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CLINICAL VIGNETTE

Ataxia and Dysarthria: A Case of Neurologic Wilson's Disease

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Case Report

A 39-year-old Asian female with a past medical history of Wilson's disease, hypertension, and chronic low back pain presented to the emergency room with lower extremity weakness, dysarthria and gait disturbance.

For the month prior to presentation, the patient was increasingly unsteady on her feet, stated that her "legs wouldn't work" and reported five falls in the past two weeks. In addition to movement initiation difficulties and prolonged reaction times, the patient and her husband reported rapidly progressive bradykinesia and chronic progressive dysarthria, which first became apparent 9 months before.

The patient also complained of anxiety, depression and rapidly progressive insomnia, to the point where she would rarely sleep more than 1-2 hours at a time.

She was diagnosed with Wilson's disease, confirmed with a liver biopsy, at the age of 19. She was initially treated with penicillamine but discontinued after five years due to excessive nausea and vomiting. She was then maintained on zinc until 3 months prior to admission when her outpatient hepatologist started Trientine for chelation therapy.

At the time of presentation to the emergency room, the patient had a temperature of 97.7 °F, blood pressure 103/78, heart rate 91 bpm, respiratory rate 18 per minute with a oxygen saturation of 100% on room air. She was in no acute distress, resting comfortably, alert and fully oriented.

Extraocular movements were intact and eye examination was notable for Kayser-Fleischer rings **(Figure 1)**. Her pupils were round, equal and reactive to light, and sclera were anicteric. Her abdomen was soft, nontender, nondistended, with no palpable hepatosplenomegaly. There were no other stigmata of chronic liver disease present.

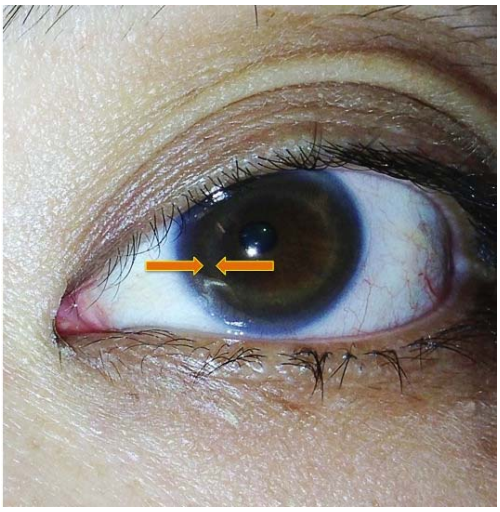

Figure 1

The Neurology team was consulted and a thorough neurological examination was significant for dysarthria, increased tone in the upper extremities (right greater than left), 5/5 distal muscle extensor strength in all four extremities and hyporeflexia throughout the right upper and lower extremities. She had a wide-based gait, was unable to perform tandem heel-to-toe and would fall to the right during the Romberg test.

Lab abnormalities included decreased serum copper of 14 mcg/dL, decreased ceruloplasmin of 2 mg/dL and a 24-hour urine copper excretion of 962 mcg (a 24-hour urine creatinine excretion was 1362 mg). Serum free copper was calculated to be 8 mcg/dL, which was within the normal range of 5-15 mcg/dL. Her liver enzymes were all within normal limits.

Given the concerning neurological findings, an MRI of the brain with and without gadolinium revealed atrophy involving the bilateral lentiform nuclei, which is typical of mineral deposition in Wilson's disease **(Figure 2)**.

