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CASE STUDY

Zonisamide-responsive myoclonus in SEMA6B-associated progressive myoclonic epilepsy

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Abstract

We present a female patient in her early twenties with global development delay, progressive ataxia, epilepsy, and myoclonus caused by a stop mutation in the *SEMA6B* gene. Truncating DNA variants located in the last exon of *SEMA6B* have recently been identified as a cause of autosomal dominant progressive myoclonus epilepsy. In many cases, myoclonus in the context of progressive myoclonic epilepsy is refractory to medical treatment. In the present case, treatment with zonisamide caused clinical improvement, particularly of positive and negative truncal myoclonus, considerably improving patient's gait and thus mobility.

Introduction

SEMA6B encodes a protein of the class 6 semaphorin family of axon guidance molecules and is highly expressed in the human brain.[1] Truncating mutations in *SEMA6B* have recently been identified as a cause of progressive myoclonic epilepsy (PME) in combination with global developmental delay and epileptic encephalopathies.[2] All previously reported, pathogenic variants were located in the last exon and presumably did not undergo nonsense-mediated mRNA decay and are associated with PME.[2,3] In general, myoclonus is often difficult to treat and can be the most disabling clinical sign in patients with PME.[4]

In this case report, we present a female patient in her early twenties with a stop mutation in SEMA6B, causing global developmental delay, progressive ataxia, epilepsy and disabling positive, and negative truncal myoclonus, which markedly improved after treatment with zonisamide.

Patient and methods

In her early twenties, this female patient presented to our movement disorders clinic because of treatment-refractory myoclonus. During pregnancy, her mother had suffered from depression, weight loss, and vomiting. There was no history of medication intake or drug abuse in pregnancy.

The mother had structural epilepsy due to a juxta-cortical lesion of unknown etiology, the father was diagnosed with an autism spectrum disorder. Other than that family history was unrevealing.

The patient was born as the only child at a gestational age of 34 weeks via spontaneous delivery after incidental amniotic sac rupture with a low birth weight of 1520g. APGAR scores were not available. She had suffered from newborn icterus and initially had to be fed via gastric tube. Motor and language development were delayed. She was able to speak first words around the age of 3–3.5 years and walked unaided at the age of 5 years. She attended a school for children with special needs.

At the age of 10 years, she developed therapy refractory, non-convulsive/dyscognitive status epilepticus. At that same time, ataxia and myoclonus were first noted, clinical diagnosis of myoclonus epilepsy was made.

Treatment with valproate caused aggression and was replaced by phenobarbital (100 mg/d), which was very effective with only one absence seizure per year. After adding levetiracetam (2250 mg/d), she was seizure-free. Also, there was some, albeit transient improvement of myoclonus. Gait ataxia and myoclonus had progressed over time, so that she needed a wheelchair at the age of 13 years. In addition, there was gradual cognitive decline and she developed urinary incontinence. Since the age of 13 years, the patient lived in care facilities and later worked in a facility for the disabled.

Repeated cranial MRIs were normal. Electroencephalography showed occipital hypersynchronous activity bilaterally with intermittent generalization without clinical correlates, awake and during sleep. In phases, when the patient had characteristic spontaneous action-exacerbated positive and negative myoclonus (for further details see below), but when she was clearly awake and responsive, EEG-recordings showed rhythmic theta activity and also high frequency discharges concomitantly with clinically apparent myoclonus suggesting that myoclonus was interictal and likely of cortical origin.

Extensive laboratory testing including amino acids in plasma and cerebrospinal fluid (CSF), organic acids in urine, and neurotransmitters in CSF was normal. Also, no anti-neuronal antibodies could be detected in CSF. Karyogram, array comparative genomic hybridization (aCGH), and gene panels for epilepsy and developmental regression were unrevealing.

At the clinical presentation in her early twenties, her main complaints were twitches in arms, legs and trunk, and gait instability rendering her unable to walk independently. She could only walk a few steps supported by another person. Of note, due to sudden "leg failure," she had fallen frequently and regularly used a wheelchair.

On examination (see Video segment 1), she had a global developmental delay. Her speech was difficult to discern because of cerebellar dysarthria, imprecise articulation, and lexical problems. She could read simple texts. There was mild weakness of hip extension (4+/5). She had cerebellar signs including incomplete fixation suppression of the vestibulo-ocular reflex, impaired and delayed saccade initiation, head–eye-, and hand–eye incoordination (oculomotor apraxia), dysmetria of the extremities, dysdiadochokinesia, and gait ataxia (SARA 23/40). Hand and finger movements were slow. There was spontaneous action-exacerbated positive and negative myoclonus, particularly when she was holding out the arms in front of her, when she was standing and walking predominantly involving proximal muscles including shoulders and trunk, which markedly impaired postural control. Atactic gait was impaired by anxiety causing her to walk very slowly and cautiously.

