subcortical parietal regions, and no metal deposition in basal ganglia or other loci. HLA typing established HLA B27 positivity. Neurological examination was abnormal with mild postural tremor of both hands, predominantly on the left, with activated rigidity also positive on the left side. Fast alternating movements were normal. Important laboratory findings during his hospital stay were as follows: platelets 129-141x10^9/L (158-424), glucose 7.3-7.7 mmol/L (4.4-6.4), creatinine 160 mmol/L (79-125), serum copper 9.3 mmol/L (12.2-25.1), ceruloplasmin 0.06 g/L (0.20-0.60), proteins in 24-hour urine 0.26 g/dU (<0.15), 24-hour urine copper 6.12 mmol/dU (<1.7), and copper in 24-hour urine after the penicillamine test 26.4 mmol/dU. Genetic testing revealed a homozygous mutation, H1069Q, in ATP7B gene. Abdominal ultrasound and liver enzymes were normal.

After discussion with a gastroenterologist of the multidisciplinary team for WD, d-penicillamine in a dose of 300 mg and vitamin B6 substitute were introduced. At two-month follow up examination, a decrease in tremor was observed. The patient felt good and laboratory tests showed the following results: copper in serum 8.3 mmol/L (12.2-25.1), copper in 24-hour urine 6.62 mmol/dU (<1.7),

AST 40 U/L (11-38), ALT 17 U/L (12-48), GGT 20 U/L (11-55), and platelets 146x10^9/ L (158-424).

We recommended genetic testing for the patient's daughter, his sister and nephew. The sister was found to be heterozygote, while her 5-year-old son was homozygote positive for H1069Q mutation, without any clinical symptoms. The patient's 6-year-old daughter was heterozygote, and testing was highly recommended for his younger, 2-year-old daughter. There were no data on the marriage of relatives in the involved families.

DISCUSSION

The incidence of WD is estimated to 1 *per* 30000 to 50000, with no discernible geographical pattern (6-8). The most common mutation in Europe is the H1069Q mutation (7), also present in the described patient. WD gene is located on chromosome 13 (13q14.3) (8).

Wilson's disease is an autosomal recessive disorder with disturbance of copper metabolism that results in the accumulation of copper in the liver, brain, cornea and other tissues. Symptoms rarely occur before the age of 5 and after the age of 50 (6,8).

Gastrointestinal disturbances in WD range from asymptomatic state to increase of liver enzymes, chronic hepatitis, or even fulminant liver failure. Neurological signs and symptoms appear due to the accumulation of copper predominantly in basal ganglia. Large deposits can be visible on MRI. The most common neurological signs are speech problems, tremor, dystonia and other extrapyramidal signs. Very large amplitude tremor ('flapping tremor') is considered pathognomonic.

Our patient experienced only mild bilateral tremor, later found to be predominantly on the left side with discrete activated ipsilateral rigidity. Tremor decreased after therapy with chelator had been introduced. This confirms the importance of keeping WD in mind as a potential cause of tremor in young people. In addition to neurological disturbances, WD can also begin with psychiatric symptoms such as depression, psychosis, etc. (1,9). Initial clinical presentation of WD in our patient was indeed psychiatric at the age of 25. Therefore, in atypical psychosis and unusual psychopathological presentations in general in a young person (up to around 55 years), we must consider WD.

Diagnostic algorithm for WD includes complete blood count, liver enzymes, kidney tests (proteinuria, creatinine clearance), ceruloplasmin, copper in serum, copper in 24-hour urine and copper in 24-hour urine after d-penicillamine challenge, biomicroscopy (KF rings), brain MRI, and in doubtful cases liver biopsy with copper concentration *per* gram of dry liver tissue and histopathologic analysis of liver tissue (1,3,6,8).

According to our patient's history data, KF rings were not recorded during ophthalmologic examinations (for other reasons) but were found on detailed examination after head trauma. This was a crucial step for our patient as it made him referred to a gastroenterologist and neurologist, and subsequently to WD experts. This obviously indicates the need and importance of education of ophthalmologists and other specialists with the aim of early recognition of WD. If WD is diagnosed and consequently appropriately treated on time, the outcome is generally good, and duration and quality of life are comparable to the general population.

