

ADCY5-Related Dyskinesia: A Genetic Cause of Early-Onset Chorea-Report of Two Cases and a Novel Mutation

Dear Sir,

Chorea is a hyperkinetic movement disorder characterized by abnormal, involuntary, non-rhythmic, non-suppressible movements.^[1] Pathogenic variants in genes such as in *NKX2.1*, *ADCY5*, *PDE10A*, *PDE2A*, *GNAO1* and *OPA3* are known to cause early-onset chorea.^[2] Hereby, we report two children from different families with infantile-onset chorea and developmental delay. There was no nocturnal paroxysmal dyskinesia. Genetic analysis showed well known pathogenic variant in case 1 and novel likely pathogenic in case 2 in *ADCY5* gene. There is paucity of reported cases of *ADCY5*-related dyskinesia from India.

CASE 1

A 7-year-old boy, born of non-consanguineous parentage with normal perinatal history presented with feeding difficulties and abnormal body movements since 1 year of age. Child had difficulty in feeding with choking episodes and drooling since age of 1 year. At one year of age, he developed perioral dyskinesia, brief, random jerky movements of the face and as limbs suggestive of multifocal myoclonus and choreiform movements of limbs; worsening with stress. Symptoms were non-progressive. There was predominant delay in cognitive and social milestones. Family history was non-contributory. On examination, he had generalized choreiform movements at rest that got exacerbated on action. He had perioral dyskinesia and multifocal myoclonic jerks [Video 1]. Motor examination showed axial and limb hypotonia with normal reflexes. There was mild swaying while walking. A clinical possibility of hereditary infantile onset chorea predominant movement disorder was considered like benign hereditary chorea due to pathogenic variants in one of the genes like *NKX2-1*, *PDE10A*, *PDE2A*, *ADCY5* was considered. Routine blood examinations were within normal limits. Serum ammonia, lactate, homocysteine, biotinidase levels and acyl carnitine levels were normal. Brain magnetic resonance imaging (MRI) was normal. Targeted exome analysis revealed a de novo heterozygous previously described [CM1513109; VCV000218354], well known pathogenic variant c.1253G>A [p.Arg418Glu] in exon 2 of *ADCY5* gene confirming the diagnosis. The variant was validated by Sanger sequencing in the proband and was found to be de novo as parents did not harbor the variant.

Child was started on trihexyphenidyl (0.3 mg/kg), clonazepam (0.01 mg/kg) leading to minimal reduction in the chorea.

CASE 2

A 2.5-year-old boy born out of non-consanguineous parentage with normal perinatal history presented with involuntary movements of face and limbs since 1 year of age. The movements were continuous at rest; aggravated by action and during intercurrent infections. There was no exacerbation of movements during sleep. Child had multiple injuries due to falls as a result of these abnormal movements. He has delayed motor and language milestones. Family history was unremarkable. On examination, he had axial and limb hypotonia with normal reflexes. Child had generalized choreiform movements at rest and increasing on action [Video 2]. As the clinical presentation was similar to our first case we upfront considered the possibility of *ADCY5*-related dyskinesia and evaluated him further. Routine blood examinations were normal. Screening for inborn errors of metabolism was negative. Neuroimaging was normal. Clinical exome analysis revealed a novel heterozygous deletion in *ADCY5* gene at position c. 1948-11_1948-2del [genomic coordinate of the variant is chr3:123044311_123044320delTGGAAGACGA (GRCh37/hg19 build) with sequencing depth of 110X]. This deletion at the 3' splice region including the consensus splice acceptor site of intron 7 is predicted to alter the splicing pattern of the transcript by various *In silico* analysis tools. This variant has never been previously reported in the 1000 Genomes, GnomAD, EVS and other databases. The phenotype in the proband very well matches with the disorder caused due to pathogenic variants in this gene *ADCY5*. By considering all the evidences, the variant was considered likely pathogenic pending segregation analysis. Child was started on trihexyphenidyl (0.2 mg/kg), clonazepam (0.01 mg/kg) and tetrabenazine and had mild reduction in the chorea.

