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Case Report

Acute-Onset Optic Neuropathy in Wilson's Disease

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Abstract
Wilson's disease (WD), also known as hepatolenticular degeneration, is a rare autosomal recessive condition of excess copper accumulation that is most commonly associated with hepatic, neurologic, psychiatric, and ocular manifestations. While Kayser-Fleischer rings and sunflower cataracts are well known in WD, visual impairment is very rare. We report the case of a 20-year-old female who presented with acute liver failure and associated monocular vision loss. WD was found to be a cause of her liver disease and decreased vision.

Introduction

Wilson's disease (WD), also known as hepatolenticular degeneration, is a rare autosomal recessive condition of copper metabolism. It is best known for its hepatic, neurologic, and psychiatric symptoms, as well as Kayser-Fleischer rings in the eyes. While decreased vision is rare, there have been a few cases of optic neuropathy in association with WD. We report the clinical course of a 20-year-old female who presented with optic neuropathy and acute liver failure. We discuss why this may be another case of WD demonstrating its association with optic neuropathy.

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Case Report

In August 2017, a 20-year-old Caucasian female presented as a transfer from an outside hospital with concern for acute liver failure. Three weeks prior to presentation, she had visited the emergency department two other times with fatigue and jaundice and had been diagnosed with acute hepatitis and urinary tract infection. She was treated conservatively for her acute hepatitis and with antibiotics for her urinary tract infection with partial improvement of jaundice. Five days prior to her admission to the hospital, she developed fatigue, nausea, vomiting, intermittent right upper quadrant abdominal pain, bloating, and lower extremity edema. She also reported blurry central vision in the right eye that had developed 5 days prior, which she described as constant and unchanged since onset. There was no tearing or photophobia, though she felt she could focus better in the dark. She denied pain with eye movements, flashes, floaters, curtains, and shadows. Her past medical history included mononucleosis at age 14 and nose surgery of unknown date. She took 200 mg ibuprofen as needed but denied using herbals or illicit drugs. She also denied cigarette and alcohol use. She had no risk factors for liver disease and no consanguinity in parents but was uncertain of her vaccination history. Family history was positive for rheumatoid arthritis in her father and colorectal cancer in her mother. There was no known family history of eye disease.

On admission, her physical exam showed scleral icterus without rash. Abdominal exam demonstrated 10 cm liver span. Symmetric bilateral pedal edema was present. There was no altered mental status, focal neurologic deficits, or asterixis. Laboratory values revealed hemoglobin 13.3 g/dL, white cell count 7.02 × 10^3/μL, and platelet count 121 × 10^3/μL. Liver biochemistry was abnormal; AST was 795 U/L (14–40 U/L), ALT 599 U/L (9–48 U/L), alkaline phosphatase 264 U/L (32–126 U/L), total bilirubin 28.1 mg/dL (<1.5 mg/dL), and direct bilirubin 13.5 mg/dL (<0.3 mg/dL). Liver function test also showed significant synthetic impairment with prolonged PT/INR and PTT, as well as low protein and albumin. Her ammonia was 133 μmol/L (11–35 μmol/L), lactate 1.8 mmol/L (0.5–1.6 mmol/L), BUN 5 mg/dL (7–22 mg/dL), and uric acid <1.5 mg/dL (2.8–6.0 mg/dL). Amylase and lipase were normal.

A search to uncover the etiology of her liver failure simultaneously began, but workup was only positive for low copies of EBV and borderline elevated VZV. Suspicion was subsequently turned to WD and autoimmune hepatitis. Titers of anti-smooth muscle antibody were mildly positive, and workup for WD revealed the following results: ceruloplasmin was low at 17 mg/dL (20–60 mg/dL) and 24-hour urine copper excretion was elevated at 64 μg/24 h (≤60 μg/24 h). A transjugular liver biopsy showed 70% panlobular necrosis most likely due to WD. While the biopsy could not completely exclude autoimmune hepatitis, it was deemed less likely given no plasma cells on histology. Hepatic copper quantitation, in addition, was high at 41 μg/g dry weight (10–35 μg/g dry weight).

Meanwhile, given the patient's complaint of decreased vision, ophthalmology was consulted to assess for Kayser-Fleischer rings, though none were noted on gonioscopy. Instead, she was found to have decreased bedside visual acuity of 20/400 (PH J16) OD, J1 OS, with a positive APD of the right eye suggesting optic neuropathy. She subsequently noticed decreased color vision in the same eye, with bedside Ishihara plate testing revealing 2/9 OD and 9/9 OS. IOP remained normal throughout. Confrontational visual field and extraocular movements were full without pain. Slit-lamp and fundus exams were also unremarkable, with no visible disc edema, pallor, or maculopathy. To determine the cause of her optic neuropathy, MRI of the brain and orbits was obtained, which showed no evidence of signal abnormality involving optic nerves or of external compressive mass lesion. Infectious serology including syphilis, Lyme, and TB was negative as well, but there was a positive toxoplasma IgG with a

negative IgM, and a positive EBV as mentioned before. Given reports of EBV and neuromyelitis optica (NMO), NMO IgG was tested, which returned negative. Lumbar puncture was not performed per consult with infectious diseases, which indicated the likelihood of infectious etiology underlying a monocular vision loss was too low to justify the risk of the procedure given her coagulopathy.