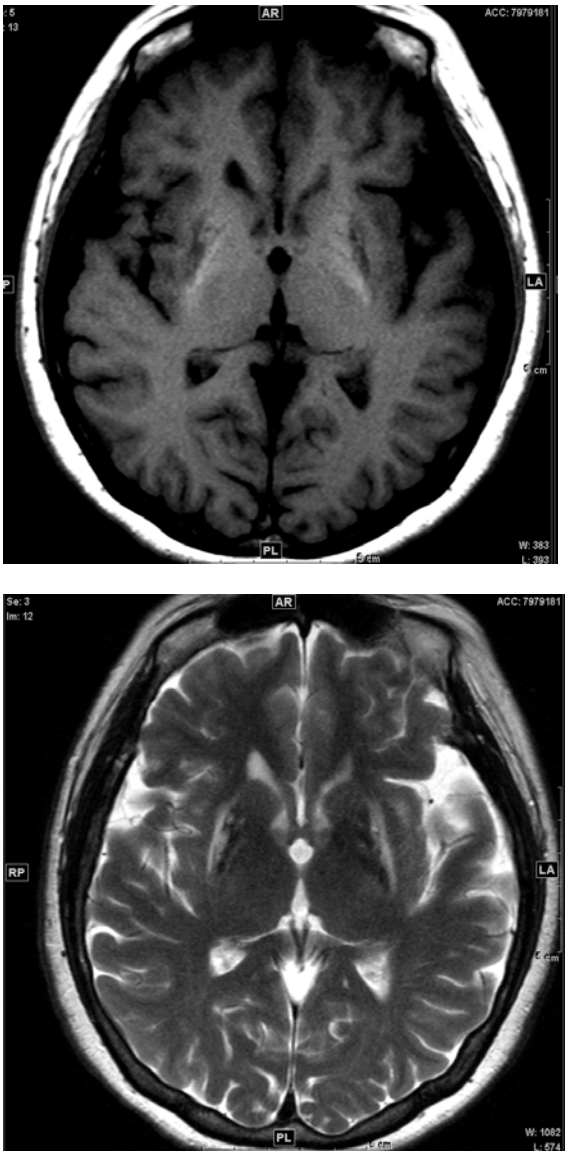

Figure 2
Axial noncontrast T1-weighted (a) and T2-weighted (b) images of the brain. There is bilaterally symmetric signal abnormality in the lentiform nuclei, with peripheral T2 hyperintensity (possibly reflecting necrosis, edema and/or degeneration) and medial T2 hypointensity and T1 hyperintensity (probably reflecting copper deposition and/or other paramagnetic substances, as can be seen with liver disease).

The patient was continued on Trientine per neurology recommendations. Neurology also recommended treatment with tetrathiomolybdate, which was deferred to her outpatient hepatologist. She was evaluated by physical therapy (PT), given a cane for ambulation and instructed to follow up with PT, speech therapy and Neurology.

Discussion

Wilson's disease (WD) is an autosomal recessive disorder associated with a mutation of the ATP7B gene and defective biliary excretion of copper[1,2]. If left untreated, copper can accumulate within organs, specifically the liver, brain, and cornea.

Hepatic features of WD can fall into one of four categories: acute hepatitis, chronic active hepatitis, acute fulminant hepatic failure, and cirrhosis[3,4]. In some cases, the liver ultimately becomes cirrhotic and patients may develop associated symptoms, such as jaundice, ascites, variceal formation, and spider angiomata. Opthalmologic findings in WD include pigmented rings in Descemet's membrane of the cornea, known best as Kayser-Fleischer rings[3] **(Figure 2)**.

Neurologic WD can have a variety of presentations, depending on the progression of the disease, and can present either prior to, along with, or following hepatic manifestations[4]. Large studies suggest a mean age of onset between 15-21 years with neurologic WD[3]. The most common findings include dysarthria, gait abnormalities (ataxia), dystonia, tremor, chorea, and parkinsonian features, such as bradykinesia, imbalance, and cogwheel rigidity[3]. Seizures are less common, reported in nearly 6% of WD cases[3]. The tremor seen in WD has often been described as "wing-beating", consisting of a coarse, proximal tremor[4].

Some neurological findings tend to present preferentially with either young-onset or adult-onset WD. For example, chorea is more common in the young-onset WD, with reported rates of 20% versus 3% in adult-onset WD[3]. Additionally, cognitive impairment and psychiatric features can present as either frontal lobe syndrome, with behavioral changes, apathy, and impaired executive functioning, or subcortical dementia, with slowed thinking and memory loss[3].

