Pearls & Oy-sters: SCA21 Due to *TMEM240* Variation Presenting as Myoclonus Dystonia Syndrome

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Neurology® 2022;99:531-534. doi:10.1212/WNL.0000000000201015

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Abstract

Spinocerebellar ataxia 21 due to *TMEM240* disease-associated variation characteristically presents insidiously with a delay in language, motor, and social skill acquisition. The condition typically progresses to severe cognitive impairment. We report a patient with SCA21 who presented with myoclonus dystonia (M-D) syndrome and whose dystonia showed a modest response to levodopa. Affected family members (mother and sibling of the proband) also had a similar phenotype. Neuropsychology evaluation of the proband and afflicted family members revealed moderate impairments in attention, executive function, short-term and episodic memory, and marked impairments in planning, abstract reasoning, language, and visuospatial functions. Normal EEG, α-fetoprotein levels, and somatosensory evoked potentials helped to delineate SCA21 from other differential diagnoses. Motor impairment, pyramidal signs, and sensory impairment are usually absent in SCA21. This case highlights the importance of genetic testing in patients with M-D syndrome and supports a trial of levodopa for patients with dystonia from SCA21 due to *TMEM240* variation.

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Videos

Pearls

- Spinocerebellar ataxia (SCA) 21 due to *TMEM240* disease-associated variation manifests insidiously, as a delay in acquisition of language, motor, and social skills later progressing to severe cognitive impairment
- SCA21 can present with myoclonus dystonia (M-D) syndrome, and *TMEM240* gene testing should be considered in patients presenting with such phenotypes
- Normal EEG, α-fetoprotein levels, and somatosensory evoked potentials help to delineate SCA21 from other diagnoses
- A trial of levodopa is advised for dystonia due to *TMEM240* variation

Oy-sters

- Ataxia may be conspicuously lacking in SCA21 unlike in the other known autosomal dominant SCAs
- Motor impairment, pyramidal signs, fasciculation, and sensory impairment are usually absent in SCA21
- SCA21 presenting with an M-D phenotype may be mistakenly attributed to disease-associated variations in *SGCE* (epsilon-sarcoglycan), especially in the setting of dominant family history

Case Report

A 17-year-old girl (proband), third child of nonconsanguineous parentage, with mild global developmental delay, presented with jerky tremors of bilateral distal upper extremities since 3 years of age. She was scholastically poor and subsequently developed posturing of her right hand while writing. Since 14 years of age, her neck was rotated toward the right with head tremor on attempted correction. She was treated with escitalopram and clonazepam for social

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phobia, anxiety, and depression at 15 years of age. Dopamine blockers were never used. Clinical examination revealed right torticollis (Video 1), dystonia of bilateral upper limbs, with superimposed spontaneous and action-induced upper limb myoclonus characteristic of M-D syndrome. The head tremor, which became more evident on attempted correction by turning toward the left, suggested the presence of a null point, favoring cervical dystonia. She also had slow saccades and intellectual disability without any pyramidal, cerebellar, or sensory dysfunction. Family history revealed an affected mother (46 years old) and elder brother (21 years old) of the proband. Both had a milder phenotype with similar intellectual disability and upper extremity myoclonus (Video 2) though of lesser intensity. Both were independent in their daily activities and drug naive. Pedigree suggested an autosomal dominant inheritance pattern.

The differential diagnosis of M-D syndrome includes genetic disease-associated variations in *SGCE* (epsilon-sarcoglycan), *ATM* (ataxia telangiectasia mutated) causing variant ataxia telangiectasia (A-T), *ADCY5* (adenyl cyclase 5), *RELN* (reelin), *GCH1* (GTP cyclohydrolase I), *ANO3* (anoctamin 3, previously DYT24), *GNAL* (guanine nucleotide-binding protein G [olf], subunit α, previously DYT25), and *PRKCG* (protein kinase C gamma causing SCA14).

Her blood investigations (hemogram, biochemistry, liver and renal functions, and thyroid and parathyroid hormone profile) were normal ruling out metabolic, endocrine, and organ dysfunction. Brain MRI (Figure), including susceptibility-weighted images were normal. EMG recordings of the proband showed irregular, myoclonic bursts, which worsened on sustained posture (arms outstretched) and action. The jerk duration ranged from 20 to 100 milliseconds (ms), maximum 200 ms, and there was no definite stimulus sensitivity. Neuropsychology evaluation showed frontal dysfunction with a Montreal Cognitive Assessment score of 15/30. Her verbal IQ of 69 was lower than her performance IQ of 74.