While extensive investigations were ongoing, our patient's status started deteriorating on day 5 of admission with worsening liver biochemistry. Decision was made to transfer her to ICU for closer monitoring. She eventually developed fulminant liver failure with hepatic encephalopathy and asterixis and underwent liver transplant. Intraoperatively, she had 4 L of estimated blood loss needing extensive transfusion. Her fascia remained open and was closed 3 days later. Postoperatively, she was placed on immune suppressants. Her recovery was complicated by acute cellular rejection, for which she was treated with methylprednisolone followed by a prednisone taper. Ophthalmology exam on postoperative day 1 showed visual acuity of at least light perception in both eyes, which improved to 20/200 OD, J1 OS. At this time, her fundus exam also revealed temporal pallor in the right disc. Visual evoked potential was obtained and showed normal finding in the left eye but absent P100 potential in the right, confirming optic neuropathy. She eventually recovered and was stable for discharge. However, no histological conclusion could be reached based on her liver explant due to massive necrosis.

Discussion

WD is a rare autosomal recessive condition of excess copper accumulation that is most commonly associated with hepatic, neurologic, psychiatric, and ocular manifestations such as Kayser-Fleischer rings. However, clinical presentations are largely variable and diagnosis is often challenging, especially in those presenting with hepatic abnormalities [1, 2]. Because of this, WD is considered in the differential diagnosis when patients present with unexplained liver disease or acute liver failure [1, 2].

As with our patient, WD soon became a concern given her young age and lack of other obvious contributing factors to her liver disease. Her optic neuropathy in the context of liver failure further increased the suspicion for WD, especially given two other case reports [3, 4]. Compared to the cases by Rukunuzzaman et al. [4] and Gow et al. [3], all three patients presented with advanced liver disease with decreased visual acuity and color vision (binocular in Gow et al. [3]; monocular in Rukunuzzaman et al. [4] and in our patient). Ceruloplasmin was low, urinary copper excretion was high, and the biopsy was in line with WD histology. Meanwhile, infectious serology was unremarkable, as was alpha-1-antitrypsin. Liver ultrasound similarly showed heterogeneous echogenicity [4] and MRI of the brain was also negative in the patient without neurologic symptom [3]. Finally, fundus exam in all 3 patients revealed pallor of the optic disc, and in both our case and that of Gow et al. [3], optic neuropathy was confirmed by abnormal visual evoked potential.

Some differences do exist among the three patients, however. Other than variations in lab tests conducted, the other patients were a 46-year-old male and a 14-year-old boy with consanguineous parents who had Kayser-Fleischer rings and urinary copper excretion in the typical Wilsonian range. If performed, anti-smooth muscle serology was negative. Liver explant was also deemed consistent with WD but remained undetermined in our patient. Additionally, the boy developed abnormal movements consistent with his positive MRI of the brain. His monocular vision loss also normalized in the end, though there was no VA reported. In con-

trast, the patient from Gow et al. [3] had binocular vision loss with rapid deterioration to legal blindness without recovery. Both of these patients also received treatment for WD, including penicillamine at various points of care, but their condition continued to decline with the adult patient needing liver transplant 10 months after initial presentation (compared to 1 month in our patient). Unfortunately, both patients eventually died due to either transplant or liver failure.

Yet, rather than challenging our patient's less classical manifestation of WD, these differences may reflect the vastly variable clinical and laboratory presentations known to WD. In fact, these variations may have roots in the more than 500 possible mutations in the ATP7B gene underlying WD, explaining the difficulty of diagnosing WD with molecular genetics especially when many patients are compound heterozygotes [1, 2]. As a result, clinical manifestations range from asymptomatic to fulminant neurologic presentation or fulminant liver failure [1]. Liver failure can also be chronic or acute, and early diagnosis can be difficult since disease-specific findings may be lacking. Kayser-Fleischer rings, for instance, can be absent in half the patients with WD affecting the liver [2, 5]. Even when found, they are not completely specific to the disease [1]. For our patient, despite the absence of pathognomonic finding, she falls into the epidemiology of patients who are young, female, and tend to present with acute liver failure [6].