In the treatment of WD we use chelators to bind and remove excess copper from affected tissues (10), or zinc salts to decrease intestinal absorption of copper. D-penicillamine is the most commonly used chelator in Europe. As it can cause vitamin B6 deficiency, all patients are required to take supplemental B6. This combination proved effective in our patient as well, and is to be taken for the rest of his life. Zinc therapy is usually the treatment of choice in asymptomatic patients and pregnant women (2,8,11). Liver transplantation is an option in patients with irreversible liver damage. In addition to medication, patients with WD must carry out a diet low in copper, which was therefore also recommended to our patient and his nephew who was found to be a homozygote for WD.

The nephew has since been under permanent supervision of pediatric hepatologist. At the moment, he is without symptoms, but depending on future findings, his doctor plans to introduce zinc salts. This demonstrates the role of genetic testing of family members of patients with WD, which is obviously of vital importance in order to ensure adequate quality of life of all family members (12). The course of events in diagnosing our patient with WD, efficacy of therapy when introduced at a proper time and the role of early genetic testing of family members speak for the importance of coordinated activities and collaboration of our polyvalent multidisciplinary team for WD. The team combines experts from various fields including a neurologist, gastroenterologist-hepatologist, pediatric hepatologist, pediatric neurologist, molecular geneticist, psychiatrist, ophthalmologist, genetic advisor, neuroradiologist, abdominal surgeon, nu-

tritionist, social worker, and other experts depending on specific needs of patients.

CONCLUSION

Wilson's disease is often unrecognized, and therefore left untreated with fatal outcome being unfortunately not rare. Considering that therapy is available and very effective if introduced in early stages (preferably before symptoms occur), the importance of early detection is obvious. Appropriate timing of therapy induction results in the quality of life and survival of patient comparable to the general population. Thus, diagnosing as early as possible, as well as routinely testing family members for mutations is of great value in dealing with WD.

In addition, as proven in the case presented, continuing education in targeted groups of medical experts and establishment of polyvalent multidisciplinary teams in national reference centers (13) is the key in combating WD today.

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Wilsonova bolest: važnost ranog prepoznavanja i genetskog ispitivanja članova obitelji

SAŽETAK – *Cilj prikaza:* Wilsonova bolest (WB) je rijetka autosomno recesivno nasljedna bolest s poremećajem metabolizma bakra, s učinkovitom terapijom ako se bolest na vrijeme dijagnosticira, osobito prije pojave kliničkih simptoma. S obzirom na to da se bolest može prezentirati nespecifičnim simptomima i znakovima iznimno je važno postaviti kliničku sumnju na nju. Stoga je za rano prepoznavanje asimptomatskih bolesnika jako važno gensko testiranje članova obitelji. Uz to, cilj ovoga prikaza je ukazati na važnost multidisciplinarnog pristupa u dijagnostici i liječenju WB. *Prikaz bolesnika i rezultati:* Prikazujemo bolesnika s WB koji je dijagnosticiran slučajno, nakon rutinskog okulističkog pregleda zbog traume glave. Cjelokupnim angažmanom svih članova Multidisciplinarnog tima za WB naše ustanove otkrivena je patološka mutacija, poremećeni parametri metabolizma bakra te je uvedena odgovarajuća terapija. Gensko testiranje također je provedeno kod bolesnikove kćeri, sestre i sestrinog sina. Bolesnikovom 5-godišnjem nećaku utvrđena je homozigotna mutacija na WB te je upućen pedijatrijskom hepatologu. *Zaključak:* Pregledani nećak je dosad najmlađi asimptomatski bolesnik našeg Tima, kojemu je dijagnosticirana WB. Postavljanje dijagnoze, planiranje kontinuiranog praćenja i uvođenje pravodobne terapije dramatično poboljšavaju ishod i kvalitetu života ovakvih bolesnika.

Ključne riječi: Wilsonova bolest, bakar, gensko testiranje