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WisdomGale

CASE REPORT

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Neurologic Wilson's disease: A case report

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ABSTRACT

Wilson's disease (WD) is a rare autosomal recessive genetic disorder characterized by an abnormal accumulation of copper, particularly in the liver, brain and eyes. The disease results from mutations in the ATP7B gene on chromosome 13, which encodes a copper transport protein essential for copper excretion. We present a case of WD in a 21-year-old female patient with significant neurological involvement. Initial brain computed tomography and magnetic resonance imaging revealed bilateral and symmetrical capsulolenticular hypodensities and involvement of the basal ganglia and brainstem, respectively. The diagnosis was confirmed by biochemical analysis of copper metabolism. Early detection and copper chelation therapy are crucial to prevent irreversible neurological and liver damage. Neuroimaging plays an essential role in assessing the extent of brain damage and monitoring treatment efficacy.

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Introduction

Wilson's disease (WD), or hepatolenticular degeneration, is a rare genetic disorder transmitted in an autosomal recessive manner. It is marked by the accumulation of copper in tissues, primarily in the liver, brain, and eyes, due to mutations in the ATP7B gene located on chromosome 13. This gene encodes a copper-transporting ATPase necessary for copper excretion in bile. When this ATPase malfunctions, copper accumulates toxically in the liver before spreading to other organs through systemic circulation [1–3]. Common clinical symptoms include hepatic (hepatomegaly and jaundice), neurological (tremors, dystonia, dysarthria, and extrapyramidal signs), psychiatric signs (anxiety and depression), and ophthalmological findings include Kayser-Fleischer rings, which are deposits of copper in the cornea and indicative of systemic copper overload [4]. In this article, we describe a case of neurological WD in a 21-year-old woman, diagnosed primarily based on radiological findings and her clinical presentation.

Case Report

The patient is a 21-year-old woman from a consanguineous first-degree marriage, and she is the second of three siblings. Her medical history includes an episode of jaundice accompanied by bilious vomiting and swallowing difficulties, which necessitated a feeding gastrostomy. At age 20, she was admitted to the neurology department due to the onset of abnormal movements, which progressively worsened over the course of a year, leading to dysarthria, generalized dystonia, and postural tremors, ultimately resulting in a total loss of autonomy (the patient became unable to feed herself).

Upon clinical examination, the patient was found to be conscious and reactive, with stable hemodynamic and respiratory status. Neurologically, she exhibited anarthria, significant generalized muscle atrophy, generalized dystonia manifesting as a sardonic smile, and both resting and action tremors in the upper limbs, along with signs of extrapyramidal syndrome. Non-neurological findings included hepatosplenomegaly. An ophthalmological evaluation revealed the presence of bilateral Kayser-Fleischer rings (Fig. 1).

Genetic testing was performed, revealing mutations in the ATP7B gene, confirming a diagnosis of WD. Laboratory tests indicated disturbed copper metabolism, with serum copper levels at 0.7 mg/l and ceruloplasmin reduced to 0.06 g/l. Thrombocytopenia was noted at 90,000/mm^3,

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Figure 1. Kayser-Fleischer ring reflecting copper overload in the Descemet membrane.

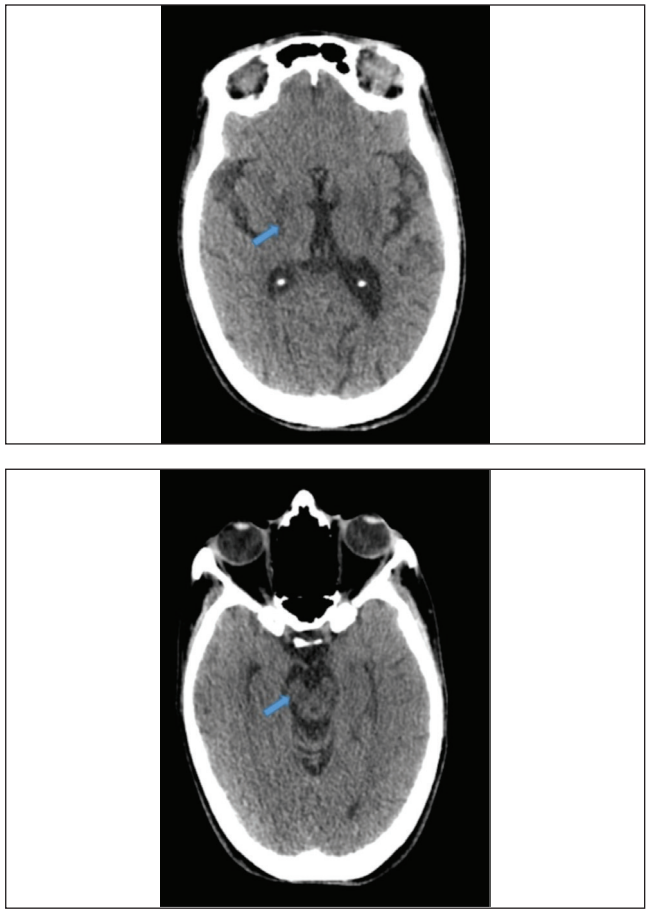


Figure 2. Axial brain CT scan showing bilateral and symmetrical hypodensities of the lenticular nuclei and cerebral peduncles (arrows).

hematocrit was at 2%, and prothrombin levels were low at 32%.

