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Bilateral Optic Neuropathy as the Prominent Manifestation of Wilson's Disease

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Dear Editor,

Optic neuropathy is rarely reported in Wilson's disease (WD).[1-3] Here we report a case of WD presenting with bilateral visual loss, thereby further establishing optic neuropathy as a manifestation of WD.

A 22-year-old Chinese male presented to the ophthalmology clinic with subacute-onset progressive painless bilateral visual loss and decreased perception of colors for 1.5 months. Kayser–Fleischer rings were noted (Fig. 1A), and so he was transferred for neurogenetics investigations. Detailed history-taking revealed that he had experienced subtle hand tremor over the previous 4 years, and had suffered from slight slurred speech, gait instability, and emotional lability for the past month. A neurological examination showed fine postural tremor in the hands, mild dysarthria, and truncal ataxia. Liver function and coagulation function tests were unremarkable. Serum ceruloplasmin was decreased at 54 mg/L (normal range: 200–420 mg/L), while 24-hour urine copper excretion was elevated at 1,914 μg (normal range: <100 μg). Ultrasonography showed coarseness of the liver parenchyma. Brain and orbital MRI findings were normal. Whole-exome sequencing detected two missense variations in *ATP7B*: c.3089G>A, p.G1030D; and c.2924C>A, p.S975Y (NM_000053.3).

The visual loss of the patient progressed during the above-mentioned investigations. Treatment with D-penicillamine and zinc gluconate improved the neurological and psychiatric manifestations, but his vision continued to slowly deteriorate over the following 2 months. He reported being unable to read a vehicle license plate number from a distance of 10 meters. He was then transferred to our neuro-ophthalmological center.

Visual acuity was 20/200 in the right eye and 20/100 in the left eye. The pupillary light reflex was normal without a relative afferent pupillary defect. A fundus examination revealed disc pallor in both eyes (Fig. 1B). Humphrey perimetry showed irregular visual field defects in both eyes (Fig. 1C). The patient could identify none of 10 Ishihara plates with either eye. Optical coherence tomography (OCT) revealed thinning of the temporal peripapillary retinal nerve fiber layer (Supplementary Fig. 1 in the online-only Data Supplement) and of the ganglion cell layer plus the inner plexiform layer (Supplementary Fig. 2 in the online-only Data Supplement) in both eyes, while OCT B-scan images of the outer retina were unremarkable (Supplementary Fig. 3 in the online-only Data Supplement). Pattern visual evoked potentials showed prolonged P100 latencies (Fig. 1D). Antibodies against aquaporin 4 and myelin oligodendrocyte glycoprotein were negative, a cerebrospinal fluid analysis was unremarkable, and mitochondrial DNA gene sequencing was normal. After excluding other causes of visual loss, we attributed the optic neuropathy to WD. After 2 months of chelation therapy with sodium dimercaptopropane sulfonate, the visual acuity had improved to 20/100 and 20/40 in the right and left eyes, respectively, along with visual field improvement (Fig. 1E).

WD is a rare genetic disorder of copper metabolism with neurological, hepatic, and psychiatric manifestations.[4] The neurological manifestations are mainly extrapyramidal (e.g., dysar-