We initiated whole-exome sequencing (WES) as described previously.[5] While a pathogenic role of the heterozygous nonsense mutation in *SEMA6B* (c.2067 G>A; p. Trp689Ter) was uncertain in a first analysis, it was subsequently prioritized in a re-analysis of the data conducted in the context of the findings reported by Hamanaka et al. in 2020.[2] The mutation predicts a truncation of the 888-amino-acid SEMA6B protein by about 20%. The variant has to our knowledge not previously been described and was absent from in-house exome and genome datasets (11,000 individuals, Tübingen) as well as public databases (https://gnomad.broadinstitute.org/; gnomAD). The variant was confirmed by Sanger sequencing in the patient but was not detected in DNA from the mother. The father was not available for carrier testing. Of note, the identified change is located in the final exon of *SEMA6B* and the mutant transcript is thus predicted to escape nonsense-mediated mRNA decay (NMD). Using an mRNA sample from the patient using the PAX gene system (Qiagen, Hilden, Germany), we confirmed the expression of both wildtype and mutant allele in the patient by Sanger sequencing of cDNA (Fig. 1). There were no further variants of interest identified by WES.

Because levetiracetam, valproate, and phenobarbital had not been helpful to treat myoclonus, we commenced treatment with zonisamide given its reported effectiveness against myoclonus in PME starting with a dose of 100 mg/d.[6,7] After initiating this treatment, the patient and her mother reported an improvement of myoclonic jerks of about 30%. The dosage was gradually increased to 400mg once a day, which was well tolerated.

After 1 year of treatment, she was able to walk using a small zimmer frame and to climb stairs with some help because her legs were not "giving way" anymore; there were no further falls. Daily chores including eating and using utensils were reported to have improved by about 70 to 80%. Urinary continence had also improved. On examination (see Video segment 2), motor speed had

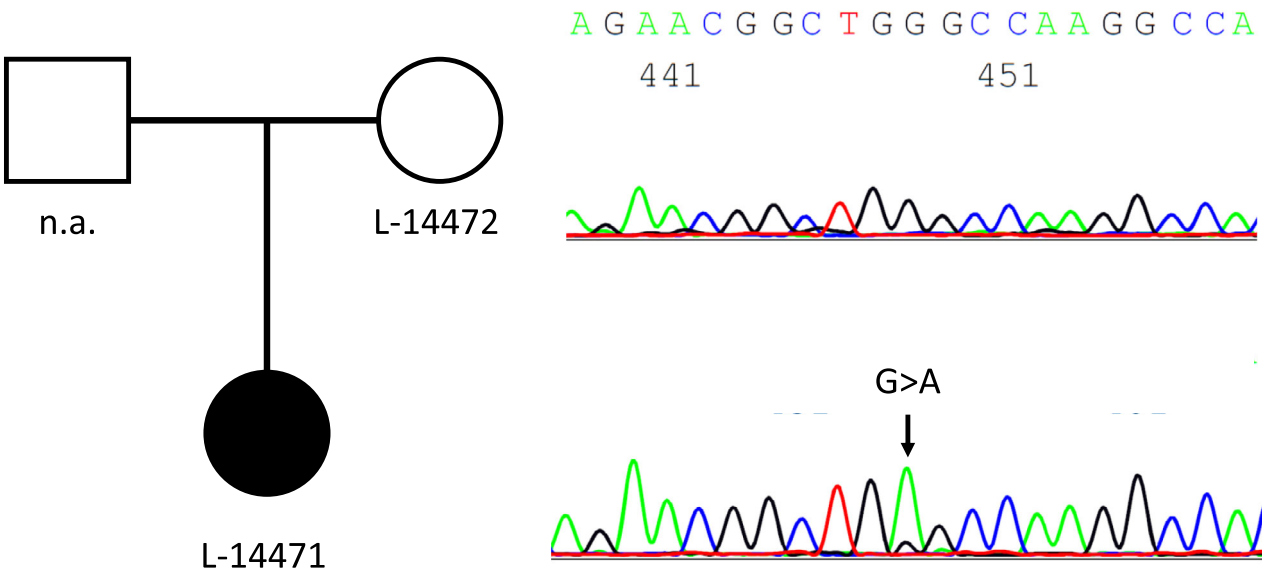

Figure 1. Pedigree of the family and results of cDNA sequencing. The mutated allele (c.2067A) is present indicating that there is no nonsense-mediated mRNA decay.

slightly increased and there was some improvement of postural positive and negative myoclonus. There was no truncal myoclonus anymore. Her gait was still wide-based but she was able to walk longer distances with some help.

