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CASE REPORT

Usefulness of the Leipzig Score in the Diagnosis of Wilson's Disease - A Diagnostically Challenging Case Report

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Abstract: Wilson's disease (WD) is a genetic disorder of copper metabolism that is inherited as an autosomal recessive (AR) due to mutations in the *ATP7B* gene, which is involved in intracellular copper transport. Approximately 40% to 50% of the patients present with neurological symptoms as their first symptom. The most common neurological symptoms are dysarthria, gait abnormalities, ataxia, dystonia, tremor, parkinsonism, and drooling. This case report aims to present a diagnostically challenging case of WD presenting with neurological symptoms. The 38-year-old male patient was admitted with complaints of imbalance, gait disturbance, weakness in the legs, speech impairment, tremors in the hands, syncope, and drooling. The MRI primarily revealed FLAIR, T1, and T hyperintensities in the bilateral globus pallidus of the basal ganglias. At first, the patient was evaluated according to the Leipzig scoring and received one point from the serum ceruloplasmin level and two points from the neurological symptoms and was evaluated as "possible WD" with a total of three points. 24-hour urine copper was collected during and after the D-Penicillamine challenge. After the test, there was an increase of more than 5 times the upper limit. The Leipzig score was recalculated, and a diagnosis of WD was made with a score of five. Even cases without important diagnostic findings such as Kayser-Fleischer ring or high 24-hour urine copper should be evaluated according to the Leipzig score. It is vital to distinguish WD in patients with young-onset movement disorder and neurological symptoms.

Keywords: hepatolenticular degeneration, magnetic resonance imaging, hepato-neurologic, Wilson's disease, neuroradiology

Introduction

Wilson's disease (WD) was first reported in 1912 by Samuel Alexander Kinnier Wilson as a fatal neurological disorder that progresses over time and is associated with liver cirrhosis and the Kayser-Fleischer corneal ring.[1,2] This disease results in malfunction of copper metabolism that is inherited as an autosomal recessive due to mutations in the ATP7B gene, which encodes the protein involved in intracellular copper transport. Symptoms often begin to appear between the ages of 5 and 35.[3] Impairment of copper excretion through bile tract to copper accumulation in various organs, especially the liver, brain, and cornea.[4] Approximately 40% to 50% of the patients present with neurological symptoms as their first symptom.[5] About 18% to 73% of Wilson's patients have neurological symptoms, including dysarthria, gait abnormalities, ataxia, dystonia, tremor, parkinsonism, and drooling.[6] Wilson's disease should be considered in patients with movement disorders that onset at a young age. While the age of onset can vary, it is generally considered to be before the age of 40.

The Leipzig score is a diagnostic tool used to help diagnose Wilson's disease. It involves assessing clinical, laboratory, and imaging findings to improve diagnostic accuracy. A total score is calculated, and a higher score suggests a higher likelihood of Wilson's disease. A score of 4 or more strongly indicates the diagnosis.[7]

It is vital to distinguish WD in patients with young-onset movement disorder and neurological symptoms. This case report aims to present a diagnostically challenging case of WD presenting with neurological symptoms.

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Case Presentation

A 38-year-old male patient was admitted to our facility with complaints of imbalance, gait disturbance, weakness in the legs, speech impairment, tremors in the hands, syncope, and drooling. According to the anamnesis, his complaints started 8 years ago with syncope, suspected seizure, slurred speech, double vision, dizziness, and numbness in various parts of the body. He was initially evaluated as having epilepsy and anti-epileptic medication was started, but he did not benefit from the medication and his complaints continued to increase. Shortly before applying to our facility, he started to experience excessive tremor in the hands and head, inability to stand up and walk, falling down, and inability to do daily routine.

In the patient's medical history, he was using carbamazepine 400 mg BID and levetiracetam 500 mg BID with a diagnosis of epilepsy. In neurological examination, recent memory was impaired, and there was a weakening of judgment and abstract thought. Speech was dysarthric and hypophonic. Muscle strength was 4/5 in the bilateral proximal and distal lower extremities. Spontaneous myoclonic jerks, action and postural tremor, and flapping tremor were detected in the upper and lower extremities. He had dysmetria and dysdiadochokinesis. He was standing with assistance. Deep tendon reflexes were hyperactive. He had bradykinesia, masked face, postural instability, and drooling.