Neurologic WD can be potentially difficult to distinguish from other chronic progressive extrapyramidal disorders; however, it is vital to make this distinction as WD is a potentially treatable disorder. Rapid diagnosis is also extremely important as research has shown that diagnostic delay is associated with poor outcomes in response to treatment. For example, diagnosis within one month

was associated with a 12% rate of poor outcome versus a 38% rate of poor outcome in delays of diagnosis greater than 18 months[3]. Furthermore, certain neurologic presentations are associated with differences in success rate. For example, the tremor and dysarthric form of neurologic WD has been shown to be associated with the best outcome following treatment. Specifically, patients with chorea, parkinsonism, and dystonia had a 75%, 63% and 53% chance of favorable outcome, respectively[3]. One prospective study of 83 patients with WD who received an initial neurologic evaluation and were followed for a mean of 34.7 months found tremor was a favorable prognostic sign; however, dystonia appeared refractory to treatment[5].

Current laboratory diagnostic tests for WD include serum ceruloplasmin, a 24-hour urinary copper collection, serum free copper and hepatic copper[1,2]. MRI findings, specifically the "face of the giant panda" sign, have been identified (as seen in **Figure 3**), in additional to tectal plate hyperintensity, central pontine myelinolysis-like abnormalities, and simultaneous involvement of the basal ganglia, thalamus and brainstem[6]. When used in conjunction with laboratory measures, imaging may solidify the diagnosis of neurologic WD.

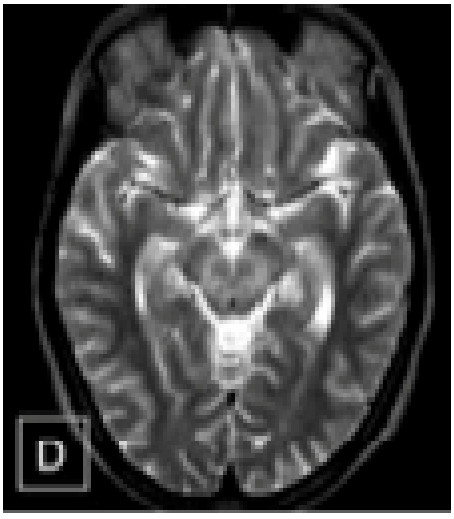

Figure 3

MRI brain findings in patients with Wilson's disease (WD)[6]. Axial T2W image showing the "Face of Giant Panda" sign. Reversibility of signal abnormality has been described with clinical improvement following copper-chelation therapy.

The current treatment options for neurologic WD include D-penicillamine, trientine, dimercaprol, and zinc[3,4]. Penicillamine, a copper chelating agent, promotes urinary excretion of copper but has been associated with initial worsening of neurologic WD symptoms[3,4]. Furthermore, nearly 50% of patients that reported worsening neurologic WD symptoms never recovered to their baseline[3]. Similar neurologic worsening is seen with trientine, a copper chelator that also promotes urinary excretion. Trientine is considered second-line therapy and useful in patients with adverse reactions to penicillamine[3,4,7]. Zinc acetate therapy has often been used as a successful therapy and preventative measure, especially given it's favorable side effect profile and the decreased likelihood of initial neurologic worsening[3,8,9]. Zinc acts to induce metallothionein production by the enterocyte, which complexes with copper in the gastrointestinal tract and prevents uptake[3,4,8,9]. One downside to zinc, however, is the slow de-coppering action[3,4,8].

Ammonium tetrathiomolybdate (TM) is a promising new compound that complexes with copper in the intestinal tract and binds to plasma copper, preventing uptake by cells. TM is still being tested in clinical trials and not commercially available, but early studies suggest that TM leads to rapid copper removal from the tissue with minimal neurologic worsening[3,4]. One RCT of 48 patients comparing trientine to TM for neurologic WD found that TM was more successful at preserving neurologic function[10].

Conclusion

Neurologic Wilson's disease much like other well known form of neurodegenerative diseases can lead to debilitating neurologic consequences. Rapid diagnosis and treatment may prevent devastating and irreversible progression of neurologic WD. Speech and physical therapy, in addition to the pharmaceutical options, can help patients to maintain functional abilities and independence.

