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CASE REPORT

A Case Report of Myoclonus-Dystonia with Isolated Myoclonus Phenotype and Novel Mutation Successfully Treated with Deep Brain Stimulation

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ABSTRACT

Introduction: Myoclonus-dystonia is an inherited disorder characterized by a combination of myoclonic jerks and dystonia. Mutations in the epsilon-sarcoglycan gene (*SGCE*) represent the main known genetic cause. In the last few years, deep brain stimulation (DBS) has shown significant promise in treating these patients. There is only one report in the literature of a patient with positive *SGCE* mutation and isolated myoclonus phenotype who has been successfully treated with DBS.

Case Presentation: We present a case of a 16-year-old young man with a history of quick jerks since childhood. They progressed gradually over the years involving the entire body and interfering with most of his daily activities. He had no dystonia. Genetic testing identified a single base deletion in exon 3 of the *SGCE* gene, considered very likely pathogenic. After unsuccessfully trying several oral medications, he underwent DBS of the globus pallidus internus (GPi). His Unified Myoclonus Rating Scale score during rest and with action improved by 92.8% and 82.6%, respectively.

Discussion: The striking effect of DBS on myoclonic jerks confirms the superior benefit of DBS over oral medications. Further study is needed to determine the role of mutation status in predicting DBS response, especially considering that myoclonus-dystonia is genetically heterogeneous.

Conclusion: Our case confirms the poor response to oral medications and supports the use of GPi DBS for patients with genetically confirmed myoclonus-dystonia and isolated-myoclonus phenotype. In addition, our case represents familial myoclonus-dystonia due to a novel *SGCE* mutation.

Keywords: Deep brain stimulation; Myoclonus-dystonia; Myoclonic jerks; *SGCE* gene; Unified Myoclonus Rating Scale

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Key Summary Points

Our case is the second report in the literature of a patient with positive *SGCE* mutation and isolated myoclonus phenotype who has been successfully treated with deep brain stimulation (DBS)

It confirms the poor response to oral medications and supports the use of pallidal DBS

Furthermore, we present a novel *SGCE* mutation, contributing to the genetic knowledge of the disease

INTRODUCTION

Myoclonus-dystonia (MD) is an inherited disorder characterized by a combination of myoclonic jerks and mild dystonia. Myoclonus may be focal or generalized and generally starts in the upper body, while dystonia mostly appears as a cervical dystonia or writer's cramp and usually causes little or no disability [1]. Both movements are often present at rest, aggravated by action, and are not stimulus-sensitive [2]. Psychiatric comorbidities including anxiety-related disorders and obsessive–compulsive disorders are common [3]. Mutations in the epsilon-sarcoglycan gene (*SGCE*) are found in 30–50% of the patients with the clinical syndrome, representing the major genetic cause. This gene is located at chromosomal region 7q21 and is inherited in an autosomal-dominant manner [4]. The Human Gene Mutation Database reports more than 100 pathogenic variants in the *SGCE* gene, including nonsense and missense mutations, as well as frameshift-causing insertions and deletions, splice site mutations, and exon deletions [5]. There is no treatment that addresses the underlying cause of MD; therefore, treatment is entirely symptomatic. In recent years, deep brain stimulation (DBS) has shown significant promise in treating these patients [6, 7]. Although patients with myoclonus or dystonia as the sole clinical feature have been described [8], there is only one report in the literature of a patient with positive *SGCE* mutation and isolated myoclonus phenotype who has been treated with DBS of the globus pallidus internus (GPi) [9]. We report a case of familial myoclonus-dystonia caused by a novel *SGCE* mutation, whose clinical presentation remained limited to myoclonus at age 16 and was successfully treated with pallidal DBS. Informed written consent was obtained for participation.

CASE PRESENTATION

A 16-year-old left-handed young man came to the clinic with a history of quick jerks since childhood. They were first noticed when he was 2 years old and were localized to the head, trunk, and arms. They occurred at rest, worsened with activity, and were slowly progressive. There was no diurnal variation. His initial assessment at age 4 included a normal brain MRI and an EEG with central sharp waves during sleep, yet he had no history of seizures. He was the product of a normal pregnancy and delivery, and reached motor milestones in timely fashion. His family history, on the other hand, was quite remarkable. He had three paternal cousins and two half-brothers on the paternal side with jerky movements. His father and paternal uncle were also affected. Some of them had mild dystonia, too. Our patient, however, was the most severely impaired of the family.