In the MRI, FLAIR, T1, and T2 hyperintensities were observed predominantly in the globus pallidus, at the bilateral basal ganglias (see Figure 1). The laboratory investigations revealed the following: 24-hour urine copper: 13.47 µg/24h (3–35), serum ceruloplasmin: 14.3 mg/dL (20–60), serum copper: 274.9 µg/L (800–1550) and ammonia in arterial blood gas 193.2 µmol/L (16–60). Other liver function tests were normal. Kayser-Fleischer ring was not observed in ophthalmology examinations. At this point, the patient was evaluated according to the Leipzig scoring and received one point

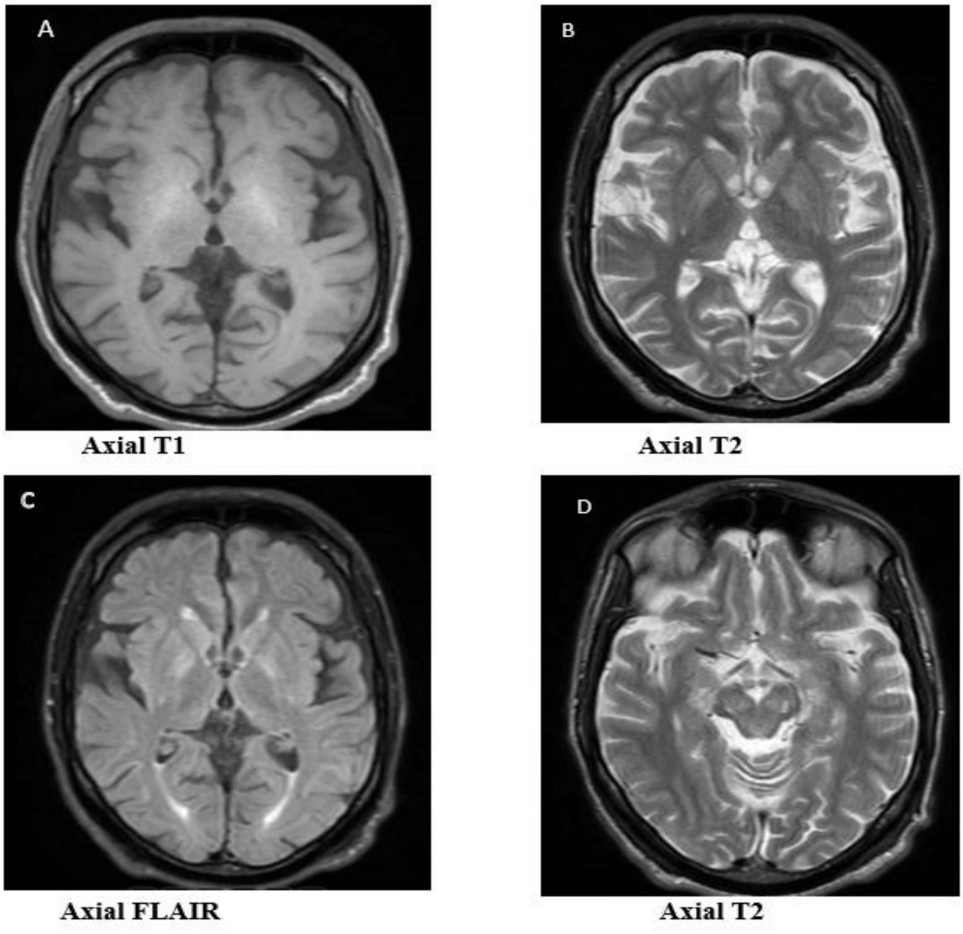

Figure 1 (**A-D**): in the FLAİR, T1 and T2, hyperintensities were observed predominantly in the in the globus pallidus, at the bilateral basal ganglia. Additionally, there were hyperintense lesions in the mesencephalon and pons.

from the serum ceruloplasmin level and two points from the neurological symptoms and was evaluated as "possible WD" with a total of three points.

