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NURTURING THE CHILD

A novel SGCE gene mutation causing myoclonus dystonia in a family with an unusual phenotype

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ABSTRACT

Background: Myoclonus dystonia is an autosomal dominant dystonia-plus syndrome, characterized by symptom variability within families. Most often is the myoclonus the most debilitating symptom, and many patients report myoclonus reduction after alcohol intake. In several families, mutations in the SGCE gene have been identified.

Method: We report of a three-generation family with myoclonus dystonia displaying a varied phenotype and maternal imprinting. Additionally, this family displays some unusual clinical presentations including alcohol-induced dystonia in an adult man, which will be discussed.

Results: A novel mutation c.386T>C [p.I129T] was found within exon 3 of the SGCE gene in all three affected family members. In addition, two additional mutations [c.305G>A and IVS3+15G>A], judged to be polymorphisms in the SGCE gene, were found in two affected and one healthy family member.

Conclusions: This report presents a novel mutation in the SGCE gene causing myoclonus dystonia and extends the phenotype of myoclonus dystonia to also include alcohol-induced dystonia.

Myoclonus dystonia (MD) is a rare autosomal dominant movement disorder with incomplete penetrance characterized by dystonia and myoclonic jerks. Disease onset is typically during the first two decades of life and the most debilitating, and for the majority of patients, the presenting symptom is often the myoclonus. Myoclonus most often affect the upper body but can be axial/truncal or affect mainly proximal, lower limb muscles. After alcohol intake, most patients experience a marked reduction in clinically important myoclonus (1–4). In about half of the affected cases, the dystonia is focal or segmental. Cervical dystonia or writer's cramp is common, but lower limbs are occasionally involved (2,5). Disease symptoms often stabilize after the first few years of slow progression, but in a minority of cases, symptoms, in particular dystonia, might improve spontaneously (1,2). Cognitive function is typically unaffected. Psychiatric illness has been reported in families with MD including depression, obsessive-compulsive disorder (OCD), anxiety disorders and substance abuse(4). Alcohol overuse/dependency as a mean of self-medication to alleviate motor symptoms is often reported in MD (3,4).

Several different mutations in the SGCE gene on chromosome 7q21, (DYT 11, OMIM number 604149) have been found causative for MD (6). SGCE codes for a transmembrane glycoprotein found in various tissues including brain and muscle. The symptoms typically follow maternal imprinting and are thus less prominent when inherited from the mother. However, mutations or large deletions in the SGCE gene are found in fewer than 40% of the patients with MD, possibly indicating that MD may also be due to changes in one or several presently unknown MD genes. In families where mutations have been identified, paternal transmission have prevailed (6). Here, we present a family with MD owing to a novel SGCE mutation and a very unusual phenotype with alcohol-induced dystonia in one family member and the coexistence of bowel symptoms and childhood onset vitiligo in another.

The index case (III_2) in this report is the only child of two reportedly healthy unrelated parents (Fig. 1). Her early development was typical and uneventful apart from periods with unexplained bowel symptoms characterized by diarrhoea. At the age of three, she rapidly developed an occasional limp with sudden falls and an inability to run. She walked with an extended right leg and was initially handled by orthopaedic surgeons and rheumatologists. After an extensive radiological and biochemical investigation and an early disease progression that included action-induced upper limb dyskinesia, she was diagnosed with a predominantly lower limb dystonia. Myoclonic jerks in arms and hip flexor muscles were first clearly observed 9 months after disease onset. Neuroradiological and neurophysiological investigations and biochemical and immunological analyses of CSF and blood were normal. During the first 2 years, there was a slow disease progress characterized by periods with more pronounced symptoms. Often during these periods, the patient's bowel symptoms worsened with diarrhoeas and even inability to control defecation. After a thorough gastroenterological work-up, paediatric

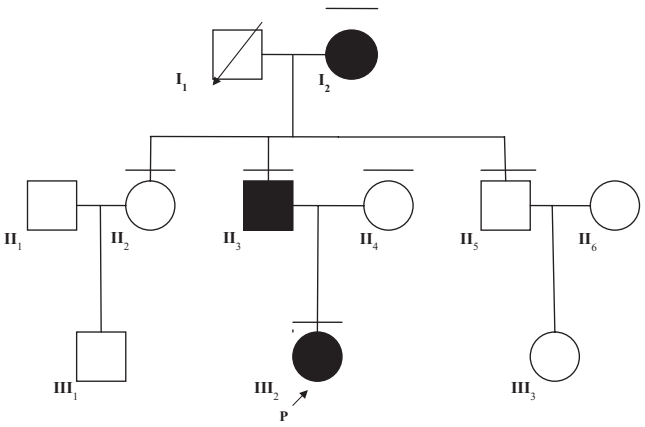

Figure 1 Pedigree of a family with myoclonus dystonia owing to a mutation in the SGCE gene. Arrow = index case; filled squares and circles = examined clinically with symptoms and with gene mutation; unfilled squares and circles with a line above = healthy family members examined clinically and/or with molecular biology.

gastroenterologists proposed that the bowel symptoms were correlated with the dystonic disorder possibly via a peristaltic mechanism. Previous reports from MD families have included non-motor symptoms in a few cases (6). Recently, depigmented skin areas started to develop bilaterally at the elbows, and at 8 years of age, the girl was diagnosed with vitiligo. The aetiology to vitiligo is unknown, but hypotheses have included biochemical, neural and autoimmune mechanisms(7).