ADCY5-related chorea is related to heterozygous missense mutations in *ADCY5* gene identified in 2012. The inheritance is autosomal dominant, with 100% penetrance.^[3] However, few cases of recessive inheritance have been reported.^[4] There are around 60 cases reported worldwide. *ADCY5* encodes adenylyl cyclase 5 enzyme that converts adenosine triphosphate to cyclic adenosine monophosphate. The onset of symptoms varies

from infantile to late adolescent. The initial symptoms include developmental delay, severe axial hypotonia, and dyskinesias. The dyskinetic movements include chorea, athetosis, dystonia, or myoclonus or a combination involving face and limbs which occur as episodic phenomenon or continuous. The severity and frequency of episodic dyskinesia worsens over a time till third decade of life wherein it may completely resolve or become constant. Episodes of “ballistic bouts” during drowsiness or sleep or on awakening and nocturnal painful paroxysmal dyskinesias can occur. These are characterized by painful truncal dystonic movements, retrocollis, and upperlimb dystonia. This has been hypothesized to result from gain of function mutation causing increased adenylyl cyclase 5 activity and thereby increased arousal in sleep and abnormal motor activity in the form of dyskinesia.^[5] The loss of function pathogenic variants has been described in literature like our case-2.^[6] The less common phenotype includes sleep predominance, chorea predominance, myoclonus-dystonia predominance, and alternating hemiplegia predominance.^[5] The neuropathological examination has shown widespread (mixed 3R/4R) tau pathology, including neurofibrillary tangles, neuritic tau, and glial tau deposition involving the cerebral cortex, midbrain, thalamus, and hippocampus.^[7]

The first reported pathogenic variant in *ADCY5* gene was p.A726T mutation and is associated with mildest disease.^[3] This was followed by the identification of the missense pathogenic variant p.R418W. The mutations p.R418W or p.R418Q cause moderate to severe disorder with axial hypotonia, limb hypertonia, paroxysmal nocturnal or diurnal dyskinesia, chorea, myoclonus, and intermittent facial dyskinesia.^[8] Carecchio M *et al.* (2015) reported 5 cases of *ADCY5* mutation wherein three patients carried the p. R418W mutation, one the p. R418Q and one the p. R418G mutation.^[9] There are 3 reported cases from India. Wali GS *et al.* (2020) from India reported a patient with change in the movement disorder phenotype from continuous fidgety movements involving the face and arms at the age of 1 year, “ballistic bouts” that appeared 10 to 15 times per days at second year of age to generalized dystonia with contractures and axial hypotonia by early third decade with de novo missense variant c. 3086T > A; p.Met1029Lys.^[10] Our first patient also had p.R418Q mutation who presented with developmental delay, axial hypotonia and infantile-onset choreoathetosis and myoclonus involving face and limbs. The second case was a novel heterozygous deletion at position c.1948-11_1948-2del altering the splicing pattern of the transcript. The medical management of dyskinesia includes trihexyphenidyl, tetrabenazine, clonazepam, propranolol, levocarnitine, melatonin, chlorthalidopoxide and methylphenidate. The pallidal deep brain stimulation has shown to offer modest improvements for the hyperkinetic movements. Caffeine has been shown to reduce nocturnal dyskinetic episodes.

ADCY5-related dyskinesia is a rare genetic disorder and has to be suspected in patients with infantile to childhood onset mixed hyperkinetic movement disorder (facial chorea, generalized chorea, myoclonus, and dystonia) with characteristic nocturnal exacerbations and dramatic fluctuations in frequency and severity of movements with little or no progression; with or without

mild cognitive impairment, in the background of developmental delay and normal neuroimaging. These cases of *ADCY5*-related hyperkinetic movement disorder are often misdiagnosed as dyskinetic cerebral palsy. A high index of suspicion is necessary.

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Conflicts of interest

There are no conflicts of interest.

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Videos available on: www.annalsofian.org

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