It is worth noting that no single clinical or laboratory abnormality can confirm WD, and neither can a normal or near-normal value exclude the disease. For one, as few as 27% to half the patients with WD have normal ceruloplasmin, which can be falsely elevated in active hepatic inflammation as it is an acute-phase protein [1, 5]. As a result, the already low level found in our patient may be higher than what it actually is. Similarly, while urinary copper excretion above 100 μg/24 h is considered the Wilsonian range, some have less than 100 μg/24 h [1], as is the case with our patient. Moreover, although liver copper quantification is deemed the gold standard for WD diagnosis, sampling variation can cause up to 500-fold difference in copper content obtained due to the greatly inconsistent hepatic copper distribution in acute hepatic failure [5, 7]. In one study, only 2/14 and 3/16 explant specimens fell within the Wilsonian range [7]. This observation may therefore explain our patient's modestly elevated liver quantification based on only three biopsy samples. Essentially, in liver disease of unknown origin, clinical and laboratory parameters are insufficient to exclude WD, which should be considered until proven otherwise [1, 2, 5].

On the other hand, WD is known histologically as the great masquerader and can present as a fatty liver pattern, cryptogenic cirrhosis pattern, or acute hepatitis pattern [6]. These patterns of injury often overlap with those from toxicity, viral infection, ductal obstruction, or autoimmune inflammation, and only in the context of clinical and laboratory findings can a pathologic diagnosis be made. For our patient, other than autoimmune hepatitis and WD, all others were excluded by laboratory or imaging studies. Unfortunately, while the massive necrosis and regenerative nodules have been described in another case of WD-induced hepatic failure [7], the necrosis that accompanied the acute liver failure made final histologic determination of the explant difficult.

Nevertheless, given our findings and diagnostic considerations surrounding WD, one cannot help but suspect WD and its association with optic neuropathy, especially given similar reports [3, 4]. Since our patient did not receive penicillamine, it is also unlikely that our patient's decreased vision was treatment induced, as seen in other patients with WD [8–10]. In addition, studies have shown abnormal visual evoked potential in both symptomatic and asymptomatic patients with established WD [11, 12]. Other causes of optic neuropathy have also been investigated and excluded: normal MRI of the brain and orbits ruled out compres-

sive, inflammatory, and infiltrative processes; positive toxoplasmosis IgG and EBV PCR were deemed past infections unlikely to explain current decreased vision; and the negative NMO IgG made NMO unlikely. Lastly, while no mitochondrial DNA analysis was performed for Leber hereditary optic neuropathy, given our patient's negative family ocular history, female gender, acute vision loss, and normal exam and MRI, it would be surprising if our patient had Leber hereditary optic neuropathy concurrent with liver failure. Certainly, if more cases are found, this report, along with the others, may one day indicate the need to recognize and screen for optic neuropathy in patients with WD.

There are, however, several limitations in our case. For one, our patient lacks confident diagnosis of WD. While her liver copper quantification, ceruloplasmin, and urine copper excretion support WD, the latter two findings can also be present in fulminant liver failure without WD [2]. They can also overlap with those of autoimmune hepatitis [1], which was a consideration given her mildly positive anti-smooth muscle antibody titer and a biopsy result that could not exclude the disease. Histologically, WD and autoimmune hepatitis can also be indistinguishable [1]. Nevertheless, a study of ocular findings in autoimmune liver disease revealed no association with optic neuropathy [13], although one patient reportedly developed NMO-positive optic neuritis in the context of ANA-positive autoimmune hepatitis [14]. Interestingly, our patient was diagnosed with both optic neuropathy and optic neuritis at her last outpatient follow-up in December 2017 based on the time course, progression, and partial recovery of her vision loss. At this visit, she was also found to have normal optic nerves on fundus exam. Visual acuity measurement at the bedside during hospitalization, however, is not the most accurate setting for testing and tracking progression. Her intraoperative 4-liter blood loss could also have complicated the interpretation of her postoperative findings. Finally, the anti-smooth muscle antibody titer of 1:80 was eventually deemed too low to provide an explanation for her condition. Repeat serology, unfortunately, was not completed.

To date, few reports have detailed WD as a cause of optic neuropathy. While the etiology behind our patient's acute liver failure remains uncertain, the laboratory findings, the histology impression by biopsy, and the lower likelihood or exclusion of other causes raise the possibility of WD and of optic neuropathy as one of its neurologic and ocular manifestations. Though more tests are desired for our patient and more reports are needed to establish an association, it is important for physicians to consider WD when faced with liver disease of unknown origin, to remain open-minded to the ocular manifestation of WD beyond sunflower cataracts and Kayser-Fleisher rings, and to be cautious when caring for patients with WD who may have subclinical disease of the optic nerve.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Liyung Tiffany Chou was the primary author and was involved in data analysis and manuscript preparation and editing. Derek Horkey was involved in manuscript preparation and editing. Mark Slabaugh was involved in data analysis and manuscript preparation and editing.

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