Additionally, urinary copper excretion was measured over a 24-hour period, revealing elevated levels of greater than 100 µg/24 hour, consistent with WD.

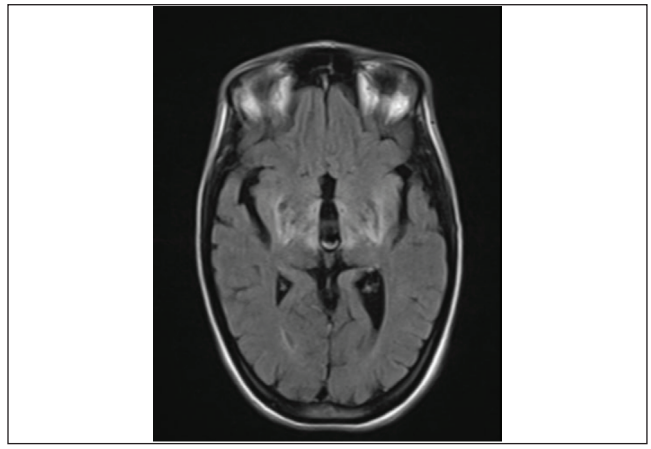


Figure 3. Axial brain MRI in flair sequence: bilateral and symmetrical hypointensity of the lenticular nuclei, with T2 and flair hyperintensity of both thalami and around the lenticular involvement.

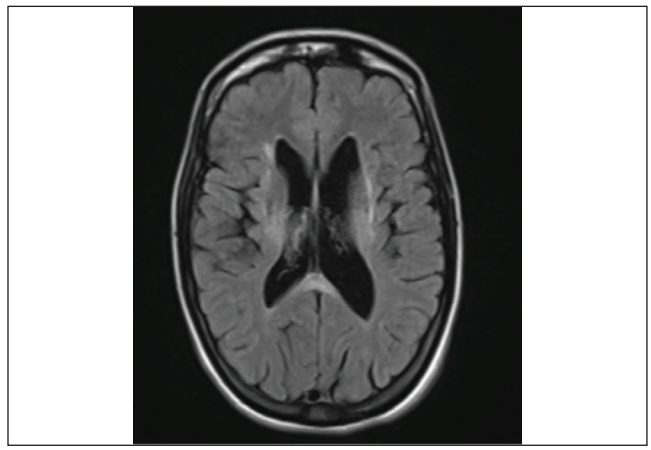


Figure 4. Axial brain MRI in flair sequence: hyperintensity at the level of the splenium of the corpus callosum.

The Leipzig score was calculated based on clinical and laboratory findings, yielding a total score of 6 points, which led to the diagnosis of WD.

Neuroimaging was performed, with a cerebral computed tomography (CT) scan showing bilateral and symmetrical intermediate density-hypodensities in the capsulolenticular region and mesencephalon (Fig. 2). An magnetic resonance imaging (MRI) demonstrated pathognomonic signs of WD: bilateral and symmetrical hypointensity in the lenticular nuclei on T1, T2, and T2*-weighted sequences, along with T2 and Flair hyperintensity in the thalami (Fig. 3), splenium of the corpus callosum (Fig. 4), and brainstem, particularly in the mesencephalon, with preservation of the red nuclei, producing a «giant panda face» appearance (Fig. 5).

Treatment was initiated as recommended by AASLD and EASL guidelines for copper chelation

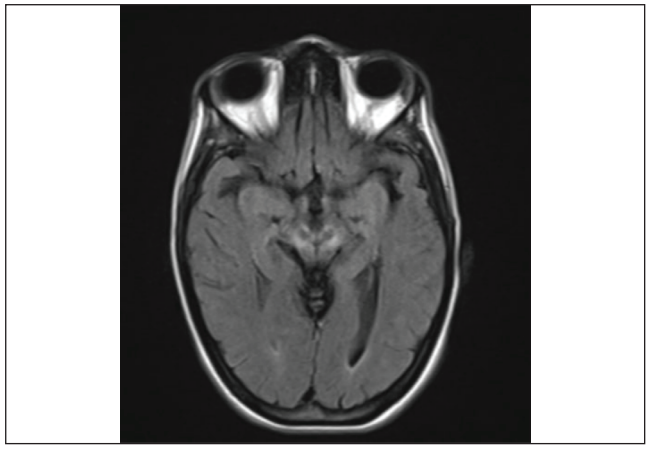


Figure 5. Axial brain MRI in T2 flair sequence showing the «giant panda face» appearance in the midbrain.

