Novel *SGCE* Mutation in a Patient With Myoclonus-Dystonia

A Case Report

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Abstract

Objectives

Characterize the presentation, workup, and management of *SGCE* myoclonus-dystonia, a rare genetic condition, in a patient with atypical presenting symptoms and no family history of movement abnormalities.

Methods

A woman with myoclonus and dystonia was identified based on clinical history and physical examination. Workup was conducted to determine the cause of her symptoms, including whole-exome sequencing. Myoclonus-dystonia is associated with more than 100 distinct mutations in MYC/DYT-*SGCE* that account for only half of the total myoclonus-dystonia patients. As such, this case required intensive genetic analyses rather than screening only for a small subset of well-characterized mutations.

Results

Childhood onset myoclonus and worsening dystonia with age were identified in a young woman. She underwent screening for common causes of twitching movements, followed by whole-exome sequencing which identified a de novo novel variant in the *SGCE* gene, resulting in a diagnosis of *SGCE* myoclonus-dystonia.

Discussion

Myoclonus-dystonia should be considered in patients with symptoms of head and upper extremity myoclonus early in life, especially with co-occurring dystonia, even in the absence of a family history of similar symptoms. Diagnosis of this condition should take place using sequencing, as new mutations continue to be discovered.

Introduction

SGCE myoclonus-dystonia, also known as DYT11, is classically caused by autosomal dominant pathologic variants in the epsilon-sarcoglycan (*SGCE*) gene, which was recently recategorized MYC/DYT-*SGCE* (OMIM: 159900).[1-3] The condition tends to present in late childhood with predominantly upper extremity dystonia characterized by "writer's cramp" and cervical dystonia.[4] Myoclonus of the upper body follows the onset of dystonia,[4] and stress or exercise exacerbate the symptoms. Myoclonus and dystonia less commonly affect the lower body in patients with *SGCE* myoclonus-dystonia.[5] Psychiatric comorbidities, particularly obsessive-compulsive disorder (OCD), anxiety, and alcohol use disorder, frequently accompany *SGCE* myoclonus-dystonia.[4] Symptomatic relief related to alcohol ingestion may contribute to habitual increase in consumption and alcohol use disorder.[1]

More than 100 pathogenic variants in the MYC/DYT-*SGCE* gene on chromosome 7q21 have been identified in patients with myoclonus-dystonia.[4] The majority of affected individuals display paternal inheritance because MYC/DYT-*SGCE* undergoes maternal allele silencing due to genomic imprinting.[6] As a result, less than 5% of patients with myoclonus-dystonia express a maternally inherited mutation in MYC/DYT-*SGCE*.[1] The remaining individuals may have de novo mutations. We present the case of a 23-year-old woman with 13 years of symptoms consistent with myoclonus-dystonia who was found to have a de novo T173C mutation causing an F58S substitution.

Clinical Report

A 23-year-old otherwise healthy woman presented with a 13-year history of difficulties with balance, subtle startle myoclonus, and writer's cramp. Her symptoms began around age 10 years with rapid head "tics" that primarily occurred when she was touched by others while distracted, for example, while she was playing piano, although she did not have a prominent startle response. Home videos from this time demonstrated sustained small amplitude tilting and extension of the neck during periods of focus, without evidence of tremor. She developed obsessive thoughts, was diagnosed with OCD, and was treated with venlafaxine.

During her late teens, she noticed difficulty tapping her feet, running on a treadmill, and stepping on an escalator. She denied falls but had occasional near-falls due to difficulty coordinating her legs. Her walking speed did not change. At the same time, she noted that prolonged writing caused cramping in her dominant hand and that her handwriting worsened the longer she wrote. She would occasionally drop objects from her hand. She presented to a pediatric neurologist who suspected a tic disorder and prescribed clonidine which did not improve her symptoms.

Her condition progressed in her early 20s when she developed full-body myoclonic jerks that occurred approximately weekly and worsened in the cold. She also identified bothersome persistent cramping and tightness of her neck. She denied improvement of her cramping or jerks with alcohol, and symptoms did not vary with the time of day. She additionally endorsed talking in her sleep. She saw multiple neurologists in her early 20s and was treated with propranolol, clonazepam, guanfacine, benztropine, and tizanidine, all without improvement. She was subsequently treated with botulinum toxin injections with some improvement of neck movements.

At age 23 years, she presented to our center, at which time she was noted to have generalized dystonia affecting her neck, trunk, and bilateral hands that was particularly worse with action, as well as generalized myoclonus involving her trunk and bilateral upper extremities at rest that increased with action (2 and 3 on the Unified Myoclonus Rating Scale, respectively). In addition, she had brisk deep tendon reflexes throughout the upper and lower extremities (3+). She started carbidopa-levodopa without improvement in her symptoms and continued to receive botulinum toxin injections for cervical dystonia with moderate benefit.

Family history demonstrated no relatives with similar symptoms. She is of German ancestry. She had a maternal grandmother with epilepsy. Her father was adopted and had sarcoidosis. Her mother and 2 brothers were healthy. Neither the patient nor her brothers have children (Figure).

Evaluation

Her childhood workup included unremarkable blood chemistries and an EEG that showed no epileptiform discharges.

