A case report of deleterious SGCE myoclonus: dystonia successfully treated with pallidal deep brain stimulation

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SGCE (epsilon (ε)-sarcoglycan gene) myoclonus-dystonia (SGCE M-D) is a pleiotropic neuropsychiatric disorder with an autosomal dominant mode of inheritance, variable severity, and incomplete penetrance. There have been few reports of patients with SGCE M-D who have been successfully treated with deep brain stimulation (DBS). This case report presents a missense mutation (c.289>T) inherited in a Northeastern Asian family affected by SGCE M-D. The individuals with the condition exhibited clinical manifestations of generalized myoclonus accompanied by sustained cervical dystonia. A 38-year-old female had a history of generalized dystonia myoclonus with paroxysmal jerks for the past 10 years. The symptoms gradually worsened over the years, affecting her entire body and interfering with most of her daily activities. Genetic testing identified a single base deletion in exon 3 of the SGCE gene, which was considered the genotype underlying her phenotypic symptoms. After failed attempts with oral medications as an outpatient, she underwent DBS targeting the globus pallidus internus (GPI). Her symptoms significantly improved after the activation of the stimulator. Our case supports the beneficial effect of GPI-targeted DBS in patients who are unresponsive to oral medications and have a genetically confirmed M-D phenotype.

KEY WORDS: SGCE gene, Dystonia, Myoclonus, Inherited myoclonus-dystonia syndrome, Deep brain stimulation

INTRODUCTION

The first case of hereditary myoclonus-dystonia (M-D) linked to epsilon-sarcoglycan gene alterations, commonly known as SGCE, was described in 2001 [1]. Currently, it is referred to as SGCE M-D. The disease exhibits a wide range of phenotypic manifestations, but most cases present a combination of rapid, brief, lightning-like muscle contractions (myoclonus) and/or sustained twitching and repetitve movements that result in abnormal postures (dystonia). The most commonly affected areas by these myoclonic jerks are the neck, trunk, and upper limbs, with less prominent involvement of the legs [2]. Another form of the illness has also been characterized as isolated lower limb dystonia with myoclonus [3]. Cervical dystonia, which can be focal or segmental, affects over half of the affected patients. In some cases, dystonia is the only symptom of the condition [4]. Onset most often occurs in the first decade of life or during adolescence.
The majority of affected adults claim that drinking alcohol soothes their myoclonus; however, the effect of alcohol on symptoms varies among individuals and within families [5]. The jerking movements of SGCE M-D are easily triggered or exacerbated by active movement of the affected body part, such as writing [6]. Other factors that can precipitate the movements include stress, sudden noise [4], caffeine, and tactile stimuli [7].

This disease is compatible with an active life of normal duration [7] but can also have a gradually progressive course, leading to functional disability and difficulty in performing normal daily activities and jobs. In some cases, spontaneous remission of SGCE M-D has been reported [8]. It has been demonstrated that patients with SGCE M-D can benefit from pallidal deep brain stimulation (DBS). Nine individuals with SGCE M-D who underwent globus pallidus internus (GPI) DBS for at least 5 years showed significant improvement in their myoclonus and dystonia, as well as improved quality of life and social adjustment. GPI is now the more frequently chosen target for DBS to treat SGCE M-D [9]. In this case report, we describe a case of familial M-D that was successfully treated with pallidal DBS, which was triggered by a novel SGCE mutation.

Ethical statements
Written informed consent was obtained from all participants.

CASE REPORT

A 38-year-old female presented to the neurology clinic with a history of generalized myoclonus that started 10 years ago. She experienced brief jerking movements primarily on the right side of her trunk. Additionally, she had cervical dystonia, which she was able to hold voluntarily. Her jerking movements appeared to worsen during activity and periods of stress. However, she found relief when resting or lying down in bed. Interestingly, she noticed that her jerking movements were soothed when she consumed alcohol.

Over the course of the intervening years, her myoclonus gradually worsened in terms of severity, reaching a point where it started to significantly impact her ability to write and perform other daily activities. To manage her symptoms, she was prescribed various oral medications, including benzodiazepine (clonazepam), an anticholinergic agent (trihexyphenidyl), and a muscle relaxant (baclofen). With the help of these medications, her symptoms were partially controlled, allowing her to continue her treatment under the follow-up care of a neurologist for a period of 8 years in an outpatient setting.