with D-penicillamine (15 mg/kg/day) as a copper chelator, to reduce copper accumulation, and zinc therapy (50 mg/day) as it helps reduce copper absorption from the gastrointestinal tract. Additionally, the patient was placed on a low-copper diet to minimize dietary copper intake, and she was prescribed Rivotril and Artane to manage neurological symptoms.

Despite some clinical improvement, the Kayser-Fleischer rings persisted, indicating continued copper deposition.

Discussion

WD is a rare autosomal recessive genetic disorder primarily affecting children, adolescents, and young adults. Most cases begin between the ages of 5 and 35, with an average onset of around 17 years [1]. The diagnosis of WD should be suspected in neurology for any extrapyramidal syndrome occurring before age 50, as demonstrated in our case. There is no gender predominance [2].

The presence of first-degree consanguinity is common in our country, strongly suggesting its role in WD, which is an autosomal recessive disorder, as noted in our case. However, sporadic cases without a family history are also well-documented. In our case, the family history of consanguinity provided an important diagnostic clue [3].

Genetic studies have shown that the responsible gene is located on chromosome 13, position 914 of the long arm (locus 13q14.3), coding for the ATP7B protein, an ATPase responsible for copper transport in hepatocytes and its elimination in bile. The ATP7B protein is either defective or absent in WD, preventing copper from reaching the bile canaliculi or the site of ceruloplasmin synthesis. This leads to reduced biliary copper excretion and a significant decrease in ceruloplasmin due to the lack of copper incorporation, resulting in positive copper balance [2,3].

Neurological involvement occurs in about 40%–50% of WD patients, developing insidiously and progressively worsening. Less commonly, the disease shows phases of transient improvement. Neurological symptoms are often the initial manifestations (73%) [4]. These symptoms are motor-related, indicating basal ganglia and brainstem involvement. The most frequent manifestations include tremors (80%), extrapyramidal dysarthria (56%) with hypersalivation, and a sardonic grimace, as seen in our patient. The neurological presentation may also include Parkinsonian syndrome (45%–55%) [1,2], pseudobulbar syndrome (20%) with dysphagia and emotional lability, gait disorders (30%), tone disturbances (40%), and apraxia with specific clinical forms [5,6].

Ophthalmological manifestations are dominated by the presence of Kayser-Fleischer rings, which are rare before age seven and reflect copper overload in Descemet's membrane. These rings, visible on slit-lamp examination, appear green, brown, or golden. They are almost constant in cases with neuropsychiatric involvement, as seen bilaterally in our patient [5–7].

Other manifestations of WD can include hepatic involvement, hematological (Coombs-negative hemolytic anemia), endocrine (amenorrhea, recurrent miscarriages, hyperparathyroidism, glucose intolerance), renal, cardiac (arrhythmias), osteoarticular, and skin involvement [5–7].

Biological investigation of copper metabolism includes measuring ceruloplasmin, serum copper, urinary copper over 24 hours, and hepatic copper after biopsy. Low ceruloplasmin levels (<20 mg/dl) strongly suggest WD. Total copper is decreased proportionally to ceruloplasmin levels, while free serum copper is increased or normal [8]. In symptomatic patients, urinary copper levels are consistently elevated (>100 µg/24 hour) [8]. This characteristic biological triad confirms the diagnosis and initiates treatment. In ambiguous cases, hepatic copper measurement from a biopsy fragment is used.

MRI plays a crucial role in assessing the severity of brain lesions. It provides information on lesion distribution in brain tissues, the pathologic and anatomical correlates of clinical symptoms, follow-up, and treatment response in WD [4–6].

In a normal brain, copper distribution overlaps with dopaminergic neurons in the basal ganglia, explaining the predominant extrapyramidal symptoms. Signal abnormalities in the basal ganglia are secondary to necrosis, cystic changes, gliosis (T2 hyperintensity), copper or heavy metal (iron and manganese) accumulation (T2 hypointensity), or porto-systemic shunting linked to post-cirrhotic portal hypertension (T1 hyperintensity).

Supratentorial and infratentorial white matter involvement is common (gliosis, demyelination, spongiform degeneration, and neuronal loss). The dentorubrothalamic, pontocerebellar, and corticospinal tracts can be affected [4,5].