REFERENCES

1. **Petrukhin K, Fischer SG, Pirastu M, Tanzi RE, Chernov I, Devoto M, Brzustowicz LM, Cayanis E, Vitale E, Russo JJ, et al**. Mapping, cloning and genetic characterization of the region containing the Wilson disease gene. *Nat Genet*. 1993 Dec;5(4):338-43. PubMed PMID: 8298640.

2. **Tanzi RE, Petrukhin K, Chernov I, Pellequer JL, Wasco W, Ross B, Romano DM, Parano E, Pavone L, Brzustowicz LM, et al**. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. *Nat Genet*. 1993 Dec;5(4):344-50. PubMed PMID: 8298641.
3. **Lorincz MT**. Neurologic Wilson's disease. *Ann N Y Acad Sci*. 2010 Jan;1184:173-87. doi: 10.1111/j.1749-6632.2009.05109.x. Review. PubMed PMID: 20146697.
4. European Association for Study of Liver. EASL Clinical Practice Guidelines: *Wilson's disease*. *J Hepatol*. 2012 Mar;56(3):671-85. doi: 10.1016/j.jhep.2011.11.007. PubMed PMID: 22340672.
5. **Burke JF, Dayalu P, Nan B, Askari F, Brewer GJ, Lorincz MT**. Prognostic significance of neurologic examination findings in Wilson disease. *Parkinsonism Relat Disord*. 2011 Aug;17(7):551-6. doi: 10.1016/j.parkreldis.2011.05.002. PubMed PMID: 21641265.
6. **Prashanth LK, Sinha S, Taly AB, Vasudev MK**. Do MRI features distinguish Wilson's disease from other early onset extrapyramidal disorders? An analysis of 100 cases. *Mov Disord*. 2010 Apr 30;25(6):672-8. doi: 10.1002/mds.22689. PubMed PMID: 20437536.
7. **Scheinberg IH, Jaffe ME, Sternlieb I**. The use of trientine in preventing the effects of interrupting penicillamine therapy in Wilson's disease. *N Engl J Med*. 1987 Jul 23;317(4):209-13. PubMed PMID: 3600712.
8. **Linn FH, Houwen RH, van Hattum J, van der Kleij S, van Erpecum KJ**. Long-term exclusive zinc monotherapy in symptomatic Wilson disease: experience in 17 patients. *Hepatology*. 2009 Nov;50(5):1442-52. doi: 10.1002/hep.23182. PubMed PMID: 19731238.
9. **Anderson LA, Hakojarvi SL, Boudreaux SK**. Zinc acetate treatment in Wilson's disease. Ann Pharmacother. 1998 Jan;32(1):78-87. Review. PubMed PMID: 9475826.
10. **Brewer GJ, Askari F, Lorincz MT, Carlson M, Schilsky M, Kluin KJ, Hedera P, Moretti P, Fink JK, Tankanow R, Dick RB, Sitterly J**. Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. *Arch Neurol*. 2006 Apr;63(4):521-7. PubMed PMID: 16606763.
11. **Magalhaes AC, Caramelli P, Menezes JR, Lo LS, Bacheschi LA, Barbosa ER, Rosemberg LA, Magalhaes A**. Wilson's disease: MRI with clinical correlation. *Neuroradiology*. 1994;36(2):97-100. PubMed PMID: 8183467.
12. **King AD, Walshe JM, Kendall BE, Chinn RJ, Paley MN, Wilkinson ID, Halligan S, Hall-Craggs MA**. Cranial MR imaging in Wilson's disease. *AJR Am J Roentgenol*. 1996 Dec;167(6):1579-84. PubMed PMID: 8956601.
13. **Roh JK, Lee TG, Wie BA, Lee SB, Park SH, Chang KH**. Initial and follow-up brain MRI findings and correlation with the clinical course in Wilson's disease. *Neurology*. 1994 Jun;44(6):1064-8. PubMed PMID: 8208401.

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