Movement Disorders
CLINICAL PRACTICE

Parkinsonism with Normal Dopaminergic Presynaptic Terminals in Cerebrotendinous Xanthomatosis

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Cerebrotendinous xanthomatosis (CTX) is a treatable, autosomal-recessive, multisystemic lipid storage disorder with various neurological and nonneurological manifestations. We report a case of CTX with progressive parkinsonism involving postsynaptic striatal iron deposition and intact dopaminergic presynaptic terminals.

A 40-year-old man with a 10-year history of progressive gait difficulties, bradykinesia, and upper-limb tremors developed cataracts at age 9, epileptic seizure at age 26, and mild chronic diarrhea at age 38. He was diagnosed with parkinsonian syndrome. Levodopa therapy was initiated (400 mg/d, gradually increased to 900 mg/d), but was ineffective.

Neurological examination revealed gait difficulties; symmetrical rigidity and bradykinesia, particularly of the legs; pronounced upper-limb postural and action tremors and mild left-arm resting tremor; left-side incoordination; bilateral incoordination; balance-related problems; lower-limb weakness, particularly of the left leg; hyperreflexia of all limbs; and bilateral Babinski reflex. His Unified Parkinson's Disease Rating Scale part II and part III scores were 28 and 49, respectively. He had impaired cognitive function but no personality changes, slow voice without aphasia, symmetrical reduction of graphic perception, 2-point discrimination perception in his lower limbs, Mini-Mental State Examination score of 18, impaired orientation, difficulties with simple calculations, mild enlargement of right Achilles tendon, and mild pes cavus.

[^{18}F]-9-fluoropropyl-(+)-dihydrotetrabenazine positron emission tomography revealed normal uptake in the bilateral putamen and caudate (Fig. 1A,B); brain susceptibility-weighted imaging (Fig. 1C and E) and quantitative susceptibility mapping (Fig. 1D,F) showed elevated iron deposition in the substantia nigra, red nucleus, bilateral globus pallidus, and cerebellar dentate nucleus. These results indicated intact presynaptic dopaminergic input function and potentially lesioned postsynaptic outputs. Brain magnetic resonance imaging revealed mild atrophy and symmetric abnormal signals in the cerebellar dentate nucleus and mild white matter degeneration (Fig. 1G,H). Sagittal T1-weighted right-ankle magnetic resonance imaging revealed fusiform thickening (Fig. 1I,J); Achilles tendon biopsy showed accumulation of multinucleated giant cells, xanthoma cells, and dispersed lipid crystal clefts (Fig. 1L,M). The patient's cholesterol level was 45.79 μmol/L (normal range, <10μmol/L); Sanger sequencing revealed 2 heterozygous *CYP27A1* mutations—chr2:219677818 c.1016C>T and chr2:219679182 c.1263+1G> A.

Initially, ursodeoxycholic acid was administered and subsequently chenodeoxycholic acid for 6 months.[1] His gait difficulties and action tremors ameliorated initially; however, his condition steadily deteriorated. He refused follow-up metabolic investigations.

Chronic diarrhea, bilateral cataracts, tendon xanthomas, and neurologic dysfunctions are pathognomonic of CTX. Our patient developed bilateral cataracts early. However, late onset of diarrhea and mild tendon xanthoma (Fig. 1K) potentially delayed diagnosis. Parkinsonism can occur in patients with CTX (prevalence, ~9%).[1] The neurological signs are restricted to parkinsonism and misdiagnosed with Parkinson's disease in some patients. Chenodeoxycholic acid and antiparkinsonian drugs were ineffective despite reported dopaminergic presynaptic denervation in CTX.[2] Our patient's intact dopaminergic presynaptic terminals corresponded with his nonresponsiveness to levodopa.

