Pearls & Oy-sters: Challenges and Controversies in Wilson Disease

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Abstract

Wilson disease (WD) is a genetic disorder of copper metabolism caused by variants in the *ATP7B* gene, which are inherited in an autosomal recessive pattern. Despite all the advances made on pathogenesis, cellular biology, and genetics, to date, WD remains a diagnostic and therapeutic challenge. With this series of cases, we aim to illustrate the main challenges that clinicians may encounter when dealing with patients with WD: the difficulties with clinical diagnosis, the therapeutic management of WD and the indication for advanced therapies, management during pregnancy, and genotype-phenotype correlations.

Pearls

- Wilson disease (WD) is a unique neurodegenerative disease with available disease-modifying therapies, and no patient should be deprived of it.
- The diagnosis of WD should always be considered in any patient with unexplained hepatic, neurologic, or psychiatric dysfunction.
- WD treatment is safe and should be maintained during pregnancy.
- No genotype has been correlated with a particular phenotype.

Oy-sters

- Brain MRI should be used as a supporting diagnostic tool but should never interfere with the clinical diagnosis if the findings are not typical for WD.
- Slow titration and appropriate dosages of chelators should always be tried before considering invasive treatments.

Wilson disease (WD) is a genetic disorder of copper metabolism caused by variants in the *ATP7B* gene, which are inherited in an autosomal recessive pattern. Copper overload primarily in the liver and the brain[1] leads to several clinical presentations, including neurologic symptoms (typically with tremor or dystonia phenotype), acute or chronic liver failure, and/or psychiatric manifestations.[2]

Case 1. Unusual Neuroimaging: The Diagnostic Challenge

A 55-year-old man with Child-Pugh B cirrhosis presented with neurologic symptoms that had worsened over the last 6 months: dysarthria, imbalance, symmetric limb tremor, rigidity, bradykinesia, and hyperreflexia. Brain MRI (Figure 1A) suggested the differential diagnosis of central pontine myelinolysis (CPM) and WD. There was no history of rapidly corrected hyponatremia, malnutrition, or alcohol abuse. Total copper and ceruloplasmin were 515 μg/L (normal values [NVs] 750–1,500) and 8 mg (NV 20–60), respectively, and the 24-hour urine copper level was 301 μg (NV 10–60). Kayser-Fleischer ring (KFR) was

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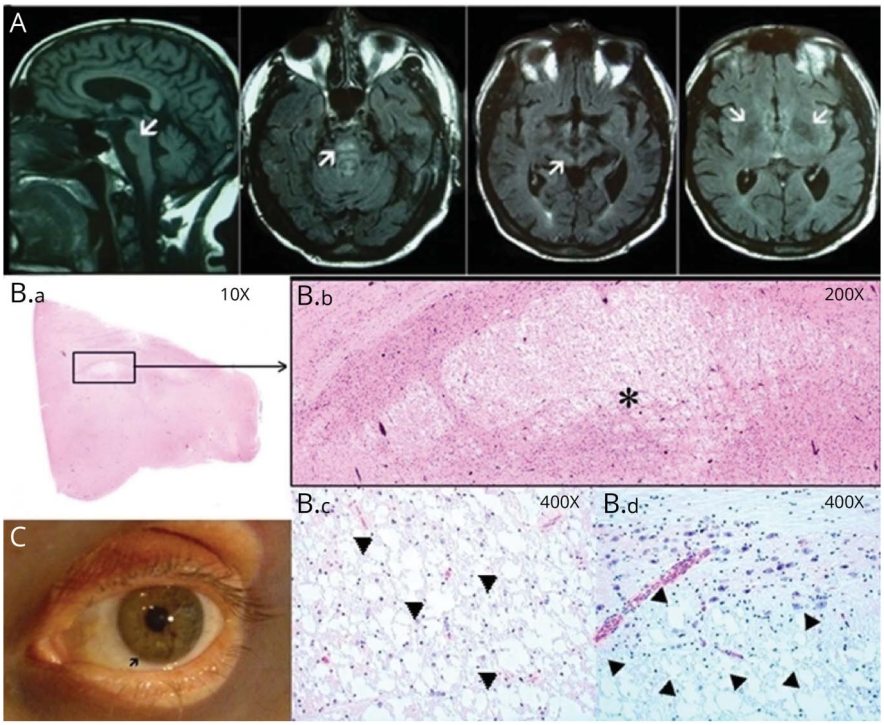
Figure 1 Ophthalmologic, Radiologic, and Pathologic Findings In Our Cases