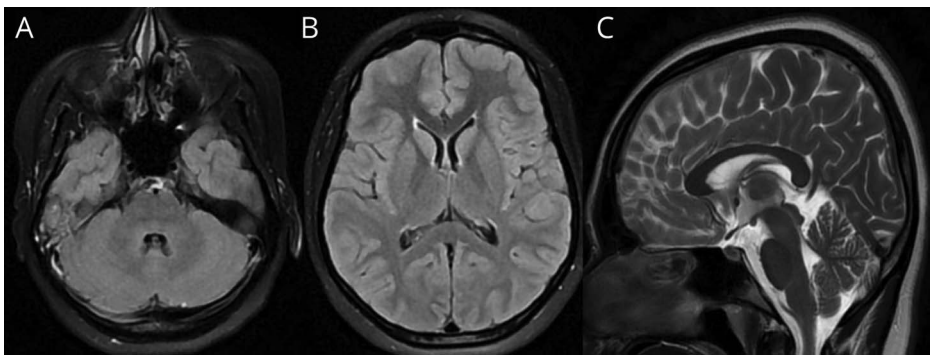
Although *SGCE* variations are the most common for M-D phenotype, slow saccades, significant subnormal intelligence, and maternal inheritance made it less likely because of genomic imprinting. Patients with *RELN* variation can resemble those with *SGCE* variation including similar psychiatric abnormalities and alcohol responsiveness, except that they may be older at onset and have a milder disease course. Normal serum α-fetoprotein, immunoglobulin levels, absent telangiectasia, and possible autosomal dominant inheritance did not favor variant A-T.[1] Saccadic abnormalities may be seen in *ADCY5* variation; however, lack of facial dyskinesia, no nocturnal aggravation of movement disorder, and absence of episodic painful dystonic posturing aggravated by stress or illness ruled against this diagnosis. Normal EEG and somatosensory evoked potentials eliminated progressive myoclonic epilepsy syndrome.

Whole-exome sequencing revealed a pathogenic heterozygous missense variation in exon 3 of the *TMEM240* gene (chr1: g.1535766C>T; depth: 164×) that results in the amino acid substitution of arginine for glycine at codon 66 (p.Gly66Arg; ENST00000378733.9). The observed variation lies in the transmembrane protein 240 (TMEM240) family domain and has previously been reported in patients affected with SCA21.[2] She was initiated on levodopa and clonazepam and had symptomatic improvement, which was noted 6 weeks after commencement of treatment.

Discussion

Initially described in patients of French ancestry, SCA21 is typically characterized by slowly progressive early onset (1–30 years) cerebellar ataxia, delayed psychomotor development, and cognitive impairment due to disease-associated variations in the *TMEM240* gene, which codes for a strongly conserved transmembrane protein of unknown function present in the cerebellum and brain.[3] Although tremor/myoclonus of upper extremities and slow saccades have been documented,[2,3] here we report the case of a *TMEM240* disease-associated variations, presenting with M-D syndrome and cognitive impairment in the absence of cerebellar ataxia. In Asia, SCA21 has been reported from China[4] and Japan.[5] Although disease-associated variations in *TMEM240* were found to be fully penetrant in the

Figure Axial T2 Fluid Attenuated Inversion Recovery (A and B) and T2 Sagittal Sections (C) of the Brain Were Normal



majority of families, de novo variations occur indicating the presence of spontaneous events in this telomeric region of chromosome 1.[3] In our case, other family members did not undergo genetic testing because of financial constraints.

M-D syndrome usually presents in childhood, mostly involving the upper body and extremities,[6] often associated with *SGCE* gene variations. A subset of patients with M-D can present with a postural tremor of the upper limbs, which is often clinically indistinguishable from high-frequency myoclonic jerks. Electrophysiologic studies can be a valuable tool in such ambiguous cases. The expanding lists of causative genes implicated in M-D syndrome include *ADCY5, ANO3, GCH1, GNAL, GNB1, KCTD17, NKX2-1, PRKCG, TH, TTPA,* and *TUBB2B*.[6] All these genes are involved in various physiologic pathways and cause a myriad of clinical manifestations, although certain clinical clues help in identifying the gene causing the M-D phenotype (Table). Among autosomal dominant ataxias, variations in the protein kinase C gamma gene (*PRKCG*) on chromosome 19q causing SCA14 have been documented to exhibit M-D phenotype in Dutch and Japanese pedigree.[7]

The underlying pathophysiology of M-D may be related to striatal monoamine neurotransmission dysfunction or disruption of cerebellothalamic networks (possibly via a GABAergic deficit of Purkinje cells),[6] and functional imaging, molecular, and neurophysiologic studies depict predominant involvement of cerebellothalamic pathways.[8] Amelioration of M-D motor signs with alcohol, a classic feature of *SGCE*, may occur by increasing GABAergic transmission in Purkinje cells. However, the response of M-D to globus pallidus internus deep brain stimulation (GPi-DBS) supports the role of striatal signaling in