When he was 6 years old, he visited a movement disorders clinic and, on the basis of his personal and family history, myoclonus-dystonia syndrome was suspected. Still, he had no complaints about stiffness or abnormal posturing. Sequencing of the *SGCE* gene identified a single-base deletion in exon 3 (c.285delA, p.Asp96Thrfs*36) (BigDye Terminator v3.1 Cycle Sequencing Kit; Applied Biosystems, Foster City, CA, USA). The deletion results in a shift in the translational reading frame, yielding a truncated protein. Five symptomatic relatives were also recruited for genetic study and they were found to have the same heterozygous

deletion as the proband. While waiting for the results, he began using carbidopa/levodopa; however, he only took it for a week because it made him sick with no benefit. He was then started on trihexyphenidyl which he tolerated well enough and did allow some improvement, although mild. Symptoms progressed gradually over the years, spreading to his legs, and interfering with most of his daily activities such as eating, writing and self-care. He had not been diagnosed with any learning disability, yet he had an individualized education plan at school due to his abnormal movements. He was later prescribed clonazepam, without benefit, and zonisamide, which caused malaise and headaches, and provided no benefit. He never tried alcohol.

When he was 16 years old, he was referred to our clinic for surgical evaluation. His examination was notable for moderate to severe spontaneous, non-rhythmic myoclonic jerks that worsened with activity but were not stimulus-sensitive. Jerks involved his head/neck, trunk, and all extremities. Surprisingly, his gait was quite normal. He was overall independent in his activities of daily living, but had problems with simple tasks such as carrying a tray or drinking a glass of water without spilling. No abnormal posturing was noted. A neuropsychological evaluation revealed mild difficulty with executive functions, mainly verbal fluency and problem-solving, and occasional difficulties with anxiety, though there were no major affective disorders nor any other psychiatric comorbidity. The remainder of the exam was unremarkable.

He underwent bilateral GPi DBS surgery. His Unified Myoclonus Rating Scale (UMRS) before and 1 month after surgery changed from 83 to 6 for myoclonus at rest and from 46 to 8 for action myoclonus. Other sections of the scale were not administered. On follow-up visits, he described a dramatic improvement in quality of life. At 1 year after surgery, myoclonus is minimal and he is doing all his activities of daily living without difficulty.

DISCUSSION

In the present report we describe a young man with familial MD due to a novel *SGCE* variant. As traditionally described, MD onset is during the first or second decade, fitting with the age of onset in our patient. In addition, phenotypes and degrees of disability are known to be highly variable among patients, even within the same family [8]. While the proband had isolated severe myoclonus, several other family members had combinations of myoclonus and dystonia, and were less severely affected. The typically paternal transmission of familial MD is explained by the maternal imprinting of the gene. Parental imprinting causes the genes to be epigenetically expressed or inhibited, and in the *SGCE* gene, this parent-specific process of inheritance renders the paternal allele exclusively dominant [4].

With more than 50 patients reported in the literature, DBS has proven to be an effective and durable therapy in medically refractory cases. In the largest review published to date, including 40 patients with MD who underwent DBS, there was a mean improvement of 72.6% in myoclonus severity (UMRS) and 52.6% in dystonia (Burke–Fahn–Marsden Dystonia Rating Scale, BFMDRS) [6]. Recent publications reported even better outcomes, with improvement in myoclonus severity score of more than 90%, associated with long-term benefits for quality of life and social adjustment [7, 10]. Consistent with these reports, our patient improved rest and action myoclonus by 92.8% and 82.6%, respectively. Although a possible bias of preferential publication of successful cases might exist, this striking effect of DBS on myoclonus provides strong evidence for the superior effect of DBS compared to medications. Oral medications such as levodopa, clonazepam, trihexyphenidyl, tetrabenazine, and various anticonvulsants have been used on the basis of anecdotal reports or general recommendations for myoclonus [11–14]. However, medications rarely provide optimal relief for these patients and, as evidenced in this case, their use is often limited by poor tolerability. Zonisamide has been suggested as a novel promising treatment

with class 1 evidence [15], yet our patient's experience was completely unsatisfactory. Alcohol was not a therapeutic option because of his age and, regardless, it has a variable effect and may result in alcohol abuse [3]. In this context, DBS appears as the best and sometimes the only valid option for patients with MD.

Although not directly studied, investigators have considered several variables that could explain the variability in outcome of DBS. For instance, both GPi and thalamus have been targeted in patients with MD. While both targets offer a safe and effective treatment option, the former appears to be better for dystonic features and is associated with less frequent adverse events [10, 16]. Regarding genetics, further study is needed to determine the role of mutation status in predicting DBS response, considering that MD is genetically heterogeneous. Even though *SGCE* mutations represent the major genetic cause, sporadic and familial cases without identifiable *SGCE* pathogenic variants have been reported and, as expected, other genes and loci have also been associated with the disease [4]. While there are no definitive conclusions, there is strong evidence that genetic factors influence DBS outcomes and so genetic testing is advisable to assist in predicting expected results [7, 17].

CONCLUSION

The current case report confirms the poor response to oral medications and the utility and effectiveness of pallidal DBS in genetically confirmed MD with isolated-myoclonus phenotype. Our patient had a novel *SGCE* mutation that is very likely pathogenic, contributing to the genetic knowledge of the disease. It would be interesting for future studies to assess the specific weight of genetics and other prognostic factors on DBS outcomes, especially within the framework of personalized medicine.

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Compliance with the Ethics Guidelines. Written informed consent was obtained from the guardian of the patient before his participation in the study and for the publication of this data.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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