Movement Disorders
CLINICAL PRACTICE
CASE REPORT

Huntington's Disease-like Syndrome as a Rare Presentation of *CACNA1A*-Related Disorder

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Huntington's disease (HD)-like syndromes or HD phenocopies account for around 1% of suspected HD cases and lack pathogenic CAG expansions in *HTT*.[1,2] Although the majority of HD-like patients remain without a molecular diagnosis, recent studies employing next generation sequencing (NGS) have broadened the genetic spectrum associated with this phenotype, identifying on very rare occasions causative variants in a diverse group of genes, including *CACNA1A*.[3–5]

CACNA1A variants are typically associated with familial hemiplegic migraine (FHM), episodic ataxia type 2 (EA2) or spinocerebellar ataxia 6. *CACNA1A* encodes the a_1 subunit of the $Ca_v2.1$ calcium channel, especially abundant in Purkinje cells. Although recent studies have expanded the phenotypic spectrum of *CACNA1A*-related disorders, an HD-like presentation is not a widely-recognized feature of *CACNA1A*-related disease.[6–8]

We presently report a patient with a typical HD-like presentation, who eventually developed episodic and progressive ataxia, and carried a heterozygous causative variant in *CACNA1A*.

Case Report

We present a 65-year-old woman, with a 15-year history of generalized choreiform movements and a family history of similar involuntary movements in her mother. There was no other significant past medical history nor history of alcohol abuse. She was first hospitalized for her movement disorder aged 56 and underwent extensive investigations to rule out secondary causes of chorea, including antiphospholipid antibodies and limbic encephalitis panels, that were unremarkable. Genetic testing for HD came back negative. She was discharged with a diagnosis of generalized chorea of unknown cause on haloperidol drops at a dose of 1 mg three times daily, which led to partial symptomatic improvement.

On examination aged 61, a generalized choreiform and dystonic movement disorder was observed (Video 1). There was mild unilateral cogwheel rigidity, mild difficulty in tandem gait and mildly affected postural reflexes. She had a unified HD rating scale motor score of 20, which is considered a relatively mild score (range 0–124, higher scores indicating more severe impairment). Cognitive testing revealed mild impairment in attention, verbal fluency and visuospatial function with a Montreal cognitive assessment (MoCA) score of 19/30. Further repeat-expansion genetic testing for *C9ORF72*-related disorder, SCA17 and SCA1,2,3,6,7 was negative.[9]

At the age of 65, she was hospitalized for the recent emergence of episodes of dizziness, severe unsteadiness and dysarthria of 4–5 hours duration, with a frequency of 1–2 per month. She was on haloperidol, trihexyphenidyl and clonazepam. On examination, the generalized choreiform and dystonic movement disorder was still present (Video 2). There was also mildly ataxic gait with moderate difficulty on tandem walking, mild dysarthria, broken pursuit, mild dysmetria with mild intention tremor, particularly on the left, and mild dysdiadochokinesis (Video 3). Her cognitive assessment revealed mild deterioration (MoCA, 14/30). Repeat imaging, EEG, and extensive blood and CSF tests were unremarkable. More specifically, there was no evidence of caudate atrophy or ischemic changes on brain MRI.

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VIDEO 1. Patient aged 61 years. Segment 1. Spontaneous choreiform and dystonic movements. Segment 2. Attempting to enhance involuntary movements by asking patient to count backwards.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.70440

VIDEO 2. Patient aged 65 years. Segment 1. Spontaneous choreiform and dystonic movements. Segment 2. Attempting to enhance involuntary movements by asking patient to count backwards.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.70440

During hospitalization, she developed an episode of severe gait ataxia, severe limb dysmetria and exacerbation of cerebellar dysarthria, which lasted 3–4 hours (Video 4). Caffeine consumption was reported on the same morning. The patient retrospectively associated some of the past ataxic episodes with caffeine intake or severe emotional stress.

Following discharge, genetic testing with whole exome sequencing revealed a novel heterozygous, likely-pathogenic, nonsense variant in *CACNA1A* (NM_001127222.2): c.5505G>A, p.(Trp1835Ter), expected to lead to a premature termination codon. Accordingly, a diagnosis of EA2 presenting as a HD phenocopy was reached. Genetic counseling was offered and a trial of acetazolamide recommended.