In June 2022, her myoclonic jerks worsened significantly, and she also experienced a severe exacerbation of cervical dystonia accompanied by cervical pain. Despite her previous use of oral medications, her symptoms were no longer manageable. As a result, she sought evaluation at our Movement Disorder Center in the Neurosurgery Department, with the intention of undergoing a thorough assessment and considering surgical treatment as an alternative option.

After her admission to our general ward, we conducted several evaluations of her condition. During the assessments, we observed the following: She exhibited right-sided truncal myoclonus, which lasted for more than 5 seconds. Additionally, she presented with right-sided laterocollis, retrocollis, right-sided blepharospasm, and ptosis. Truncal tremors were occasionally observed in her right upper back and both upper limbs. She also displayed involuntary spasms in her right neck, affecting the ipsilateral splenius muscle and the contralateral sternocleidomastoid muscle. If these jerking movements were triggered, they were not stopped by voluntary holding, and they persisted. Consequently, carrying out daily activities became difficult. Her cervical dystonia, occurring simultaneously with the jerking movements, worsened cervical pain to a level of 6/10 on the Numeric Rating Scale. While writing, she complained of an unusual arm posture, but she did not report any leg cramps, stiffness, or abnormal posturing in the lower limbs (Supplementary Video 1).

We performed electromyography and tonometry to evaluate her dystonia. The results revealed motor unit action potentials in a tremor-like pattern in several muscles, including the right splenius capitis, right obliquus capitis inferior, left sternocleidomastoid, both upper lumbar paraspinal muscles, both latissimus dorsi, and both external oblique abdominis muscles. These findings provide further insight into the abnormal muscle activity associated with her condition (Fig. 1).

Magnetic resonance imaging scan of the brain with a 3.0-T Siemens scanner was not shown any abnormalities.

Her family history was significant for myoclonic jerks with cervical dystonia in her father and her first aunt in the paternal lineage. Her father experienced myoclonus with laterocollis, while her first aunt had myoclonus and cervical dystonia. Additionally, her second aunt exhibited myoclonus and cervical dystonia, her deceased older uncle had myoclonus, and her youngest aunt also had myoclonus and cervical dystonia. These familial cases further suggest a potential genetic component to the condition (Fig. 2). Most members of the paternal family have experienced myoclonic jerks, with varying degrees of intensity. Specifically, the proband’s father has suffered from more severe myoclonus and has previously undergone DBS surgery, although he is currently not using the impulse generator. The proband’s younger sister has also experienced similar myoclonus with cervical dystonia, primarily affecting the left
### Needle EMG

#### EMG summary table

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#### Turns and amplitude

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![Graphs](https://doi.org/10.52662/jksfn.2023.00045)

**Fig. 1.** Electromyography (EMG) and tonometry to evaluate her dystonia, showing motor unit action potentials in tremor-like pattern on right (R.) splenius capitis, R. obliquus capitis inferior, left (L.) R. Trapezius, Amp: amplitude (Continued to the next page.).
Fig. 2. SGCE (epsilon (ε)-sarcoglycan gene) myoclonus-dystonia (SGCE M-D) genetic pedigree chart. The proband has three female siblings, all of them has suffered myoclonus with cervical dystonia and second sister confirmed nonsense mutation of heterozygous variant in SGCE, c.289C>T like her. The proband's father has DBS: deep brain stimulation.

Fig. 1. (Continued from the previous page.).
side, which is currently managed with oral medication and botulinum toxin injections.

A dystonia multigene panel using next-generation sequencing (NGS) was conducted by laboratories, revealing a novel and likely pathogenic variant in the SGCE gene. The specific variant identified was c.289C>T (p.Arg97Ter) in exon 3 (NM_003919.2), which is a nonsense mutation. Additionally, a single gene test conducted on the proband’s younger sister showed the same heterozygous variant in the SGCE gene. These genetic findings provide further evidence of a potential genetic cause for the myoclonus and dystonia observed in the family. On October 19, 2022, after obtaining informed consent, DBS was performed to target GPI. The procedure was carried out using intraoperative microelectrode recording with the Ben Gun microdrive system. The left GPI target was set at a center coordinate of +0.4 mm compared to preplanning target, while the right GPI target was set at a center coordinate of +1.0 mm. The procedure was completed without any complications (Fig. 3). Postoperatively the correct electrode placement and no intracerebral hemorrhage was checked by brain computed tomography scan (Fig. 4).

