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Case Report

A case of Wilson disease with the ATP7B mutation presenting movement disorders

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ABSTRACT

Background: Wilson disease is an autosomal recessive condition manifested when abnormal copper accumulation in the body particularly involving many organs such as brain, liver, and cornea. Diagnosis is challenging with the completion of tests in blood and urine, a liver biopsy, and clinical evaluation. ATP7B mutations with more than 600 identified variants are the genetic disorders of Wilson disease.

Case Description: We report an adolescent case with no family history presented with extrapyramidal dyskinesia. Other symptoms include liver cirrhosis and Kayser–Fleischer ring. The typical presentation of blood test results and brain MRI images helps us to suspect Wilson disease in this case. We confirmed to have a p.R778L form and a p.S105X form in ATP7B mutations. After combining therapy with trihexyphenidyl and trientine, the patient's medical condition was stable and no side effects were observed.

Conclusion: Screening for the diagnosis of Wilson disease is essential in helping patients benefit from early treatment and genetic counseling.

Keywords: ATP7B, Movement disorders, p.R778L, p.S105X, Wilson disease

INTRODUCTION

Wilson disease is an autosomal recessive condition occasionally caused by the ATP7B mutation, which results in the collection of superfluous copper in the liver, brain, cornea, and other organs. The prevalence of this disease is approximately 1/30,000 persons, both males and females are affected in the same way.[8] The frequent age of presentation is 4–40 years of age, but some cases in 3 years old and 70s have been described.[3] Nearly half of patients will have neurological manifestations, for example, tremors, disorders of language, abnormal movements, personality changes, autonomic nervous system, and psychotic disorders. While early diagnosis based on biochemical and clinical symptoms, the supporting standards for Wilson disease diagnosis are sequencing of ATP7B or molecular scanning for known genetic mutations. In clinical practice, detecting ATP7B gene mutation helps avoid severe progression, detect healthy carriers, and make prenatal diagnosis to reduce the incidence. Treatment of Wilson disease mainly restores the balance of copper in the body with a limited copper diet, zinc intake to decrease copper absorption, combine with D-penicillamine, trientine, and complex dimercaprol. In addition,

supplementing trihexyphenidyl and levodopa play a role in improving symptoms.

CASE REPORT

Clinical features

A 17-year-old girl presented with hand tremors at rest and worsened by stress. There was no family history of hereditary disease and metabolic disorders. Tracing back her medical history, it was found that the onset of the tremors in both hands had occurred for 6 months. The patient's handwriting was atrocious and illegible. Her daily activities and learning became more problematic and difficult. Clinical examination revealed the features of extrapyramidal symptoms included tremors with a frequency of about 4–6 Hz, mainly in the upper extremities, slow and scribbled writing. Furthermore, there were no signs of pyramidal tract lesions, ophthalmoplegia or hallucinations, and behavior disorders. Although the patient had malaise, she could still manage to walk independently. The clinical features of slowly progressing extrapyramidal symptoms in a young patient suspected that a metabolic disorder or intoxication affecting central gray nuclei.

With respect to laboratory findings, that diagnosis was supported. The elevated 24 h ceruloplasmin level (224 μg/day [<40 μg/day]) and the decreased serum ceruloplasmin level (3 mg/dL [20–40 mg/dL]) were identified. Complete blood count biochemistry and urinary routine were within normal limits. Brain MRI showed high signal intensities of both basal ganglia, head of caudate nucleus in T2W, fluid-attenuated inversion recovery, and diffuse-weighted imaging [Figure 1]. Abdominal ultrasound revealed morphological changes in the liver with regenerative nodules, consistent with cirrhotic image. Serum transaminase (AST and ALT) and prothrombin time were normal. A slit-lamp examination revealed a typical Kayser–Fleischer ring. These results provided a high suspicion of Wilson disease. Therefore, the patient has performed sequencing of 21 exons on the ATP7B gene and detected two pathogenic mutations c.2333G>T (p.R778L) and c.314C>A (p.S105X).

Treatment results

The patient has received trihexyphenidyl (10 mg/day) and trientine (1.5 g/day) and had no significant side effects. After about 6 months of treatment, the movement function has partially improved, her writing and movement have been more flexible.

DISCUSSION

Wilson disease has been described since 1912 as a copper metabolic disorder, with neurological manifestations, cirrhosis and eye symptoms caused by superfluous copper collection in many organs.[9] This protein is located in the trans-Golgi network of the brain and liver. Thus, the copper absorption in the small intestine and transport to the liver was not affected in the disorder, however, the synthesis of ceruloplasmin from copper and excretion of surplus copper through the density was decreased. The result of this process is accumulated gradually of copper and injures many organs, including the brain.[5]

The initial symptoms of the disease in approximately 50% of patients are neurologic. Basal ganglia-based movement disorders are features of the disease. Asymmetric tremor is the first neurologic characteristic in approximately 50% of individuals and may be proximal or distal and manifest at rest or with movement. Other presentations include dysarthria, dysphasia, ataxia, and Parkinsonian-like extrapyramidal signs. In children, early signs are fine motor disorders as atrocious and illegible handwriting. Later, patients present with dystonia, spastic quadriplegia, and possible seizures. Clinical examination usually reveals generalized extrapyramidal hypertonia. Mood disorders are common, but depression and behavioral disturbances can occur. Kayser–Fleisher rings are the result of the deposition of copper in the descemet membrane of the cornea. These findings with the rings are usually enough for diagnosis but the most accurate test for an alternative diagnosis is a liver biopsy.