Table Differential Diagnosis of Myoclonus Dystonia With Differentiating Features

Gene (gene product)	Differentiating features in the myoclonus dystonia phenotype
TMEM240 **(transmembrane protein 240)**	• AD, childhood or adolescent onset, mildly progressive course, with no alcohol responsiveness • Myoclonus of UE + dystonia of the neck and UEs • Moderate to severe cognitive impairment present in all • Ataxia, slow saccades can be present • May respond to levodopa
PRKCG **(protein kinase C gamma type) known as SCA14**	• AD, childhood or adolescent onset, mildly progressive course, with no alcohol responsiveness • Myoclonus of the neck/UEs + dystonia of the neck • Psychiatric abnormalities and no alcohol response • Gait and limb ataxia, progressive course
ATM **(*ATM* kinase protein)**	• AR, adolescent onset, mildly progressive course, with no alcohol responsiveness • Myoclonus of the neck + dystonia of the neck and UEs • Ataxia, telangiectasia, oculomotor apraxia, and immunodeficiency can be present in up to half the subjects • Milder degrees of supranuclear eye movement abnormalities (slow or hypometric saccades), parental consanguinity, and modest elevation in serum α-fetoprotein
SGCE **(epsilon-sarcoglycan)**	• AD, adolescent onset; myoclonus of UEs (proximal > distal) and the neck • Myoclonus more prominent and debilitating than dystonia, psychiatric abnormalities, and exquisite alcohol response
Maternal uniparental disomy (mUPD7)	• Features similar to epsilon-sarcoglycan (same chromosome 7) • Short stature, triangular facies, postnatal growth retardation, association with Silver-Russell syndrome
ADCY5 **(adenyl cyclase 5)**	• AD, first decade onset; dystonia is often generalized and progressive • Saccadic abnormalities may be seen • Nocturnal aggravation of movement disorder, facial dyskinesia, axial hypotonia, delayed milestones, dysarthria, and episodic painful dystonic posturing aggravated by stress or illness
RELN **(reelin)**	• AD, third decade onset • Psychiatric abnormalities and response to alcohol similar to epsilon-sarcoglycan patients though with a milder disease course • Enhanced startle, later age at onset
GNAL **(guanine nucleotide-binding protein G(olf), subunit α) known as DYT 25**	• AD, fourth decade onset with a progressive course • No alcohol responsiveness or psychiatric features • Myoclonus of UEs; dystonia of the neck, oromandibular region, larynx associated with tremor of the head, UEs
ANO3 **(anoctamin 3) known as DYT 24**	• AD, first to fourth decade onset, slowly progressive • Myoclonus affects the neck and UEs • Dystonia involves cervical, oromandibular region, larynx, blepharospasm • Tremor affecting the head, UEs >> voice
GCH1 **(GTP cyclohydrolase I)**	• AD, first decade onset • Myoclonus onset in UEs, then spreading to LLs, the face, trunk plus dystonia in the neck and UEs • Parkinsonian features and excellent response to levodopa

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; UEs = upper extremities.

its pathophysiology.[9] In autopsy-proven SCA21,[5] the cerebellar cortex shows severe loss of Purkinje cells (PCs) with Bergmann gliosis, and the remaining PCs are atrophic, lacking somatic sprouts, possibly implying a GABAergic deficit.

TMEM240 gene product, a transmembrane protein, is expressed highest in the cerebellum, followed by the dentate gyrus, putamen, and caudate nucleus. The majority of patients with *SGCE* (encoding a transmembrane protein epsilon-sarcoglycan) and *TMEM240* variation have associated psychiatric symptoms[3] similar to those of our patient. The emotional and behavioral symptoms that characterize the cerebellar affective changes occur within the domains of attentional control and emotional control, a form of dysmetria of thought applied to intellectual function and emotional processing.[10] This has been termed cerebellar cognitive affective syndrome (CCAS) characterized by impairments in executive, visuospatial, linguistic functions and changes in affect, which reflect loss of connections between the cerebellum and associative/paralimbic regions of the cortex that are essential for normal development. SCA1, 2, 3, and 6 can also have impaired visual attention and memory, color discrimination, sequencing abilities, visuospatial/constructional processing, verbal memory and fluency, frontal attention, and executive function as part of CCAS.[10]

SCA21 is a multifocal neurodegenerative disease extending beyond cerebellar dysfunction. Extracerebellar oculomotor disturbances (slow horizontal saccades) suggest affliction of paramedian pontine reticular formation, hyporeflexia and pyramidal signs imply peripheral nerve and corticospinal tract involvement, respectively.[3] SCA21, unlike other SCAs, is a nonrepeat expansion SCA. Missense variations of the *TMEM240* gene support the gain-of-function hypothesis in SCA21. Among the plasma membrane proteins implicated in SCAs, disease-associated variations in the *KCNC3* (potassium channel subtype) and *ITPR1* (inositol triphosphate receptor) cause SCA13 and SCA15, respectively, and SCA5 is caused by variations in β-III spectrin, which normally plays a role in stabilizing a glutamate transporter in Purkinje cells.[11] Because the TMEM240 protein is a membrane-spanning protein, it too could be involved in modulating ion channel function at the neuronal cell membrane.

In conclusion, M-D syndrome can be a new clinical phenotype of SCA21, and awareness is required to differentiate it from the more commonly implicated genes.

Acknowledgment

The authors acknowledge Ms. Mary Glenda for assisting in videography of the patient.

Study Funding

No targeted funding reported.

Disclosures

The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* October 3, 2021. Accepted in final form June 10, 2022. Submitted and externally peer reviewed. The handling editor was Roy Strowd III, MD, Med, MS.

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Neurology 2022;99;531-534 Published Online before print July 8, 2022
DOI 10.1212/WNL.0000000000201015