Figure Pedigree of Patient With *SGCE* Myoclonus-Dystonia
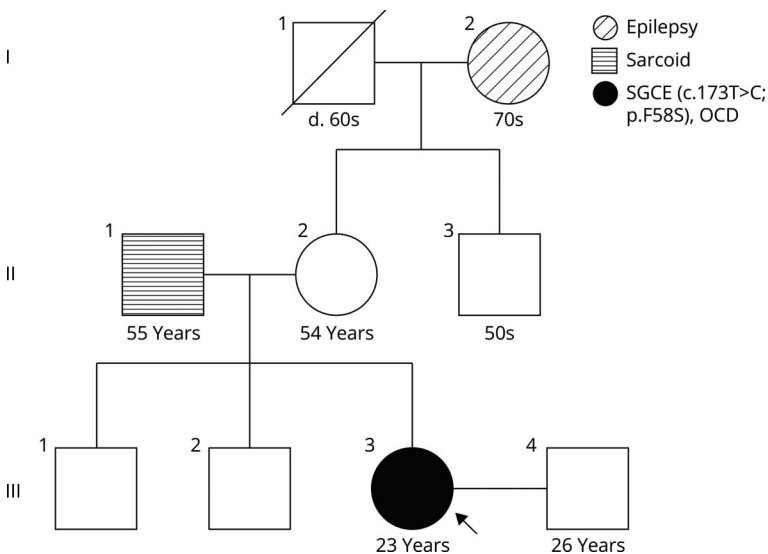
The proband (III-3) developed startle myoclonus and dystonia of the legs and hands at approximately age 10 years, which worsened over time. No other individuals in the family were known to have similar symptoms, and neither parent was a carrier of the identified mutation. The proband's father (II-1) has an unknown family history due to adoption. Unrelated conditions in the family include epilepsy in the maternal grandmother (I-2) and sarcoid in the father (II-1).

The serum ceruloplasmin level was normal at 20 mg/dL, prior Huntingtin gene testing was reportedly unremarkable, and brain and cervical spine MRI were normal.

She underwent whole-exome sequencing using the XomeDx-Plus Trio clinical exome sequence analysis through GeneDx. The results were notable for a heterozygous T to C variant at residue 173 of the MYC/DYT-SGCE gene, causing a F58S substitution in the last amino acid in exon 2 at the border of intron 3. Neither parent carried the identified variant.

Discussion

This patient was diagnosed with SGCE myoclonus-dystonia, with concomitant OCD, due to a novel de novo missense mutation. Although functional implications of this novel variant are unknown, it is classified as likely pathogenic (ACMG guidelines): the mutation arose de novo, nearby missense mutations involving residue H60 within the same beta-pleated sheet of the topological domain of MYC/DYT-SGCE have been implicated in decreased protein stability and subsequent degradation,[7] and a single mutation in the same residue (F58L) was previously identified as likely pathogenic. Symptomatic management of myoclonus-dystonia due to a mutation in MYC/DYT-SGCE relies largely on antiepileptic treatment of the myoclonus, with separate therapy for focal dystonia. First-line treatment for myoclonus includes zonisamide, benzodiazepines, levetiracetam, or valproate.[4] Anticholinergic medications and botulinum toxin are often used for dystonia.[1] For more generalized presentations, carbidopa-levodopa or sodium oxybate have been used. More recently, deep brain stimulation (DBS) targeting the globus pallidus internus (GPi) or the ventral intermediate nucleus of the thalamus has been described for more severe cases.[8] Zonisamide did not substantially improve this patient's persistent leg cramping or myoclonus and was discontinued due to fatigue. She continued botulinum toxin injections for cervical dystonia with partial response. DBS targeting the GPi may be considered if symptoms progress.

This case highlights the importance of a broad differential diagnosis when evaluating complex movement disorders. The patient had been evaluated by multiple subspecialty providers since childhood, before her symptoms coalesced into an identifiable clinical entity. The initial diagnosis of tic disorder and dystonia were reasonable, as these conditions are far more common than SGCE myoclonus-dystonia. Moreover, the absence of any family history of movement disorders may have reduced suspicion of an inherited condition. Of note, this is only the fourth reported case of a de novo mutation in MYC/DYT-SGCE resulting in myoclonus-dystonia. Finally, although her initial symptoms of startle myoclonus of the neck and dystonia of the upper extremity are typical for myoclonus-dystonia, atypical features including subsequent gait symptoms within 5 years of onset, lower extremity myoclonus, and lack of improvement with alcohol consumption may have obscured the diagnosis.

Taken together, this relatively uncommon presentation of an already rare disorder underscores the need to consider rare or de novo genetic mutations for patients with undiagnosed neurologic syndromes. Furthermore, patients with multiple or unclear patterns of phenomenology, in this case "tics" which likely represented myoclonus, and dystonia, especially involving multiple body parts, merit consideration of less common disorders including rare genetic etiologies. In particular, SGCE myoclonus-dystonia should be considered in patients with fast hyperkinetic movements of the limbs associated with dystonia of the neck or other body parts, especially if these symptoms started in childhood. Because MYC/DYT-SGCE is typically expressed from the paternally inherited allele, carrier fathers of affected individuals could be clinically asymptomatic if they inherited the mutation from their mother.[9] This highlights the need for comparative familial genetics and the strength of whole-exome sequencing in these conditions. Although much work remains to facilitate the evaluation and care of patients with suspected or confirmed inherited movement disorders, recent advances in whole-exome sequencing and genetic counseling offer great promise for syndrome identification and appropriate selection of available therapies, which may improve quality of life for patients and families.

Appendix Authors

Name	Location	Contribution
Eva Klinman, MD, PhD	Department of Neurology, Washington University School of Medicine, St. Louis, MO	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
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Continued

Appendix *(continued)*

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