Discussion

Here, we present a case of probably SEMA6B-associated PME, in whom troublesome interictal likely cortical myoclonus was successfully treated with zonisamide. As in the previously described cases, the nonsense variant in our patient is also located in the last exon and escaped NMD. This observation is in line with a postulated pathomechanism of a dominant-negative effect of a stably produced truncated SEMA6B protein. Of note, only truncating variants in the last exon seem to be disease-causing since variants in other exons (NMD(+) region) are predicted to undergo NMD and will thus rather result in a loss-of-function that does not seem to be pathogenic (haploinsufficiency-tolerant). This hypothesis is underlined by the presence of such variants in the general population.[2] The six cases of SEMA6B-associated PME previously described are quite similar to our case: All had developmental delay, various types of epileptic seizures that were difficult to treat and gradually developing ataxia. Also, around the age of 10 years, additional negative myoclonus and other neurological symptoms including spasticity commenced leading to wheelchair dependence within a few years. In most cases, brain MRI was normal, in some slight cerebellar abnormalities have been described.[2,3] Given the type of mutation (truncating, escaping NMD) and the clinical phenomenology, it appears very likely that the variant in the patient presented here is pathogenic.

Inter-ictal myoclonus in patients with PME can be difficult to treat. Classical anti-myoclonic agents including piracetam, valproate, and levetiracetam often only have limited lasting efficacy. Clonazepam is often helpful but typically leads to considerable sedation and tolerance over time. This was also the case in the four detailed published cases with SEMA6B-associated PME: In three of the four cases epilepsy was described as "intractable," with only partial response to Clonazepam and short improvement after treatment with valproic acid and levetiracetam; the myoclonus also persisted after treatment.[2] None of them has been treated with Zonisamide, a blocker of Na^+ and T-type Ca^{2+}-channels.[8] Zonisamide has long been used as an add on-therapy in patients with myoclonic epilepsies with good anti-epileptic effectiveness, sometimes with a long-lasting effect. In addition to its anti-epileptic properties, Zonisamide has been shown to improve inter-ictal myoclonus.[6,7,9,10] In the present case, whereas shoulder/arm and hand myoclonus were only slightly improved by zonisamide, it effectively reduced disabling truncal myoclonus and therefore led to a clinically relevant improvement of gait and patient's mobility. Given this effectiveness to treat proximal/truncal positive and negative myoclonus in this case of *SEMA6B*-associated PME, zonisamide might also be considered in other disorders presenting with disabling proximal myoclonus.

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Author Contributions

Generating genetic data: KL, TBH, MG. Literature search: RH. Manuscript preparation: Writing of the first draft: RH; Review and Critique: RH, AM, YH, KL, SvS, TBH.

Conflict of interest

The authors declare that there are no conflicts of interest relevant to this work and that there are no additional disclosures to report.

Ethical Compliance statement

Written declaration of consent was obtained in personal contact from patient and legal guardian. We affirm that all authors have read the Journals position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Video S1. Before zonisamide treatment. This segment shows the patient sitting in a wheelchair when she first presented to our Department at the age of 20 years. When holding out the arms in front of her, there is intermittent positive and negative myoclonus predominantly affecting proximal muscles but occasionally also distal hand muscles. Myoclonus is also present during finger-nose testing which is slightly dysmetric. Of note, there is also truncal myoclonus. Finger movements are slow bilaterally (left more than right), and there is some co-activation contralaterally, but there is no fatiguing. Articulation is imprecise and there is mild scanning of speech. She has difficulties getting up from her wheelchair because of a combination of mild weakness of hip extension and proximal myoclonus interfering with muscle activation. Gait is cautious, wide-based, and intermittently disturbed by proximal myoclonus.

Video S2. On zonisamide treatment. In this segment, the patient is shown at the age of 21 years. When holding out the arms in front of her, intermittent positive and negative myoclonus in arms and hands is still present, but slightly less severe compared to the first segment. Speed of finger movements has slightly increased. Getting up from her wheelchair is still impaired by the mild weakness of hip extension. Importantly, however, there is no disabling truncal myoclonus anymore. Gait is still cautious, and she wishes to be accompanied by the examiner, but gait is stable and less wide-based compared to segment 1.

