Adult-Onset Movement Disorder Associated with a Pathogenic CACNA1C Variant: Extending the Clinical Spectrum

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Background

The *CACNA* gene family encodes for alpha subunits of voltage-gated calcium channels (VGCCs), which play pivotal roles in muscle contraction, hormone or neurotransmitter release, and gene expression. Particularly, CACNA1C gene encodes the alpha-1 subunit of L-type voltage-gated calcium channels, primarily located in neuronal synapses and dendrites of the brain and cardiac muscles. Although CACNA1C pathogenic variants have been associated with cardiac arrhythmias, neurodevelopmental disorders, autism, mental retardation, and single nucleotide polymorphisms (SNPs) with schizophrenia, depression and bipolar disorder. Movement disorders have not yet been linked to mutations of CACNA1C gene.

Case presentation

A 66-year-old female with a long history of postural tremor (since the age of 30) presented to our outpatient clinic for a worsening of her tremor and the onset of general slowness and cervical pain.

Past medial History: type II diabetes mellitus, history of urinary retention, diabetic polyneuropathy, fatty liver disease, irritable bowel syndrome, major depressive disorder since the age of 20.
Psychiatric fluctuations of major depressive disorder necessitated multiple therapy adjustments (Lyrica, Mirtazapine, Brintellix, Duloxetina were have been combined and interchanged during years)
Family neurological history: one 40-year-old son affected by **essential tremor** since the age of 18.

Neurological evaluation revealed:
- Hypomimia
- Painful tremulous cervical dystonia with right laterocollis e left torticaput
- Bilateral distal symmetric action tremor in upper limbs
- Bilateral asymmetric upper limbs bradykinesia (right>left)
- Plastic rigidity (right>left)

The following instrumental investigations have been proposed:
- **Brain MRI** (mild cortical atrophy and a minute cerebellar ischemic outcome, see Figure 1A)
- **EEG** (unremarkable)
- **Neuropsychological evaluation (**global cognitive decline was observed, with showing significant deficits in verbal and prospective memory, executive functions, and praxis.)

Dopa-responsive dystonia was been excluded thanks to DatSCan (Figure 1B) and testing with LD up to 600 mg per day, which did not result in any clinical changes in neurological symptoms.
A hereditary genetic form was hypothesized.

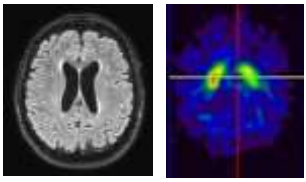

Figure 1. RM (Part A) and DatScan (Part B)

Genetic testing

- Genomic DNA extracted from peripheral blood was analysed by short-read whole-genome sequencing. (Illumina platform)
- Genetic analysis identified an extremely rare heterozygous nonsense variant in the CACNA1C gene (NM_199460.3: c.481C>T; NP_955630.3: p.Arg161*), predicted to introduce a premature stop codon resulting in early protein truncation and causing haploinsufficiency of the protein.

Treatment decisions

Initially, the patient was treated with
- Anticholinergic therapy (Artane up to 6 mg daily) without benefit and discontinued due to side effects.
- Botulinum toxin Dysport (2 attempts, total dose up to 1000 IU) without side effects but without benefits, except for pain relief.

In december 2024 the patient was implanted bilateral GPi deep brain stimulation (DBS), Achieving a marked improvement in the dystonic component and regression of blepharospasm. In June 2025, the device was removed due to an infection of the surgical wound, exacerbated by uncontrolled diabetes, thus losing the benefits obtained and return to oral therapy.

Discussion and conclusions

The CACNA1C gene encodes the 1C subunit of L-type voltage-gated calcium channels, which are crucial for neuronal activity and brain development. Its polymorphisms are linked to various psychiatric and neurological syndromes. This case report describes a presentation not previously documented in the literature, a phenotype where motor manifestation, cognitive imparement and psychiatric issues occur.
This case broadens the phenotypic spectrum within CACNA1C-related disorders.
GPi-DBS may represent a valuable therapeutic option in selected cases.

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