Movement Disorders
CLINICAL PRACTICE
CLINICAL VIGNETTE

Adult-Onset Myoclonus-Dystonia Syndrome Preceding Characteristic Facial Myoclonus in Indian *ADCY5*-related Dyskinesia

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A 21-year-old man presented to us with involuntary jerking movements of his hands and head that started at the age of 13. In the early years, the movements would come in intermittent spells, and sometimes his whole body would tremble when anxious, concentrating on an activity, or riding his scooter. Initially mild, the movements had progressed to moderate severity over the last few years. While he could still do all activities unhindered, and symptoms were mostly an inconvenience, they were increasingly causing him embarassment. Family history was negative, and he had never used alcohol. On examination, myoclonic jerking of the neck and both hands was present at rest and action (Video 1, Segment 1). There was no involvement of face, trunk, or lower limbs, and brain MRI, metabolic testing, EEG, and SSEP were normal. A clinical diagnosis of myoclonus-dystonia (M-D) syndrome was made.

Targeted gene sequencing for a dystonia gene panel revealed a heterozygous missense variation in exon 2 of *ADCY5* gene (chr3:123071310C > T; Depth: 261x), resulting in an amino acid substitution of glutamine for arginine at codon 418 (p.Arg418Gln). This variant (p.R418Q) and a different amino acid substitution affecting the same codon, have previously been reported in patients with *ADCY5*-related dyskinesia.[1]

Two years later, perioral action-induced facial myoclonus was noted (Video 1, Segment 2). Propranolol and clonazepam provided moderate symptomatic relief from myoclonus.

Discussion

ADCY5-related disease causes a young-onset mixed hyperkinetic disorder with chorea/ballism, dystonia, myoclonus (characteristically with a facial predilection), or tremor.[1,2] Episodic worsening, triggered by anxiety, stress, or inactivity, and characteristically, periods before or after sleep (with or without ballistic bouts) may be present.[1,2]

Our patient fulfilled criteria for M-D syndrome,[3,4] including the presence of primarily myoclonic jerks and milder dystonia confined to the upper body, onset before age 18, initially intermittent symptoms, no additional neurological features, normal cognition, and normal neuroimaging. However, the lightning jerks in the cervical region, classic for true *SGCE*-related M-D, were absent. In patients with M-D syndrome, an *SGCE* mutation is found in only 30 to 40% of patients,[4] and the genetic basis of other patients is largely unknown.

On reviewing the phenotypic presentations of previously published *ADCY5* cases,[1,2,other] we could only find two instances where M-D was considered to be a presenting feature by the authors. One, in 1 of 7 cases reported by Chang,[1] and the other, in some members of a recently reported, separate family.[5] However, in both these reports, additional features that are clearly atypical for M-D were present, including chorea,[1] leg and oro-lingual dystonia, speech impairment, facial jerks, and ataxia.[5]

Interestingly, a number of clinical similarities can be noted to exist between the M-D syndrome and *ADCY5*, including a young-onset presentation, craniocervical region myoclonus and/or dystonia, and a benign course. However, additional features in *ADCY5* can include facial myoclonus, oculomotor apraxia, sleep exacerbations, axial hypotonia/developmental delay in children, and paroxysmal episodes (the latter could be an early clue to *ADCY5* in our patient)—all of which are notably absent in M-D.

ADCY5 mutations in residues 418 (as in our patient) and 726 are particularly functionally impactful for pathogenesis,[5] causing a gain-of-function change in *ADCY5* protein, leading to altered dopaminergic striatal signaling.[6]

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In summary, we report M-D as a presentation of *ADCY5*. This case is also the first reported Indian occurrence of any adult-onset movement disorder due to *ADCY5*, and it underscores the importance of considering *ADCY5* in adult Indian patients with hyperkinetic movement disorders.

Author Roles

1. Research Project: A. Conception, B. Clinical Examinations, C. Literature Review, *D. video* Recording and Editing, E. Genetic Testing; 2. Manuscript: A. Writing of the First Draft B. Review and Critique

P.A.A.: 1A, 1B, 1C, 1D, 2A, 2B

V.L.R.: 1C, 1E, 2B

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Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. The patient has given written and informed consent for online publication of his videos. We also 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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Supporting Information

Supporting information may be found in the online version of this article.

Video 1. **Segment 1**: At initial presentation, myoclonic jerks are seen in both hands when outstretched, and when they are held in the wing-beating position. Myoclonic jerking of the neck is also present at rest and is increased with mental distraction with counting numbers, finger tapping, and reciting the alphabet. Subtle dystonic posturing of neck with a turn to the left and occasionally backwards is noted. Myoclonus is also noted in both hands, on walking. **Segment 2**: Two years after initial presentation, facial perioral action-induced myoclonus, induced by speaking, is seen (in addition to previously noted myoclonic jerks of the neck) when the patient is excited (e.g., after being asked to describe his favorite sportsperson).