CT is less sensitive than MRI, showing infra- and/or supratentorial atrophy and basal ganglia hypodensity [5].

MRI abnormalities evolve with the disease, and morphological severity correlates with neurological symptoms [5–9]. MRI abnormalities have been described in 3/4 of hepatic form patients without neurological symptoms [4–6].

Atrophy primarily affects the supratentorial region but can also involve the brainstem and, less often, the cerebellum. Basal ganglia involvement is the most frequent focal lesion [4,5].

- Diffuse and symmetrical T2 hyperintensity in the putamen.
- T2 hyperintensity of the claustrum («outer rim»), a specific but insensitive sign.
- T2 hypointensity of the globus pallidus, rarely T1 hyperintensity.
- Bilateral and symmetrical caudate signal abnormalities.
- Thalamic signal abnormalities mainly affect the lateral nuclei.

Brainstem involvement is common:

- The midbrain is the most affected area. Signal abnormalities are more often focal than diffuse, affecting the tectum or periaqueductal region. The pathognomonic but insensitive «giant panda face» sign consists of high signal intensity in the midbrain, sparing the red nuclei, lateral parts of the pars reticulata of the substantia nigra, and parts of the superior colliculus [9].
- Pontine signal abnormalities, less frequent, may mimic central pontine myelinolysis; bulbar involvement is rare.

Supratentorial white matter signal abnormalities are observed in 1/4 of patients, predominantly in the frontal region, often asymmetrical.

- Diffusion characteristics vary with lesion age: restriction in the putamen in the initial, presymptomatic phase, and subsequent increase [5–9].

Spectroscopy shows [5]:

- Decreased NAA/Cr ratio in the parieto-occipital cortex, frontal white matter, and basal ganglia due to neuronal loss.
- Increased myo-inositol/Cr ratio in the basal ganglia due to gliosis and copper and/or iron deposits.

Untreated, WD is always fatal. Treatment involves administering a copper chelating agent, such as D-Penicillamine, achieving survival rates close to those of the general population. According to the AASLD and EASL guidelines, D-Penicillamine is administered at a starting dose of 250 mg/day, gradually increased to 1,000–1,500 mg/day in divided doses. Most patients experience biological and clinical improvements within 3 to 6 months of treatment initiation. However, D-Penicillamine can cause side effects, including an initial worsening of neurological symptoms due to rapid copper mobilization and preferential redistribution to the brain. Trientine is an alternative chelating agent, typically prescribed at 750–1,250 mg/day in divided doses for those intolerant to D-Penicillamine [4,5]. Zinc, administered at a dose of 150 mg/day in divided doses (50 mg three times daily), is also recommended, particularly for presymptomatic patients or as maintenance therapy after initial chelation, as it reduces copper absorption by inhibiting its uptake in the intestines [8]. In cases of severe hepatic involvement, acute liver failure, or severe neurological or neuropsychiatric signs unresponsive to medical treatment, liver transplantation is indicated, as it offers a curative approach for both hepatic and neurological manifestations of WD [4,5].

The treatment of WD also involves the symptomatic management of neurological disorders. While anti-copper medications reduce the accumulation of copper in the body, specific treatments are often necessary to alleviate neurological symptoms such as tremors, dystonia, and parkinsonism. For example, trihexyphenidyl can be used for dystonia, and clonazepam for tremors. These treatments

improve the patient's quality of life but do not replace anti-copper therapy [7]. A multidisciplinary approach is often required to ensure comprehensive management of the disease [5].

Recent studies have shown that neurological deterioration in WD patients undergoing treatment is less common than previously thought [9]. Early recognition and adherence to anti-copper therapy are key factors in preventing progression. However, initial worsening of neurological symptoms can occur in up to 20% of patients treated with D-penicillamine due to rapid copper mobilization. In such cases, close monitoring and potential adjustment of therapy are necessary. As of 2023, more frequent occurrences of stable or improved neurological symptoms have been reported with consistent long-term therapy [9,10].

In this case, while the patient experienced neurological improvement, the persistence of Kayser-Fleischer rings suggests the need for continued treatment and long-term follow-up. Liver transplantation remains a consideration if neurological or hepatic function worsens despite medical intervention [10].

Conclusion

WD, though rare, is a critical diagnosis to consider in young patients presenting with unexplained neurological and hepatic symptoms. Early recognition, confirmed through biochemical and radiological testing, is essential for initiating appropriate treatment. This case highlights the significance of MRI findings, clinical symptoms, and biochemical markers in diagnosing neuro-Wilson. Timely initiation of anti-copper therapy can improve outcomes and prevent irreversible damage, emphasizing the importance of awareness and early intervention in this treatable condition.

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