Movement Disorders
CLINICAL PRACTICE

Partially Levodopa-Responsive Parkinsonism in a Carrier of a Novel Pathogenic *CLTC* Variant

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Recently, a girl with parkinsonism and developmental delay associated with a variant in the Clathrin heavy chain polypeptide gene (*CLTC*) and clinical improvement following Selegiline treatment was reported in this journal.[1] Variants in the *CLTC* gene (OMIM 118955) have been associated with variable phenotypes, including developmental delay, hypotonia, epilepsy, and movement disorders.[1–3] *CLTC* encodes the clathrin heavy chain 1 involved in endocytosis, intracellular trafficking, and synaptic recycling.[4]

The patient was born to non-consanguineous parents after an uneventful pregnancy. There was no family history of neurological diseases. She has two healthy elder brothers. She presented with developmental delay and hypotonia in her first year. At the age of 20 months, she had brisk reflexes. Gait was unstable and broad-based. At the age of 4 years and nine months, pes valgus and a shuffling gait were noted. Her developmental milestones were delayed but she attended a regular school with special support. Fine motor skills were noted to be impaired, particularly on the left.

At presentation at the age of 23 years, she was living independently and working in a nursing facility. She reported having developed left-sided weakness and stiffness and trembling in both hands (L > R) over a period of about 1.5 years. She had bilateral bradykinesia, rigidity (L > R) (Video 1 segment 1), bilateral postural arm (L > R) tremor and mild left-sided hemidystonia. Walking was slow with reduced arm swing (L > R), but postural stability was preserved. Cranial MRI at the ages of 21 and 23 showed stable right frontotemporal pachygyria.

Whole-exome sequencing (WES) revealed a heterozygous pathogenic variant [NM_004859.4:c.4686_4687del (p.Glu1564Valfs*48)] in the *CLTC* gene predicted to be subject to nonsense mediated decay, which leads to a loss of function. However, it cannot be ruled out that a residual amount of a truncated protein remains. This variant has not previously been described and was not detected in her parents.

Previously, Baclofen was ineffective. She was taking Tizanidine 2 mg, which had improved limb stiffness. She was started on Levodopa/Benserazide 50/12.5 mg tid. Five months later, on a dosage of 150/37.5 mg, bradykinesia and rigidity had slightly improved and speed of her gait had increased. Also, toe clawing had subsided. However, eight months after starting Levodopa (total daily dosage: 525 mg), she reported reduced effectiveness (Video 1 segment 2). We commenced a treatment with Amantadine. On a daily dosage of 400 mg (200–200 – 0 mg) she reported marked improvement (Video 1 segment 3), which however only lasted for about 4–5 h after intake. On a dosage of 200/50 mg Levodopa/Benserazide tid, she developed dyskinesia (Video 1 segment 4).

This case underscores that pathogenic variants in the *CLTC* gene can cause lateralized parkinsonism and should therefore be added to the growing list of genetically determined parkinsonism.[5] Levodopa-induced dyskinesia developed early after initiation of treatment, so that alternative treatment, for instance, with Amantadine, might be considered. In previous reports, MAO inhibitors, including Selegeline, have also been shown to be helpful in these patients,[1,3]

Author Roles

(1) Clinical care of the patient; (2) Genetic Analysis: A. Execution, B. Review and Critique; (3) Manuscript: A. Writing of the first draft, B. Review and Critique.

T.U.: 1, 2B, 3A
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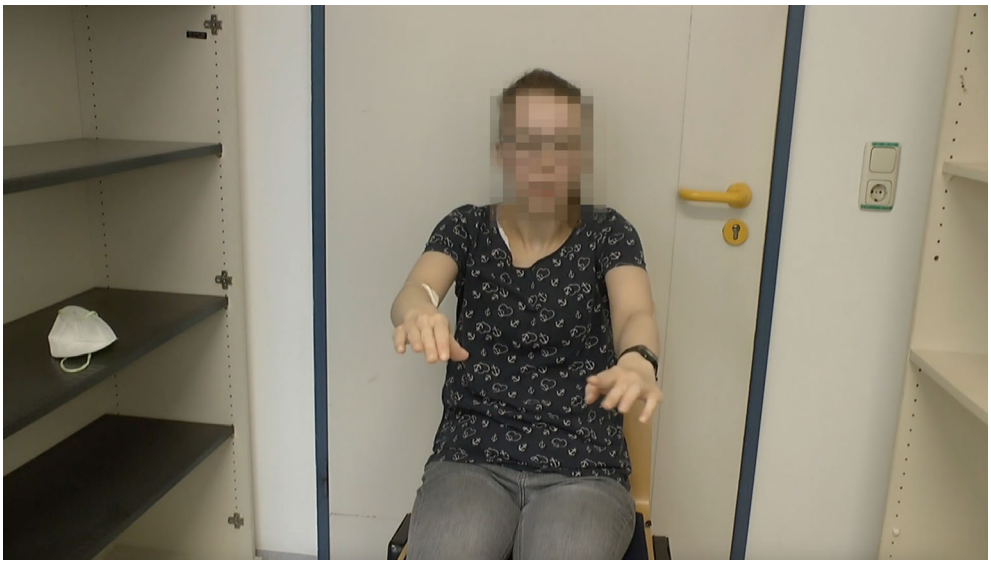

Video 1. Segment 1. This segment shows the patient before Levodopa treatment. When holding out the arms in front of her, she has mild irregular and intermittent postural tremor that is slightly more pronounced on the left. There is severe bradykinesia on the left and moderate bradykinesia on the right, rendering finger tapping nearly impossible on the left. Walking is slow with small steps and reduced arm swing, again clearly more marked on the left. There is mild dystonic posturing of the left arm. Heal-to-toe walking is unimpaired and postural stability is largely preserved. Segment 2. The patient is shown on this segment while taking 200/50 mg – 175/43.75 mg – 150/37.5 mg Levodopa/ Benserazide. Bradykinesia has improved. It is still more pronounced on the left. Walking is faster and steps are larger, but arm swing continues to be markedly reduced on the left. Segment 3. This video was taken at home while she was on 150/37.5 mg – 150/37.5 mg – 150/37.5 mg Levodopa/Benserazide and 200 mg – 200 mg – 0 mg Amantadine. This video would show the best improvement after intake, which occurs 30 min after intake and lasts 4–5 h. There is a further improvement of bradykinesia with less left-sided predominance. Some of the improvement may have been caused by her dancing to music, i.e., acoustically guided motor performance, which is known to improve signs of parkinsonism. Segment 4. Extra movements predominantly appearing choreatic, can be appreciated in this segment showing the patient while she is on 200/50 mg – 200/50 mg – 200/50 mg Levodopa/Benserazide.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14037

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. Patient informed consent has been obtained. 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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