About 95% of Wilson patients have serum ceruloplasmin below 20 mg/dl (normal range 20–40 mg/dl). Meanwhile, increasing the urine ceruloplasmin over 100 μg/24 h (normal range <40 μg/24 h) is valid for screening and a diagnostic criterion for determining the disease. Wilson disease should be suspected if symptoms persist with the disease are present or if a proportionate has been found to determine the disease. Most had lightly abnormal liver function tests and increased aspartate transaminase, alanine transaminase, and bilirubin levels. If damaging the liver significantly, the prothrombin time is prolonged since clotting factors are not produced enough. If neurological symptoms are present, brain MRI may show hyperintensities in the basal ganglia in the T2 sequence.

The first established diagnosis criteria were Sternlieb (1978), then Ferenci (2003) added genetic analysis factors for early diagnosis.[7] The most used method of gene analysis ATP7B mutations is sequence 21 exons. So far, there were more than 600 mutations in ATP7B genes that have been published in the gene database, with single-nucleotide missense and nonsense mutations being popular, followed by insertions/deletions and splice site mutations.[6] The most common mutation in North America and Europe is the missense mutation p.H1069Q, with a population allelic frequency of 10–40% (30–70% among Caucasians). The missense p.R778L mutation affects transmembrane

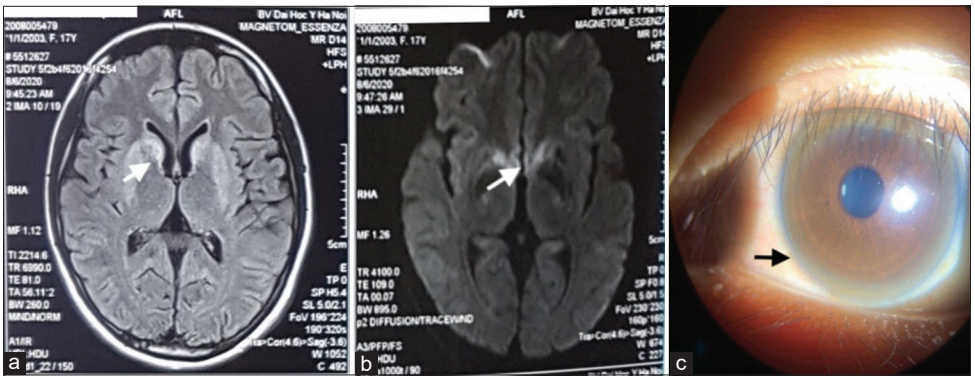

Figure 1: (a and b) High signals of bilateral basal ganglia in fluid-attenuated inversion recovery and diffuse-weighted imaging modality (white arrows). (c) Kayser–Fleischer ring on slit-lamp examination (black arrow).

transport of copper is the most common mutation in East Asian populations.[1,2]

The treatment for Wilson disease consists of copper chelation therapy, reducing the symptoms, and physiotherapy. The mainstay chelation is preferred is trientine because of its side effects. Anticholinergics (trihexyphenidyl), GABA antagonists, and levodopa can be used for muscle rigidity and Parkinsonian features. The benefits of liver transplantation in improving neurological disorders in some patients responding inadequately to basic therapy were demonstrated.[4] Physiotherapy and occupational therapy are chosen as support strategies.

Our patient had an adolescent onset with inconspicuous neurological manifestations, characterized by bilateral extrapyramidal syndrome with hand tremors and writing disorders, cirrhosis, and the typical eye sign. The patient fully met diagnostic criteria with clinical N1 form (nerve combined with liver damage). Confirmed the diagnosis by genetic sequencing of the patient found two heterozygous mutations in the ATP7B gene, which are the stop codon mutation c.314C>A (p.S105X) and the missense mutation c. 2333G>T (p.R778L). In the c.314C>A mutation, the nucleotide sequence C is replaced to A, so the 105th TCG codon encodes serine (S) to replace it into the TAG (X) terminating. In the c.2333G> T mutation, the nucleotide sequence G replaced T resulted in a 778th CGG encoding arginine (R) to convert to leucine (L).

According to the previous studies, patients with the p.S105X mutation often had clinically severe signs caused by the complete loss of copper transport function of ATP7B protein. The more mutant allele appear, the more the copper transportation of the ATP7B protein is affected, which correlates with the earlier and more severe clinical manifestations. Our patient exhibits hepatic neurological coordination with poor clinical symptoms but severe subclinical manifestations with exceptionally low urinary ceruloplasmin concentration, eye damage, and cirrhosis. We recommend analyzing two maker mutation regions in the ATP genes of a patient's family members, especially to determine which member carries the p.S105X mutation (a missense mutation that can cause symptoms even carrying one mutant allele) for early diagnosis and treatment without clinical manifestations.

CONCLUSION

Wilson disease is a rare genetic condition caused by a metabolic disorder that causes copper deposits in many organs. Neurological manifestations are usually inconspicuous, mostly following liver damage. Our clinical case with early onset of juvenile extrapyramidal syndrome suggests screening for liver and eye lesions. In addition to conducting genetic sequencing to identified mutations to provide an important basis for genetic counseling, patients can benefit from early treatment. It is important to keep in mind the genetic etiology in a young patient presenting with extrapyramidal symptoms even with no relevant family history.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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