(A) Brain MRI images from case 1. Pontine hypointensities are observed in T1 sequences and hyperintensities in midbrain, pontine nucleus, tegmentum, and periaqueductal gray matter (arrows in the upper left of the figure) in fluid-attenuated inversion recovery-T2 sequences, suggesting the diagnosis of central pontine myelinolysis. It is also shown that the hyperintensity of the midbrain contrasts with the hypointensity of the red nucleus, the pars reticularis of the substantia nigra, and the aquaductus (arrows), which are relatively spared, resembling the face of a panda. Bilateral lenticular hypointensities can also be seen (arrows in the upper right of the figure). (B) Pathologic findings are shown (hematoxylin and eosin stain), both (B.a) macroscopically and (B.b–B.d) microscopically, showing central pontine vacuolization and loss of glial cells. Both findings are consistent with central pontine myelinolisis. (B.b–B.d) Vacuolization is marked with arrowheads and a star in microscopic samples. (C) Kayser-Fleischer ring is marked with an arrow.

present (Figure 1C). WD was diagnosed, and zinc was started. Unfortunately, he died 8 months later because of neurologic impairment. Necropsy confirmed the diagnosis (Figure 1B).

Case 2. Advanced Therapies: The Therapeutic Challenge

A 44-year-old woman, without a family history, presented at the age of 30 years with abdominal pain, nausea, and vomiting. Diagnostic workup revealed total copper of 8 μg/L, serum ceruloplasmin of 2.8 mg/dL, and 24-hour urine copper of 855 μg/24 h. KFR was present. Genetic testing showed a heterozygous pathogenic variant in the *ATP7B* (NM_000053.4:c.1739del). Neurologic examination was unremarkable. WD was diagnosed according to the Leipzig criteria.[3] Treatment with copper chelators was started. Unfortunately, she had a severe skin allergic reaction with D-penicillamine and severe vomiting with trientine. She tolerated zinc 50 mg thrice a day. Her symptoms remained under control until her forties, when a rapidly progressing postural tremor rendered her unable to use her hands, needing help for all daily activities. Advanced therapies of WD were considered, including both liver transplantation (LT) and deep brain stimulation (DBS). However, a second copper chelation therapy trial was decided before invasive treatments. She was admitted in hospital, and D-penicillamine was slowly titrated up in association with a desensitization therapy based on penicillamine patch, polaramine, and cortisone. She tolerated dosages up to 1,000 mg a day without side effects. Her symptoms markedly improved, recovering the ability to manage daily activities on her own. Advanced therapies will be reconsidered, if needed, in the future.

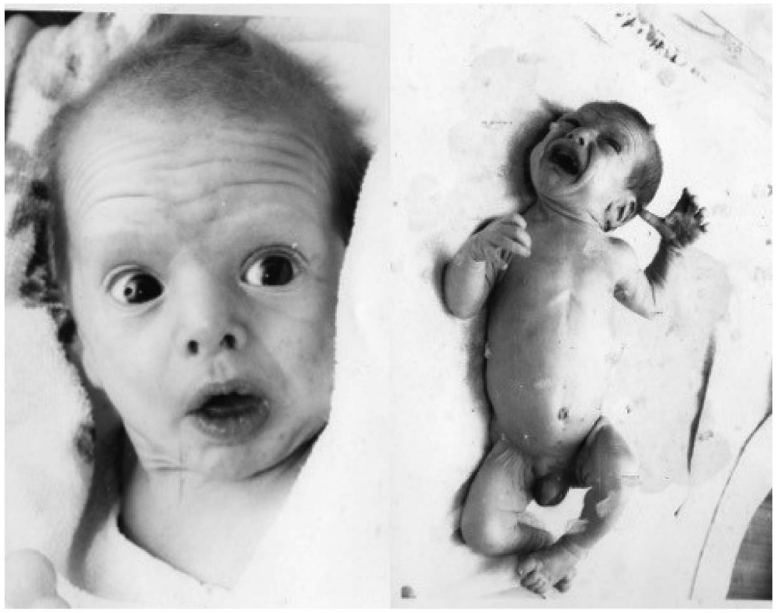
Cases 3 and 4. The Controversy on Phenotype-Genotype Correlations

A sibling pair (72-year-old and 66-year-old women) were diagnosed with WD at the ages of 23 and 21 years, respectively. They both shared the same phenotype, with Child-Pugh A cirrhosis, mild nondisabling postural tremor, mild parkinsonism, and paroxysmal chorea. KFR was present. Genetic testing showed a compound heterozygous variant in the *ATP7B* (NM_000053:c.3295G>A; NM_000053:c.1946+2T>C). For the last 40 years, their disease has remained stable with D-penicillamine 750 mg per day.

