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Novel SGCE mutation in a patient with myoclonus-dystonia syndrome - Diagnostic delay of more than 40 years

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Abstract

We present a case of myoclonus-dystonia syndrome illustrated by three videos in which we found a novel SGCE mutation. As the patient described here was suffering from predominant psychiatric comorbidities it took more than 40 years from the first manifestation of the disease until the diagnosis. Having detected the genetically proven cause for his motor and non-motor symptoms was an enormous relief to our patient. We want to share this instructive case in order to prompt neurologists and psychiatrists to look closely at both movement disorders and neuropsychiatric signs in order to diagnose and treat patients to the latest standard.

Case report

Myoclonus-dystonia syndrome (M-D) is a rare movement disorder characterized by myoclonic jerks and dystonic symptoms, typically writer's cramp and cervical dystonia. Here we present a case of a novel SGCE mutation with prominent psychiatric comorbidity including videos of this typical presentation of M-D.

The movement disorder presents in the first or second decade with an estimated prevalence of 1-9/1,000,000 in Europe [1]. In 40–50% of cases a mutation in the SGCE gene is found (DYT-SGCE, formerly DYT11, OMIM#159900) encoding the epsilon-sarcoglycan protein, a transmembrane glycoprotein that mediates the stability of the plasma membrane [2]. More than 100 SGCE mutations have been described, with the majority of mutations leading to premature protein truncation, i.e. nonsense, splicing or frameshift mutations (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=SGCE). Psychiatric comorbidities include depression, anxiety and obsessive-compulsive disorders as well as alcohol abuse [3] as myoclonic jerks are typically responsive to alcohol. They are considered part of the DYT-SGCE phenotype though it is not clear if this reflects a pleiotropic function of SGCE within the CNS causing primary psychiatric disorders or a secondary effect of the movement disorder [4].

A 54-year old male of European descent from non-consanguineous parents presented in our movement disorders outpatient clinic. He reported involuntary movements since childhood. The patient exhibited complex bilateral myoclonic jerks mainly involving the upper trunk and neck, a lateral shift of the head to the right and a writer's cramp. Three videos (coordination, handwriting and walking) are accompanying the online version of this manuscript. Importantly, he reported mild depressive symptoms, obsessive thoughts and actions for more than 20 years as well as nightly panic attacks. These psychiatric symptoms were interfering with his activities of daily living triggering psychiatric consultations during adulthood. Neuropsychological testing had always been normal. Routine laboratory tests including blood, urine and CSF performed repeatedly showed unremarkable results. Various MRI scans of the brain indicated no abnormalities. Repetitive EEGs did not reveal signs of increased cortical excitability. During childhood, the diagnosis of Dyssynergia Cerebellaris Myoclonica (Ramsay Hunt syndrome) was made but no epileptic seizures were reported. Later differential diagnosis comprised a tic disorder because of the reported ability to suppress the involuntary movements for several seconds and the prominent obsessive thoughts and compulsions. Moreover, a psychogenic movement disorder was taken into account as movements were considered bizarre. Medication trials included valproate, primidone and clozapine without beneficial effects. Only clonazepam led to a reduction in myoclonus but was not tolerated because of excessive sleepiness. Amelioration of the symptoms could only be achieved by drinking alcohol. After his divorce at the age of 32 years, he became alcohol dependent. Following several withdrawal treatments he finally managed to become abstinent one year prior to his first appointment in our department. The family history was unremarkable except for alcohol dependency in his father with whom he had not been in contact for 20 years. His mother and two maternal half siblings were reported healthy. The patient himself did not have children of his own.

Due to the characteristic presentation of myoclonic jerks predominantly at the upper limbs and trunk starting in early childhood together with mild dystonic symptoms, we considered the diagnosis of M-D. Genetic testing of the SGCE gene was performed where a novel heterozygous deletion of a single base pair (c.623delG) in exon 5 was detected leading to a frameshift with premature protein truncation (p.G208Vfs⁄11). The mutation was predicted to be pathogenic (CADD-Score 34; Fig. 1). Further analysis showed that only the mutated allele is expressed on the RNA level. Since SGCE is a maternally imprinted gene (meaning that the maternal allele is silenced through DNA methylation) only the paternal allele is expressed. This indicates that the mutation was inherited from the probably affected father who was not available for genetic testing. The mother did not carry the mutation.

