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Conference paper

Case report

THE MANY FACES OF WILSON'S DISEASE

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INTRODUCTION

Wilson's disease was named after Samuel Alexander Kinnier Wilson, who in 1912 first described a hereditary disorder of the copper metabolism (Ala et al. 2007). The ATP7B gene responsible for WD is located on the fourteenth exon of the thirteenth chromosome (13q14.3) and the most common mutation in this region is p.His1069Gln (Ferenci 2006). Due to a defect in the cellular cooper transport, copper accumulates in the liver, brain and other extrahepatic tissues, including the Descemet's membrane in the cornea, in the form of the so called Kayser-Fleischer rings.

Clinical presentation depends on the predominant area of copper accumulation and can thereby primarily be neurological, gastrointestinal, psychiatric, osteoarticular, hematological and other, or the patient can present with a diverse mixture of symptoms. Presentation of symptoms is rare before the age of 5 and after the age of 50 years (Ala et al. 2007). Gastrointestinal disease in WD can range from an asymptomatic form with an increase in liver enzymes as the only clinical finding, to chronic hepatitis or fulminant liver failure. Neurological manifestation occurs primarily due to the accumulation of cooper in the basal ganglia, a pathological sign detectable in MRI in the case of large deposits. The most common neurological presentation includes speech problems, tremor, dystonia and other extrapyramidal symptoms and signs. "Flapping tremor", a typical large-amplitude tremor, is considered pathognomonic. Psychiatric symptoms, most commonly found in patients with neurologic involvement, can vary from mild to very severe. Most commonly, these include depression, personality change, incongruous behavior and irritability.

The initial evaluation of patients suspected of having WD is non-invasive and includes liver biochemical tests, serum analysis for copper and ceruloplasmin concentration, ocular slit-lamp examination and 24-hours urinary cooper concentration. The definitive diagnosis is confirmed by genetic testing for ATP7B mutations (Ferenci 2006). If the person is not homozygous for the most frequent mutation (p.His1069Gln), the complete sequencing of the gene is indicated (Kalauz et al. 2010). European Association for the Study of the Liver recommends using the Leipzig scoring system that numerically combines the results of the tests described above to navigate the diagnosis (EASL 2012).

Treatment of WD includes copper chelators (penicillamine, trientine, tetrathiomolybdat) and zinc salts (Roberts 2011). Chelators draw the copper out of the organs, while zinc salts block absorption of copper from the gastrointestinal tract. Zinc salts are the first line therapy in asymptomatic patients and in pregnancy (Roberts 2008).

Wilson's disease in Croatia

Croatian authors have recently published a study of the genetic analysis of Croatian patients with WD (Ljubić et al. 2016). In brief, DNA was extracted from peripheral leukocytes. Patients were first screened for the most frequent mutation in populations of European origin, p.His1069Gln. Heterozygous patients or patients without the p.His1069Gln were additionally analyzed by sequencing 21 exons of the ATP7B gene. The median age at the onset of symptoms was 20, while the median age at diagnosis was 24, suggesting a delay in diagnosis of WD. As predicted, the most common mutation in Croatia was p.His1069Gln. Interestingly, out of the 18 different mutations detected, the authors identified three novel, previously undetected mutations in the ATP7B gene present in the Croatian population.

CASE REPORTS

In the following section, three case reports are shown, with the aim to illustrate and accentuate the role of a multidisciplinary approach to diagnostics and treatment of Wilson's disease.

Case 1

35-year-old woman presented to the extrapyramidal outpatient unit due to tremor. On neurological examination, severe bilateral postural hand tremor was noted. As a part of the routine workup for a young patient presenting with tremor, copper metabolism parameters were analyzed and revealed high probability of WD. Genetic analysis confirmed the diagnosis and d-penicillamine was introduced.

The patient had a non-identical twin sister, who was subjectively asymptomatic. On examination, a mild tremor was detected. Genetic analysis revealed the sister to also be positive for WD. Given the mild symptoms, the sister was started on zinc salts.

This case illustrates the importance of genetic testing of asymptomatic relatives with the aim of early introduction of therapy which can halt the disease progression.

Case 2

A 37-year-old man was playing football suffered head trauma while playing football. He was admitted to the emergency unit and examined by a surgeon and an ophthalmologist. The ophthalmologist detected dark rings encircling the iris of the eye, and correctly identified these as Kayser-Fleischer rings. The patient was promptly referred to the gastroenterology and neurology departments for further diagnostic workup.

Initial evaluation revealed a decrease in the serum copper concentration, a decrease in the serum ceruloplasmin level, and an increase in the copper concentration in the 24-hours urine. On neurological examination, a fine bilateral postural hand tremor was described. Family history revealed that the patient's mother suffered from liver cirrhosis. Following genetic testing, the patient was diagnosed with WD and started on d-penicillamine. With a further in-depth analysis of the patient history, it was discovered that the patient exhibited psychiatric symptoms in the form of a delusional disorder at the age of 25 (12 year prior to WD diagnosis), for which he was treated with fluphenazine and biperiden. We speculate this was the initial presentation of then unrecognized WD.

Genetic testing was recommended for the patient's sister, daughter and nephew (his sister's son). A heterozygous mutation was detected in the sister and the daughter, while the 5-year-old nephew tested positive for a homozygous mutation. The nephew was referred to a pediatric hepatologist who initiated treatment. This 5-year-old patient was the youngest asymptomatic person to be diagnosed with WD since the formation of the Multidisciplinary team for WD of the University Hospital Centre Zagreb. Such an incidental diagnosis significantly improved his prognosis and future quality of life.

This case shows the importance of a multidisciplinary approach in diagnosing WD, as well as the importance of genetic testing in relatives of patients with WD.

Case 3

A 28-year-old pregnant woman presented with a first episode of psychosis at 32 weeks of gestation. The patient showed akinetic mutism and sever aphagia, which prompted the insertion of a nasogastric tube. She was admitted to a psychiatric hospital as a case of psychosis in pregnancy. Due to an atypical clinical presentation, however, a neurologist was consulted, and the subsequent diagnostic workup revealed WD.

The patient was referred to the Multidisciplinary team for WD of the University Hospital Centre Zagreb. Considering that d-penicillamine has shown teratogenic effects in animal studies, zinc salts are the first-line therapy of WD in pregnancy. Therefore, the patients received zinc salts as the initial treatment, with incomplete resolution of symptoms. The birth was induced via cesarean delivery at 34 weeks of gestation. Male infant exhibited low birth weight and mild motor impairment which was later resolved with physical therapy. Following the birth, the patient was started on d-penicillamine and recovered fully.

This case illustrates the importance of a high degree of suspicion in diagnosing WD, especially in the case of atypical presentation of psychiatric disorders.

CONCLUSION

WD is still very often unrecognized, and consequently left untreated. Without timely treatment, fatal outcome is unfortunately not rare. Early diagnosis and therapy can prevent the organ damage and halt the progression of disease, thereby resulting in the prolonged overall survival and a significant improvement of quality of life. In addition to a high degree of clinical suspicion in undiagnosed individuals presenting with atypical symptoms, it is important to perform genetic testing in the relatives of the patients. A young person presenting with atypical psychiatric symptoms is especially suspicious and should undergo a diagnostic workup for WD. Furthermore, it is important to continuously educate medical doctors from different disciplines on the topic and to form multidisciplinary teams in national referral centers, with the aim to identify WD patients as early as possible, ideally already in the asymptomatic stage, and thereby to improve overall survival and quality of life of these patients (Kalauz et al. 2010).

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