According to the Leipzig scoring, D-penicillamine challenge test was performed, and *ATP7B* gene analysis was sent. The *ATP7B* gene analysis was negative. 24-hour urine copper was collected during and after the D-penicillamine challenge. After the test, the amount of 24-hour urine copper was increased to 777.6 µg/24h and there was an increase of more than 5 times the upper limit (3–35). The Leipzig score was recalculated, and a diagnosis of WD was made with a score of five. The patient was started on Trientine 250 mg 2*500 (1000 mg/day) chelation therapy and Zinc 50 mg BID 2*150 (300 mg/day) supportive therapy. Low copper diet was started.

Discussion

Patients with WD often have low blood ceruloplasmin levels, low blood copper levels, abnormal ALT and AST levels, and high 24-hour urine copper levels. However, all tests may be normal as well.[8] Most sensitive single screening test for the diagnosis is 24-hour urine copper levels.[9] Initially, serum copper and ceruloplasmin were low but 24-hour urine copper was normal in our case.

The clinical presentation of WD is very diverse, therefore diagnosis can be very challenging. Leipzig criteria was adopted in 2003 in order to overcome diagnostic difficulties and develop a common perspective. This scoring system includes several clinical signs (Kayser-Fleischer rings, neurologic symptoms), liver biopsy (total liver copper level), and laboratory features (copper in serum, urine, liver; serum ceruloplasmin; hemolytic anemia; genetic testing). If the total score is 2 or less, WD diagnosis is unlikely, 3 is considered as diagnosis possible and 4 or above are considered as diagnosis established.[10] After the first evaluation according to the Leipzig score, the case was evaluated as possible WD with total score 3. The *ATP7B* genetic mutation analysis and D-penicillamine challenge were performed to make the diagnosis. Liver biopsy was not considered because it is an invasive and risky procedure. After the tests, the amount of 24-hour urine copper was increased more than 5 times and the Leipzig score became 5 in total. Hence, the diagnosis of Wilson's disease was established.

Kayser-Fleischer rings are detected in 50 to 60% of the patients with hepatic form Wilson's disease. In patients with Wilson's disease with neurologic manifestations, the percentage of finding Kayser-Fleischer ring is up to 98%.[8] Kayser-Fleischer rings were not found in repeated examinations in previous centers and in our center.

While the diagnosis of Wilson disease is typically based on genetic testing, it is possible to make a diagnosis in the absence of identifiable mutations. This is especially true in cases where the clinical presentation is highly suggestive of Wilson disease and other potential causes have been ruled out. The Leipzig score, family history, copper metabolism tests, and response to treatment can all be helpful in supporting a diagnosis of Wilson disease.[11] The Leipzig score is a diagnostic tool used to assess the likelihood of Wilson disease based on clinical features. A high Leipzig score can increase the likelihood of Wilson disease even in the absence of a confirmed genetic mutation.[7]

The most common pathological MRI findings among patients with WD are the occurrence of symmetric hyperintensities in T2-weighted image in the globus pallidus, putamen, mesencephalon, and pons. Lesions are most commonly found in the putamen (45–85%). According to the literature, symmetric hyperintensities in T1-weighted image in the striatum can be detected in association with hepatolenticular degeneration.[12] Hyperintensities in T2 and T1-weighted images were compatible with the literature.

Conclusion

Wilson's disease should be considered especially in movement disorders that begin at a young age. Even cases without important diagnostic findings such as Kayser-Fleischer ring or high 24-hour urine copper should be evaluated according to the Leipzig score. In possible cases, further investigations such as D-penicillamine challenge test, liver biopsy, or *ATP7B* gene analysis should be performed.

Ethical Approval

Institutional approval was not required to publish the case details.

Consent for Publication

Written informed consent was obtained from the patient to have the case details and any accompanying images published. The patient's anonymity was protected.

Author Contributions

All authors made a significant contribution to the work reported whether that is in the conception, drafting, revising, or critically reviewing the case; gave final approval of the version to be published; have agreed on the journal to which the case report has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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