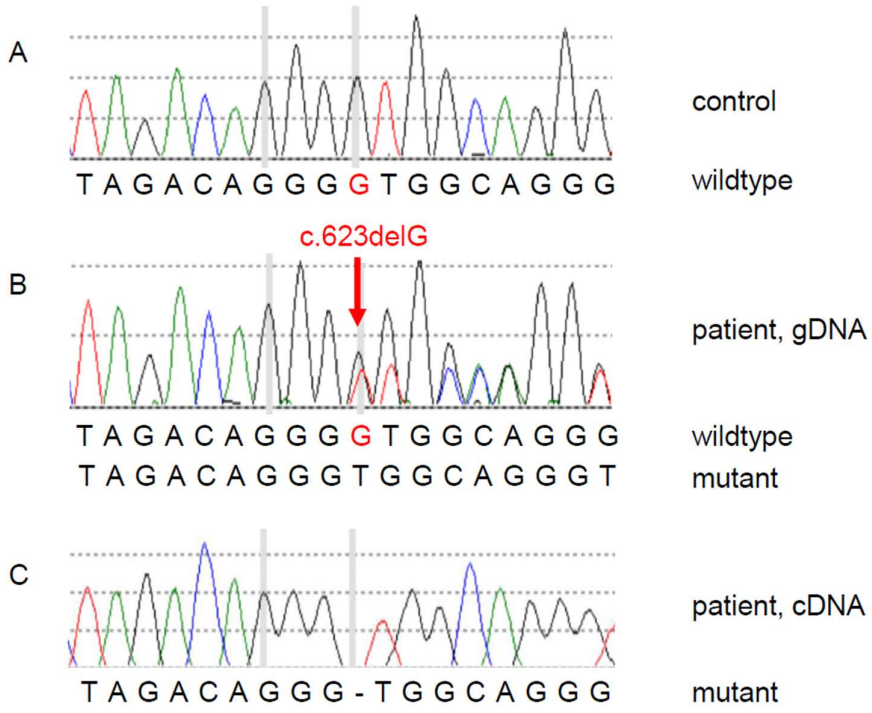

Figure 1: Electropherograms of the SGCE variant. The upper two electropherograms indicate the heterozygous c.623delG, p.208Vfs*11 variant changing the reading frame due to a deletion of guanine on genomic level (gDNA) in the index patient (B) compared to a healthy control (A). As shown below, on level of the coding DNA only the mutated allele is expressed (C).

Discussion

We present a case of genetically proven M-D with a novel SGCE frameshift mutation with characteristic motor features but also prominent psychiatric comorbidities that led to a diagnostic delay of several decades. This specific mutation has not been described yet.

It is important to note that during adulthood our patient was significantly compromised in his quality of life due to psychiatric comorbidity with anxiety and more than 20 years of severe alcohol dependency. Detecting the genetically proven cause for his motor and non-motor symptoms was an enormous relief to our patient. Anxiety has been stabilized with psychotherapy. The patient is currently under treatment with zonisamide that recently has been shown effective for myoclonus [5].

This case illustrates the concurrence of movement and psychiatric disorders seen in DYT-SGCE and hence the importance of considering the movement and psychiatric disorders diagnosis in patients with similar phenotypes. The overlap between movement and psychiatric disorders often results in psychiatric misdiagnoses which in turn hampers adequate therapeutic approaches.

Conflict of interest: None.

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References

[1] Rachad L, Kadmiri N, Slassi I, Otmani H, Nadifi S. Genetic aspects of myoclonus-dystonia syndrome (MDS). Mol Neurobiol 2016:1–4.

[2] Ritz K, Van Schaik BD, Jakobs ME, Van Kampen AH, Aronica E, Tijssen MA, et al. SGCE isoform characterization and expression in human brain: implications for myoclonus–dystonia pathogenesis? Eur J Hum Genet 2011; 19: 438–44.

[3] Weissbach A, Kasten M, Grunewald A, Bruggemann N, Trillenberg P, Klein C. Prominent psychiatric comorbidity in the dominantly inherited movement disorder myoclonus-dystonia. Parkinsonism Relat Disord 2013; 19: 422–5.

[4] Peall KJ, Dijk JM, Saunders-Pullman R, et al. Psychiatric disorders, myoclonus dystonia and SGCE: an international study. Ann Clin Transl Neurol 2015; 3 (1): 4–11.

[5] Hainque E, Vidailhet M, Cozic, et al. A randomized, controlled, double-blind, crossover trial of zonisamide in myoclonus-dystonia. Neurology 2016; 86 (18): 1729–35.