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

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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.

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
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), ADCYS (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 ADCYS 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 China4 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
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), and functional imaging, molecular, and neurophysiologic studies depict predominant involvement of cerebellothalamic pathways. 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

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<th>Gene (gene product)</th>
<th>Differentiating features in the myoclonus dystonia phenotype</th>
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| 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 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 alpha-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 |
| ADCYS (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 a) 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.\textsuperscript{9} In autopsy-proven SCA21,\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{5} 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 SCAS is caused by variations in β-III spectrin, which normally plays a role in stabilizing a glutamate transporter in Purkinje cells.\textsuperscript{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.

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**References**

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