Discussion

HD-like syndromes are defined by the presence of a movement disorder compatible with HD (typically choreiform, but also relatively pure dystonic or akinetic-rigid); one or more of: family history compatible with autosomal dominant inheritance, behavioral/psychiatric symptoms or cognitive deterioration; and negative molecular testing for HD.[2] Our patient, at presentation, fulfilled the definition of an HD-like syndrome. Subsequently, with the emergence of the episodic nature of ataxic symptoms, the diagnostic possibility of a channelopathy was raised, leading eventually to the identification of a *CACNA1A* causative variant.[10]

Despite the expanding phenotypic spectrum of *CACNA1A*-related disorders, including, beyond EA2 and FHM, epilepsy, progressive ataxia, developmental delay, autism spectrum disorder, psychiatric manifestations and even early-onset paroxysmal dystonia, an HD-like presentation is not a widely-recognized feature of *CACNA1A*-related disease.[6–8] In fact, only two cases of HD-like syndrome with *CACNA1A* variants have been

VIDEO 3. Patient aged 65 years. Segment 1. Mildly ataxic gait. Dystonic and choreiform movements also present. Segment 2. Moderate difficulty on tandem gait. Segment 3. Testing for dysmetria. Segment 4. Testing for intention tremor. Segment 5. Testing for dysdiadochokinesis. Segment 6. Heel along shin slide.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.70440

VIDEO 4. Patient aged 65 years. Ictal and post-ictal video showing episodic ataxia and its resolution. Segment 1. Exacerbated dysarthria. Segment 2. Severe dysmetria and intention tremor. Segment 3. Standing with bilateral support. Segment 4. Ataxic gait with bilateral support. Segment 5. Resolved episode showing independent gait. Segment 6. Resolved episode showing independent stance.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.70440

reported, both from a French HD phenocopy cohort.[4] These cases had a typical HD-like presentation, one subsequently developing a mild cerebellar syndrome and the other pure dysarthria. Neither developed features of episodic ataxia.

The presently identified *CACNA1A* variant, which would not have been picked up on standard SCA6 repeat expansion testing in *CACNA1A*, is a novel nonsense variant, expected to act through a loss-of-function (LoF) mechanism. LoF variants are thought to be often associated with EA2, so the emergence of episodic ataxia in our patient is consistent with the type of variant identified.[7] Interestingly, the *CACNA1A* variants carried by the previously reported patients with HD-like syndrome were missense variants, usually associated with gain-of-function, and did not lead to episodic ataxia. The authors postulated that *CACNA1A* variants might cause an HD phenotype because of a possible interaction with junctophilin 3 in the nanoenvironment of the Cav2 channel shown using a proteomic approach, given that CTG repeat-expansions in junctophilin 3 cause HD-like 2.[4]

In conclusion, the present case expands the phenotypic spectrum of *CACNA1A*-related disorders and the genotypic spectrum of HD-like syndromes and illustrates how the use of NGS in daily clinical practice can identify a growing number of genes that may rarely be associated with unusual neurological phenotypes.

Author roles

(1) Research project: A. Conception, B. Organization, C. Execution. (2) Clinical methodology: A. Design, B. Execution, C. Review and Critique. (3) Genetic analysis: A. Design, B. Execution, C. Review and Critique. (4) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

P.B.: 2B, 4A;
C.P.: 2A, 2B, 2C, 4B;
C.K.: 2A, 2B, 2C, 4B; VC: 2A, 2B, 2C, 4B;
N.R.: 2B, 4B;
C.Kon.: 2B, 2C, 4B;
S.A.: 1C, 2B, 4B;
C.Ka.: 1B, 3B, 3C, 4B;
E.L.: 1B, 1C, 3B, 3C, 4B;
N.T.: 1A, 3A, 4B;
E.A.: 2A, 2B, 2C, 4B;
L.S.: 1A, 1B, 4B;
S.P.: 2A, 2B, 2C, 4B;
G.K.: 1B, 3A, 3C, 4B;
G.Kou.: 1B, 2A, 2B, 2C, 3A, 3C, 4A.

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Disclosures

Ethical Compliance Statement: The study conformed to the Declaration of Helsinki. Written informed consent was obtained from the patient for the performance of genetic studies and participation in the study. Special consent was given for the inclusion of the videos in which the patient may be identified. We confirm that all co-authors 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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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. ■

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