To assess the clinical outcome of the stereotactic operations, the patient underwent an examination on the first postoperative day after the impulse generator was turned on. The settings for DBS were as follows: voltage set at 1.5 V, pulse width at 60 microseconds, and a stimulation rate of 130 Hz. During this evaluation, the patient’s response to the activated pulse generator was assessed to determine the initial effects of the treatment.

After turning on the generator, the patient experienced an improvement in her dystonia symptoms. However, she began to exhibit intermittent truncal ataxia and left laterocollis. To address these issues, the DBS parameters were adjusted on the sixth postoperative day. The voltage was gradually increased to 1.7 V while keeping the frequency and the pulse width. As a result of these adjustments, her myoclonus and cervical dystonia nearly disappeared.

The assessment using dystonia clinical scales has yielded remarkable results. Following the surgery, there was a substantial reduction in the Toronto Western Spasmodic Torticollis Rating Scale score for myoclonus at rest, which decreased from 35.5 to 10, indicating a 71.8% improvement. Other scales, such as the Fahn Marsden score, the Unified Dystonia Rating Scale, and the Global Deterioration Scale, also demonstrated significant improvements, with rates of 85%, 80.9%, and 66.6%, respectively.

During follow-up visits, the patient expressed a significant improvement in her overall quality of life. The myoclonus has become minimal 1-month post-surgery, enabling her to carry out her daily tasks without any difficulty. A video recording of the clinical assessment was made before and after surgery (Supplementary Video 2).

**DISCUSSION**

The phenotypic manifestation of SGCE M-D exhibits a wide range of symptoms. However, in most cases, individuals experience a combination of rapid, brief, lightning-like muscle contractions known as myoclonus, as well as sustained twitching and repetitive movements that lead to abnormal postures known as dystonia. The myoclonic jerks commonly affect the neck, trunk, and upper limbs, causing involuntary movements and postural abnormalities in these areas. SGCE M-D is generally compatible with an active life during well-controlled state [7]. However, it is important to note that the disease can also exhibit a gradual progression over time, potentially leading to functional disability that makes it challenging to perform normal daily activities and work responsibilities [10]. While the condition can cause difficulties, it is worth mentioning that spontaneous remission of SGCE M-D has been reported in some cases [8]. This means that in certain instances, individuals may experience a significant improvement or resolution of their symptoms without specific intervention or treatment.

If SGCE M-D is resistant to conservative management approaches such as oral medication, botulinum toxin injections, or spray and stretch therapy, surgical neurostimulation can be considered as a potential treatment option.

Recent research has provided insights into the underlying mechanisms of M-D. It suggests that the disruption of the cerebello-thalamo-cortical or striato-pallido-thalamo-cortical pathway may contribute to the development of M-D [8,11]. This knowledge can guide the selection of appropriate surgical targets for neurostimulation interventions.

Pathogenic variants in the SGCE gene located on chromosome 7q21.3 are the most commonly identified genetic cause of M-D. It is important to note that these pathogenic variants exhibit maternal imprinting, which means that the disease phenotype is only expressed when the affected individual inherits the pathogenic variant from their father’s alleles [2]. In most cases of SGCE M-D, the symptomatic individual inherits the pathogenic variant from their paternal alleles. This inheritance pattern highlights the significance of parental origin in the transmission of the disease.

Understanding the genetic basis of SGCE M-D, including the specific location of pathogenic variants and their inheritance patterns, is crucial for accurate diagnosis, genetic counseling, and potential targeted interventions or treatments.

These additional genetic variants and loci highlight the genetic heterogeneity of myoclonus-dystonia syndromes (MDS). Proper
Fig. 3. Microelectrode recording target on left, center +0.4 mm (top) and target on right, center + 1.0 mm (bottom).
genetic testing and evaluation are necessary to accurately identify the specific genetic cause in individual patients, as it can have implications for diagnosis, prognosis, and treatment approaches.

