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Pearls and Oyst-ers: Challenges and Controversies in Wilson Disease

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ABSTRACT
WD is a genetic disorder of copper metabolism caused by mutations 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 WD patients: the difficulties with clinical diagnosis, the therapeutic management of WD and the indication for advanced therapies, the management during pregnancy and genotype-phenotype correlations.

Pearls
- 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 to a particular phenotype.

Oysters

• 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.

Introduction

Wilson’s disease (WD) is a genetic disorder of copper metabolism caused by mutations in the \textit{ATP7B} gene, which are inherited in an autosomal recessive pattern. Copper overload primarily in the liver and the brain 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 neurological symptoms that had worsened over the last 6 months: dysarthria, imbalance, symmetric limb tremor, rigidity, bradykinesia and hyperreflexia. Brain MRI (Fig1A) 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 (NV) 750-1500] and 8 mg [NV 20-60], and 24-hour urine copper level 301 µg [NV 10-60]. Kayser-Fleischer ring (KFR) was present (Fig1C). WD was diagnosed and zinc was started. Unfortunately, he died 8 months later due to neurological impairment. Necropsy confirmed the diagnosis (Fig1B).

Case 2. Advanced therapies: the therapeutic challenge
A 44-years-old woman, without family history, presented at the age of 30 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/24h. KFR was present. Genetic testing showed a heterozygous pathogenic variant in the *ATP7B* (NM_000053.4:c.1739del). Neurological examination was unremarkable. WD was diagnosed according to the Leipzig criteria. 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 became 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 prior to invasive treatments. She was admitted in hospital and D-Penicilamine was slowly titrated-up in association with a desensitization therapy based on Penicillamine patch, polaramine and cortisone. She tolerated dosages up to 1000 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 3-4. The controversy on phenotype-genotype correlations**

A sibling pair (72-years-old and 66-years-old-women) were diagnosed with WD at the age of 23 and 21, respectively. They both shared the same phenotype, with Child-Pugh A cirrhosis and mild, non-disabling postural tremor, mild parkinsonism and paroxysmal chorea. KFR were 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-Penicilamine 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 function were monitored every three months. She had a healthy baby at 39 weeks of gestation.
Case 3 became pregnant at the age of 24. By then, she was on D-Penicilamine 1500 mg a day. Before WD diagnosis, she had two miscarriages. Chelation treatment was maintained during her third pregnancy. Follow-up was unremarkable. A boy was delivered at 40 weeks of gestation. The baby was born with a reversible D-Penicillamine-induced cutis laxa syndrome (Fig 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, 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 WD patients.

To date, the diagnosis of WD is based on clinical manifestations along with classic abnormal findings. Availability of diagnostic criteria ease the diagnostic process. KFR is present in 100% of patients with neurologic dysfunction but might be absent in cases with just hepatic involvement. Brain MRI is also useful, being typical findings the ‘panda sign’, paramagnetic deposition of basal ganglia and hyperintensities on T2/hypointensities on T1 involving basal ganglia and brainstem. 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 due to 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.

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 $\text{ATP7B}$ mutations. 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 neurological symptoms. Since 1993, only 50 patients transplanted for pure neurologic/neuropsychiatric indication have been reported. The most recent publication showed a marked improvement in the motor score (UWDRS) in 12 of 18 patients. Despite these results,
the indication of LT for neurological symptoms remains controversial. On the other hand, DBS has shown improvement over the main neurological symptoms in WD: dystonia, tremor and parkinsonism, but scarce of information in the literature makes clinicians reluctant to the procedure. Both invasive treatments were considered in case 2. However, as the patient was not on chelators due to intolerance, D-Penicilamine was reconsidered successfully. We encourage neurologist 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 life-long. This also applies to pregnant women, who need to continue therapy during pregnancy.

However, the treatment of choice is still debated. We report two therapy regimens: zinc and D-Penicilamine. 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. However, zinc alone is often insufficient in symptomatic patients and chelators are required. Side effects of D-Penicilamine 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. Additionally, miscarriages are more common in WD. D-Penicilamine therapy has shown to improve the chance of successful pregnancy. Case 3 had two miscarriages before treatment initiation, achieving her first full-term gestation after starting chelators. This reinforces the indication of maintaining treatment during pregnancy in WD.

Case 3 and 4 illustrate the controversial topic of genotype-phenotype correlations. Even though 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, our sibling pair presented not only the same phenotype but also identically good response to treatment and outcomes. The shared variant (NM_000053:c.1946+2T>C) to our knowledge, has not been described before.

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


Figure 1 legend:
Figure 1. A: shows the brain MRI images from case 1. Pontine hypointensities are observed in T1 sequences and hyperintensities in midbrain, pontine nucleus, tegmentum and periaqueductal grey matter (arrows in the upper left of the figure) in FLAIR-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, reminding the face of a panda. Bilateral lenticular hypointensities can also be seen (arrows in the upper right of the figure). B: pathological 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 myelinolysis. (B.b-B.d) Vacuolization is marked with arrowheads and a star in microscopically samples. C: Kayser-Fleischer ring is marked with an arrow.
Figure 2 legend:

Figure 2. 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.