Furthermore, brain susceptibility-weighted imaging and quantitative susceptibility mapping revealed bilateral iron deposition, which suggests postsynaptic disruption of the striatal

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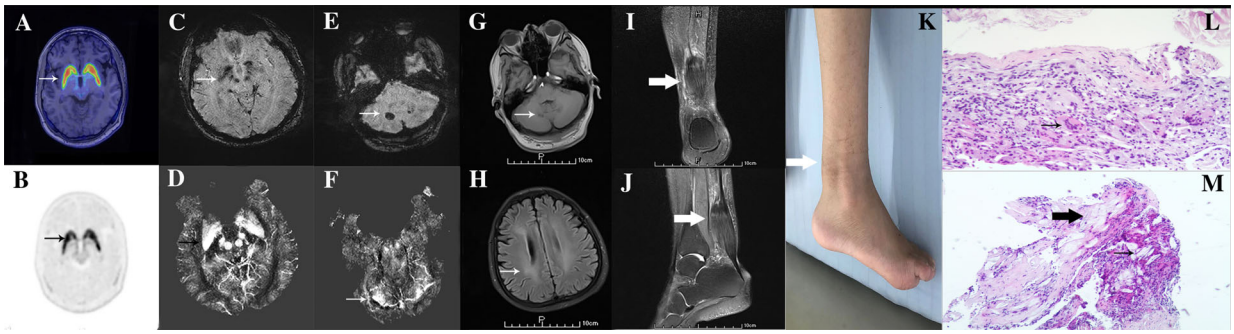

FIG. 1. Imaging results. (**A,B**) [^{18}F]-9-fluoropropyl-(+)-dihydrotetrabenazine positron emission tomography revealed normal striatal uptake of [^{18}F]-9-fluoropropyl-(+)-dihydrotetrabenazine (arrows). Susceptibility-weighted imaging (**C,E**) and quantitative susceptibility mapping (**D,F**) revealed iron deposition within several brain regions (arrows). T1-weighted brain magnetic resonance imaging revealed abnormal, symmetric signals in the cerebellar dentate nucleus (**G**) as well as white matter degeneration (**H**). T1-weighted right-ankle magnetic resonance imaging revealed fusiform thickening (**I,J**; arrows). (**K**) Photograph of the enlarged Achilles tendon. Hematoxylin-and-eosin stained biopsy specimen of the Achilles tendon shows multinucleated giant cells (**L**; arrow), xanthoma cells (**M**; thick arrow), and dispersed lipid crystal clefts (**M**; thin arrow). Magnifications: **G**, 200×; **H**, 100×.

dopaminergic loop as causal to his parkinsonism. Many neurodegenerative diseases, including Parkinson's disease, manifest iron dyshomeostasis.[3] Iron deposition may be a potential predictor of parkinsonism.[4] Excessive neuronal iron deposition potentially induce apoptosis, autophagy, necrosis, or ferroptosis and impair neuronal functions.[5] Our patient's parkinsonian syndrome might have involved postsynaptic iron deposition, but not presynaptic denervation. However, identifying the role of iron deposition in CTX requires further investigation.

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Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

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Disclosures

Ethical compliance statement: This study was conducted in accordance with the principles of the Declaration of Helsinki. The patient gave written informed consent for all treatments and the publication of this case report. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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References

1. Stelten BML, Warrenburg BPCVD, Wevers RA, Verrips A. Movement disorders in cerebrotendinous xanthomatosis. *Parkinsonism Relat Disord* 2019;58:12–16.
2. Makary MS, Kisanuki YY, Amin NN, Slone HW. Teaching neuroimages: cerebrotendinous xanthomatosis: a rare treatable adult-onset lipid storage disease. *Neurology* 2018;90(7):e637–e638.
3. Ndayisaba A, Kaindlstorfer C, Wenning GK. Iron in neurodegeneration–cause or consequence? *Front Neurosci* 2019;13:180.
4. Brar S, Henderson D, Schenck J, Zimmerman EA. Iron accumulation in the substantia nigra of patients with Alzheimer disease and parkinsonism. *JAMA Neurology* 2009;66(3):371–374.
5. Hider RC, Longo DL, Hoffbrand AV. The role of deferiprone in iron chelation. *N Engl J Med* 2018;379(22):2140–2150.