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

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Abstract
Spinocerebellar ataxia (SCA) 21 due to TMEM240 mutation 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, 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 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 electroencephalogram, alpha-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 mutation.

Pearls
- Spinocerebellar ataxia (SCA) 21 due to TMEM240 mutation 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 electroencephalogram (EEG), alpha-fetoprotein levels, and somatosensory evoked potentials help to delineate SCA21 from other diagnoses
- A trial of levodopa is advised for dystonia due to TMEM240 mutation
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 a M-D phenotype may be mistakenly attributed to mutations in SGCE (epsilon sarcoglycan) especially in the setting of dominant family history

Case report
A 17-year-old girl (proband), third child of non-consanguineous 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 towards 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 towards 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-year-old) and elder brother (21-year-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 naïve. Pedigree suggested an autosomal dominant inheritance pattern.

The differential diagnosis of M-D syndrome includes genetic mutations 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, thyroid and parathyroid hormone profile) were normal ruling out metabolic, endocrine and organ dysfunction. Brain magnetic resonance imaging (MRI) (figure 1), including susceptibility weighted images (SWI) were normal. Electromyography (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 millisecond (msec), maximum 200 msec, and there was no definite stimulus sensitivity. Neuropsychology evaluation showed frontal dysfunction with a Montreal cognitive assessment score of 15/30. Her verbal intelligence quotient (IQ) of 69 was lower than her performance IQ of 74.

Though SGCE mutations are the most common for M-D phenotype, slow saccades, significant subnormal intelligence and maternal inheritance made it less likely due to genomic imprinting. Patients with RELN mutation can resemble those with SGCE mutation including similar psychiatric abnormalities and alcohol responsiveness, except they may be older at onset and have a milder disease course. Normal serum alpha-fetoprotein, immunoglobulin levels, absent telangiectasia, and a possible autosomal dominant inheritance did not favor variant A-T. (1) Saccadic abnormalities may be seen in ADCY5 mutation; 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 (PME) syndrome.

Whole exome sequencing revealed a pathogenic heterozygous missense variation in exon 3 of the \textit{TMEM240} gene (chr1:g.1535766C>T; Depth: 164x) 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 six 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 mutation in \textit{TMEM240} gene which codes for a strongly conserved
transmembrane protein of unknown function present in cerebellum and brain (3). Though
tremor/myoclonus of upper extremities and slow saccades have been documented (2,3), here we
report the case of a \textit{TMEM240} mutation, 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 mutations in \textit{TMEM240} were found to be fully penetrant in majority
families, \textit{de novo} mutations 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
due to financial constraints.
M-D syndrome usually presents in childhood, mostly involving the upper body and extremities (6) often associated with SGCE gene mutations. A subset of M-D patients can present with a postural tremor of the upper limbs, which is often clinically indistinguishable from high-frequency myoclonic jerks. Electrophysiological 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, GNL1, GNB1, KCTD17, NKX2-1, PRKCG, TH, TTPA and TUBB2B (6). All these genes are involved in various physiological pathways and cause a myriad of clinical manifestations, though certain clinical clues help in identifying the gene causing M-D phenotype (Table 1). Among autosomal dominant ataxias, mutations 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 neurophysiological studies depict predominant involvement of the 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 its pathophysiology. (9) In autopsy proven SCA21 (5), cerebellar cortex shows severe loss of Purkinje cells (PCs) with Bergmann’s 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 dentate gyrus, putamen, and caudate nucleus. The majority of patients with SGCE
(encoding a transmembrane protein epsilon-sarcoglycan) and \textit{TMEM240} mutation have associated psychiatric symptoms (3) similar to 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 as cerebellar cognitive affective syndrome (CCAS) characterized by impairments in executive, visuospatial, linguistic functions and changes in affect which reflect loss of connections between 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 nerves and corticospinal tract involvement respectively. (3) SCA21, unlike other SCAs, is a non-repeat expansion SCA. Missense mutations of \textit{TMEM240} gene supports the gain-of-function hypothesis in SCA21. Among the plasma membrane proteins implicated in SCAs, mutations in the \textit{KCNC3} (potassium channel subtype) and \textit{ITPR1} (inositol triphosphate receptor) cause SCA13 and SCA15 respectively, and SCA5 is caused by mutations in β-III spectrin, which normally plays a role in stabilizing a glutamate transporter in Purkinje cells. (11) As the \textit{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.

### Table 1: Differential diagnosis of myoclonus dystonia with differentiating feature

<table>
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<tr>
<th>Gene(Gene product)</th>
<th>Differentiating features in 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 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 neck/UEs + dystonia of 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 neck + dystonia of 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, modest elevation in serum α-fetoprotein |
| **SGCE (epsilon sarcoglycan)** | • AD, adolescent onset; myoclonus of UEs (proximal> distal) and 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 & progressive  
  • Saccadic abnormalities may be seen |

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<table>
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<tr>
<th>Disorder</th>
<th>Clinical Features</th>
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<tr>
<td>Nocturnal aggravation of movement disorder, facial dyskinesia, axial hypotonia, delayed milestones, dysarthria, episodic painful dystonic posturing aggravated by stress or illness</td>
<td><strong>RELN</strong> (Reelin)</td>
</tr>
<tr>
<td>AD, third decade onset</td>
<td><strong>Psychiatric abnormalities and response to alcohol similar to epsilon sarcoglycan patients though with a milder disease course</strong></td>
</tr>
<tr>
<td><strong>Enhanced startle, later age of onset</strong></td>
<td><strong>GNAL</strong> (Guanine nucleotide binding protein G(olf), subunit α) known as DYT 25</td>
</tr>
<tr>
<td>AD, fourth decade onset with progressive course</td>
<td><strong>No alcohol responsiveness or psychiatric features</strong></td>
</tr>
<tr>
<td><strong>Myoclonus of UEs; dystonia of neck, oromandibular region, larynx associated with tremor of head, UEs</strong></td>
<td><strong>ANO3</strong> (Anoctamin 3) known as DYT 24</td>
</tr>
<tr>
<td>AD, first to fourth decade onset, slowly progressive</td>
<td><strong>Myoclonus affects neck, UEs</strong></td>
</tr>
<tr>
<td><strong>Dystonia involves cervical, oromandibular region, larynx, blepharospasm</strong></td>
<td><strong>Tremor affecting head, UEs &gt;&gt; voice</strong></td>
</tr>
<tr>
<td><strong>GCH1</strong> (GTP cyclohydrolase I)</td>
<td><strong>AD, first decade onset</strong></td>
</tr>
<tr>
<td><strong>Myoclonus onset in UEs, then spreading to LLs, face, trunk plus dystonia in neck, UEs</strong></td>
<td><strong>Parkinsonian features and excellent response to levodopa</strong></td>
</tr>
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AD = autosomal dominant; AR = autosomal recessive; UEs = upper extremities

**Legend to Fig 1:** Axial T2 FLAIR (a,b) and T2 sagittal sections of the brain was normal.
Legend to Video: Video 1- Video shows proband with cervical dystonia with neck rotated to right with dystonic tremor. There was dystonia and dystonic tremor of distal upper extremities with superimposed action-induced myoclonus. There was no appendicular or gait ataxia. Vertical and horizontal saccades were slow.

Video 2 - segments a and b shows mother and sibling of proband respectively with dystonia and dystonic tremor of distal upper extremities with myoclonus and hypometric saccades without appendicular or gait ataxia.

Video 1 - http://links.lww.com/WNL/C183
Video 2 - http://links.lww.com/WNL/C184

References


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