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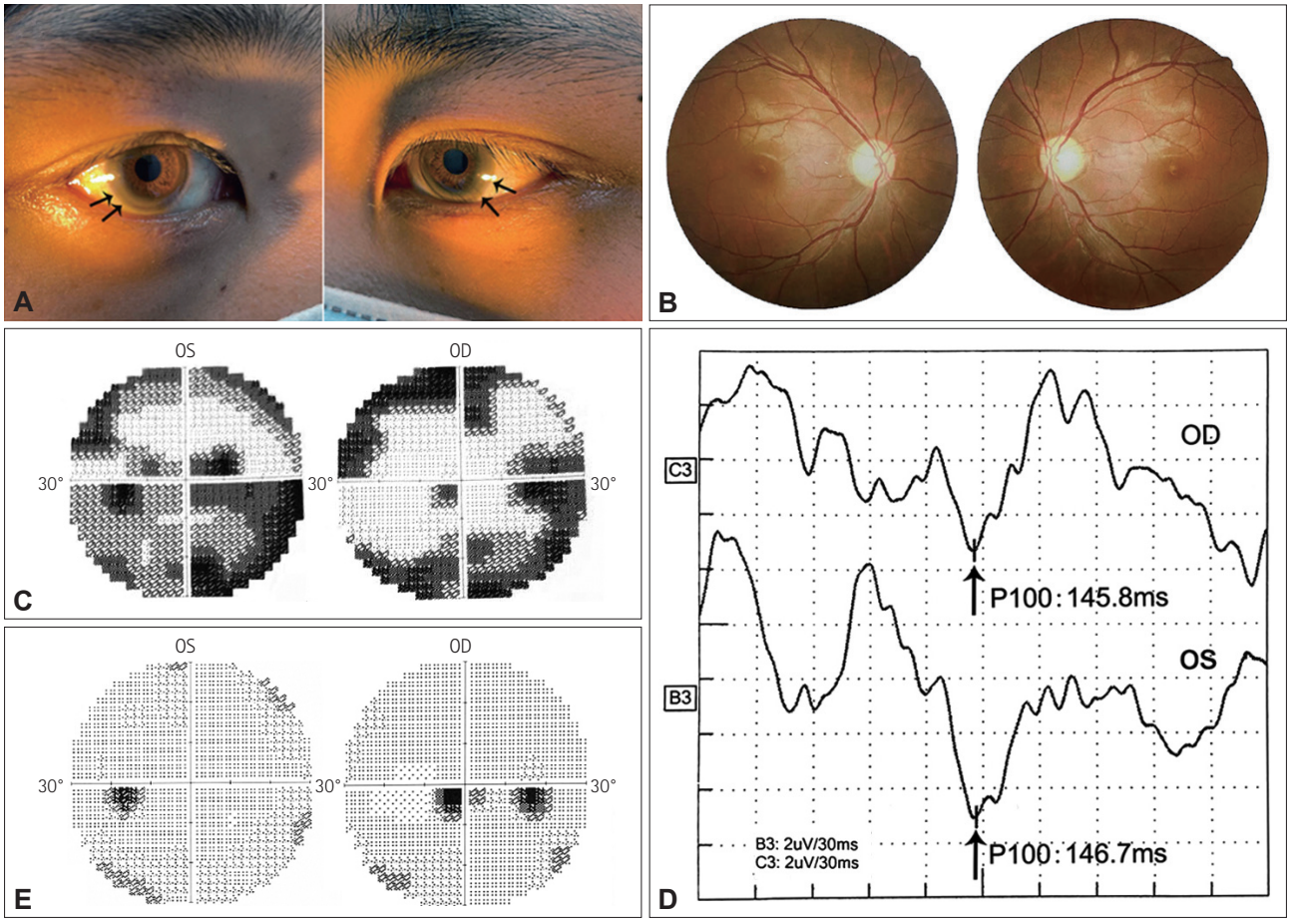

Fig. 1. Kayser–Fleischer rings, perimetry, and visual-pattern-evoked potentials of the patient. A: Kayser–Fleischer rings in both eyes (arrows). B: Fundus photography showed disc pallor in both eyes. C: Humphrey perimetry showed irregular visual field defects in both eyes. D: Pattern visual evoked potentials showed prolonged P100 latencies (145.8 ms and 146.7 ms in the right and left eyes, respectively). E: Humphrey perimetry showed visual field defect improvement after chelation therapy with sodium dimercaptopropane sulfonate. OD, right eye; OS, left eye.

thria, gait abnormality, dystonia, and tremor), although there is great variability.[4] Optic neuropathy as a complication of penicillamine treatment for WD has been recognized,[5,6] but the association between optic neuropathy and WD per se has not been well established. Only four cases of WD presenting with optic neuropathy (including our case) have been reported[1-3] (Supplementary Table 1 in the online-only Data Supplement).

The ages of the four reported patients (three males and one female) ranged from 14 to 46 years, with two presenting with binocular visual loss and the other two with a monocular pattern. Visual impairment occurred in the context of advanced cirrhosis or acute liver failure in the three previously reported patients, while our patient had only early-stage cirrhosis. Only two had neurological manifestations beyond optic neuropathy.

The patient reported by Gow et al.[1] progressed to legal blindness without recovery, even after treatment with penicillamine and high-dose methyl-prednisolone. In contrast, the other three patients experienced either partial or complete visual recovery after drug treatment[2] or liver transplantation.[3]

The mechanism of optic neuropathy in WD remains unclear. We speculated that copper toxicity mediated by oxidative stress and free radicals can play an important role in the pathogenesis, given that *ATP7B* mutations lead to excessive copper deposition.[4] Genetic testing was not performed for the previously reported cases, and the mutations in our patient are uncommon in the Chinese population.[7] More cases with genetic confirmation are required to determine whether optic neuropathy is associated with certain genotypes.

Genetic defects are an important cause of optic neuropathy. Besides well-known Leber's hereditary optic neuropathy and dominant optic atrophy, optic neuropathy can be caused by various mechanisms in certain uncommon hereditary disorders such as Wolfram syndrome, cryopyrin-associated periodic syndrome, Charcot-Marie-Tooth disease, and WD (as shown in our case).[8,9] Therefore, genetic testing is useful in certain cases of optic neuropathy, especially in children and young adults.

We have reported a case of bilateral optic neuropathy as the prominent manifestation of WD. Optic neuropathy should

be listed as a neurological/neuro-ophthalmological manifestation of WD.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2022.18.4.492.

Ethics Statement

Informed consent was obtained from the patient for the analysis and publication of photographs.

Availability of Data and Material

All data generated or analyzed during the study are included in this published article and its supplementary materials.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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