Heterozygous variants in the *SGCE* gene have been estimated to account for approximately 30–50% of cases of MDS [1]. However, it’s important to note that there are other genetic variants and loci associated with similar phenotypes. Some of these include:

1. RELN: Variants in the *RELN* gene have been reported to have a similar phenotype to SGCE-related M-D. RELN is involved in brain development and has been associated with various neurological disorders [12].

2. ANO3: Variants in the *ANO3* gene have also been implicated in MDS. ANO3 codes for a protein involved in neuronal function and movement control [13].

3. TOR1A: Variants in the *TOR1A* gene are associated with another form of dystonia called DYT1 dystonia. Although DYT1 dystonia and SGCE-related M-D may have overlapping features, they are distinct genetic entities [14].

4. DYT15 locus: The DYT15 locus is associated with a form of M-D. Variants in this genetic region can result in similar clinical manifestations as SGCE-related M-D [15].

In our study, we reported a missense mutation (c.289 > T) in the *SGCE* gene, which was inherited in an M-D Northeastern Asian family. This variant was identified through a dystonia multigene panel using NGS. The affected individuals in this family exhibited clinical manifestations of generalized myoclonus accompanied by sustained cervical dystonia. The identified genotype revealed a heterozygous variant in the *SGCE* gene.

Understanding the genetic basis of the disease in this family contributes to accurate diagnosis, genetic counseling, and potential targeted interventions or treatments tailored to their specific genetic variant. It also adds to the body of knowledge surrounding *SGCE* gene mutations and their association with MDS in the Northeastern Asian population.

It has been demonstrated that patients with SGCE M-D can benefit from pallidal DBS. In addition, studies using DBS to the ventralis intermediate nucleus (Vim) of the thalamus in people with M-D have produced effective long-term effects [10,16].

However, there are few studies regarding the long-term effects of GPI DBS in patient with SGCE M-D and comparative study by making randomization on targeting between GPI and Vim of thalamus.

Our neuro-stimulation improve the quality of life and social adaptation after the marked improvement in motor disability. Nevertheless, as anxiety disorders, depression, and alcohol addiction have been reported in the series of non-DBS patients with M-D, more attention should be given to the transition from severe dis-
ability to adaptation to a “new body,” with careful guidance to help the patients to adapt to new challenges and to successfully achieve life re-adjustment after surgery [9]. Further observation in outpatient setting should be needed, paralleled with fine tuning parameters of DBS.

Pathogenic variants in SGCE on chromosome 7q21.3 are the most frequently known genetic cause of M-D with maternal imprinting, and in most cases, a symptomatic individual inherits the pathogenic variant from paternal alleles [2].

Our work reported a missense mutation c.289 > T inherited in Paternal lineage with clinical manifestation with generalized myoclonus accompanying sustained cervical dystonia with genotype of a heterozygous variant in SGCE single. By investigating family history of our patient thoroughly, we found that our patient and her sisters inherited the pathogenic variant by missense mutation from her father. And the mutation in the paternal inherited allele makes heterozygous genotype that express the symptoms of inherited M-D. This means that abnormal expressed maternally imprinted gene of SGCE on chromosome 7q21.3 should run in offspring from paternal allele making pathologic phenotype with autosomal dominant mode of inheritance with variable severity and incomplete penetrance. In other words, the paternally derived SGCE allele generally results in disease [17].

Since the SGCE variant is likely inherited from the father, it may be appropriate to evaluate all family members from paternal genealogy who may or may not have clinical signs of M-D to prevent the adverse effect after being expressed of pathologic variant although the disease could show varied penetrance.

CONCLUSION

In genetically confirmed cases with SGCE M-D, the current case study validates the poor response to oral medicines as well as the usefulness and efficacy of pallidal DBS. Our patient had a novel SGCE mutation that is very likely pathogenic, contributing to the genetic knowledge of the disease.

Subsequent research on the significant influence of genetics and other prognostic factors on DBS results would be needed particularly in the context of customized medicine.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

SUPPLEMENTARY MATERIALS

Supplementary Video 1. Cervical dystonia with right turn, myoclonic jerks affecting the neck and trunk and right arm. Myoclonus is elicited by arousal by auditory and tactile stimuli and and worsened in the trunk and arms with posture and intention.

Supplementary Video 2. After turning on the generator, her symptom with dystonia improved but showed intermittent trucal ataxia and left laterocollis, her myoclonus and cervical dystonia almost disappeared.

REFERENCES