Case 5. WD and Pregnancy

A 33-year-old woman presented to our clinic at 16 weeks of gestation. She was diagnosed with WD 16 years earlier. Since then, she was on zinc 50 mg thrice a day. Medication was continued at half dosage throughout pregnancy. She remained asymptomatic. Serum ceruloplasmin, copper levels, and liver

Figure 2 Images of a Baby Boy Born to One of the Sisters From Case 3



Penicillamine-induced cutis laxa syndrome in a baby boy born to a mother on D-penicillamine during pregnancy (case 3). The wrinkled appearance of baby's skin can be seen, which is particularly evident in his forehead, lips, neck, and fold areas, such as underarms and groins.

function were monitored every 3 months. She had a healthy baby at 39 weeks of gestation.

Case 3 became pregnant at the age of 24 years. By then, she was on D-penicillamine 1,500 mg a day. Before WD diagnosis, she had 2 miscarriages. Chelation treatment was maintained during her third pregnancy. The follow-up was unremarkable. A baby boy was delivered at 40 weeks of gestation. The baby was born with a reversible D-penicillamine-induced cutis laxa syndrome (Figure 2). At the age of 4 months, his appearance was normal. He grew up with no further issues.

Discussion

Since its first description in 1912,[4] major advances in the understanding of WD pathogenesis and genetics have occurred. Unfortunately, despite these advances, WD remains a diagnostic and therapeutic challenge. With this case series, we aim to illustrate some of the main challenges that clinicians may encounter when managing patients with WD.

To date, the diagnosis of WD is based on clinical manifestations along with classic abnormal findings. The availability of diagnostic criteria eases the diagnostic process.[3,5] KFR is present in the majority of patients with neurologic dysfunction but might be absent in cases with just hepatic involvement. Brain MRI is also useful, with typical findings being the "panda sign," paramagnetic deposition of basal ganglia, and hyperintensities on T2/hypointensities on T1 involving basal ganglia and brainstem.[6] However, MRI findings might be atypical, and they should never get in the way if there is a high clinical suspicion of WD. Although infrequent, CPM can be seen because of the sensitivity of oligodendrocytes to copper toxicity, with hydropic swelling of myelin sheaths and demyelination being one of the earliest consequences of cerebral copper overload.[6]

Copper chelators and zinc are effective treatments in most patients. Unfortunately, treatment initiation is followed by neurologic deterioration in up to 20%, often leading to treatment discontinuation. Despite better tolerability of zinc, several cases of failure of zinc monotherapy have been reported, which might result from pheno-genotypic differences in the ability of zinc to induce metallothionein based on the *ATP7B* variants.[7] Although LT is the recommended therapy in WD with acute liver failure or end-stage liver cirrhosis, it is not so clear in the case of severe neurologic symptoms. Since 1993, only 50 patients transplanted for pure neurologic/neuropsychiatric indication have been reported.[8] The most recent publication showed a marked improvement in the motor score (Unified WD Rating Scale) in 12 of 18 patients.[8] Despite these results, the indication of LT for neurologic symptoms remains controversial.[9] On the contrary, DBS has shown improvement over the main neurologic symptoms in WD: dystonia, tremor, and parkinsonism,[10] but scarcity of information in the literature makes clinicians reluctant to perform the procedure. Both invasive treatments were considered in case 2. However, because the patient was not on chelators due to intolerance, D-penicillamine was reconsidered successfully. We encourage neurologists to always try slow titration and desensitization to improve tolerability before dismissing chelators. Furthermore, treatment should be started immediately after diagnosis, and it has to be lifelong. This also applies to pregnant women, who need to continue therapy during pregnancy. However, the treatment of choice is still debated. We report 2 therapy regimens: zinc

and D-penicillamine. Zinc pursues a local gastrointestinal effect, reducing the absorption of copper. Zinc itself is absorbed in low amounts, a quality that might make zinc the ideal therapy for WD during pregnancy.[11] However, zinc alone is often insufficient in symptomatic patients, and chelators are required. Side effects of D-penicillamine affecting babies during pregnancy are infrequent. However, chelators, by removing copper stores, could inhibit collagen synthesis and maturation, which could explain the reversible cutis laxa syndrome of our patient's baby.[12] In addition, miscarriages are more common in WD. D-Penicillamine therapy has shown to improve the chance of successful pregnancy. Case 3 had 2 miscarriages before treatment initiation, achieving her first full-term gestation after starting chelators. This reinforces the indication of maintaining treatment during pregnancy in WD.

Cases 3 and 4 illustrate the controversial topic of genotype-phenotype correlations. Although a correlation between a certain phenotype and the most common variants on the *ATP7B* has been hypothesized, there is no consensus on whether a certain genotype predetermines the disease's phenotype. Although cases of monozygotic twins with different phenotypes have been described,[13-15] our sibling pair presented with not only the same phenotype but also identically good response to treatment and outcomes. We also report a shared new variant: NM_000053:c.1946+2T>C.

To conclude, we emphasize the importance of awareness of clinical suspicion in WD and of early treatment and the need to further investigate genotype-phenotype correlations in this disorder.

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