Presently, when the girl is 8 years of age, the strong myoclonic jerks, mostly from proximal thigh or hip flexor muscles, which can thrust her to the floor, is the most limiting symptom, and she is totally dependent of a walker.

The patient's paternal grandmother (I_2), now in her late 50s, had been suffering from hemidystonia in her left neck, trunk and leg as well as some kind of brief jerks in her left hand since her 20s. This had at the time of her grandchild's assessments only recently been diagnosed as dystonia and had earlier been interpreted as a functional psychiatric disorder rendering decades of neuroleptic treatment. The myoclonal jerks evolved over time and, within a decade, interfered severely with balance and walking. She described reduced myoclonus after alcohol intake. Her social situation was restricted owing to the stigma of the constant myoclonus.

Suspecting an autosomal dominant disorder, the girl's father (II_3) was repeatedly questioned of signs of dystonia until he incidentally revealed symptoms fully accordant with writer's cramp starting in his early teens. As he worked as sommelier, symptom alleviation after alcohol was presumed. Surprisingly though his wife described, and he agreed, that alcohol rather induced dystonia in her husband with the hands assuming a position with wrists dorsally flexed and fingers extended after alcohol intake. The father's siblings (II_2 and II_5) displayed no signs of dystonia or myoclonus when being evaluated in their 30s.

Samples were taken from the patient, her parents and her grandmother and sent to Centogene Institute of Molecular Diagnostics in Rostock, Germany. The entire coding region of the SGCE gene – including the intron–exon boundaries as well as the promoter – was analysed by PCR and dideoxy-sequencing using standard protocols. Three novel mutations, within exon3 of the SGCE gene on DYT11, were identified where two (c.305G>A and IVS3+15G>A) were deemed to be polymorphisms as they were found in both parents. The third c.386T>C [p.I129T] was found in the patient, her father and her paternal grandmother, all of which have symptoms. The affected amino acid position is moderately conserved, and using theoretical prediction programs (Polyphen, SIFT, AGVGD and MutationTaster), there is a moderate physicochemical difference between isoleucine and threonine, but the mutation is in a functional domain of the protein. Based on the family analysis is the mutation very likely to be clinically relevant, and we considered it as causative to the disorder.

DISCUSSION

This report highlights several aspects of a genetically transmitted disorder with varying penetrance and a novel mutation (c.386T>C) within exon 3 of the SGCE gene on chromosome 7q21, DYT11, causing MD. Firstly in this family, three mutations in the SGCE gene were identified in two affected family members (III_2 and II_3), but two were present also in the girl's healthy mother (II_4), emphasizing the need to perform molecular analysis of unaffected relatives. Secondly, the heterogeneous genotype–phenotype correlation in this case is very illustrative of maternal imprinting. The father having writer's cramp, a mild focal dystonia, and an alcohol-induced dystonia in the wrists, while his mother and daughter are more severely affected with marked difficulties walking. The index patient also displayed an early disease onset within the first decade of life.

Furthermore, this case shows how complex it can be to obtain a good and thorough patient history of a mild dystonia where the father of the proband had been asked on numerous occasions about specific dystonic symptoms. The questions had been specific but had not yielded any answers until he after several visits brought out the information about having difficulties writing 'more or less like everybody else'.

Lastly, we can report of a hitherto unreported association in MD, alcohol-induced dystonia of hands and wrists. The father in this report presented with three mutations within the SGCE gene, two of these judged to be polymorphisms might still have an augmenting influence explaining the novel symptom of alcohol-induced dystonia. Overall, alcohol seems to be both a potent cure to and the trigger of various movement disorders. In the group of diseases known as the paroxysmal dyskinesias (PNKD), alcohol and caffeine are well-known symptom activators (8). Alcohol to patients on neuroleptic drugs significantly increases the risk of tardive dyskinesias or acute dystonic reactions (9). For many affected with essential tremor, task-specific tremor or MD, symptoms will lessen after alcohol intake(3,4,10,11).

For the child in this report, as for most other reported patients, oral treatment has been disappointing (12). She has had two trials with L-dopa up to 12.5 mg/kg with some, but not convincing, effects on the dystonia. Clonazepam gave many adverse effects such as mood swings and irritability, while valproic acid increased the dystonia. Piracetam was ineffective as myoclonus treatment. Zonisamid has proven to be effective either alone or as an add-on to other antiepileptic drugs in myoclonus(13,14) and should be tried also in this girl. If oral treatment fails, bilateral deep brain stimulation (DBS) to the internal pallidum (GPi) when the girl gets somewhat older is an option. A recent pilot study in five adults with severe and refractory SGCE-positive MD and median disease duration of 23 years displayed a median improvement of > 80% for both dystonia and myoclonus scores 6 and 9 months after DBS to the internal pallidum (GPi) (15).

In conclusion, when investigating or suspecting MD in an individual or family, a comprehensive clinical examination, including a careful accounting for non-motor signs and a complete history where possible effects of alcohol are included, should precede molecular investigations. It is essential that if novel mutations are identified, non-affected family members are included in the molecular analysis.

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Congenital central hypoventilation syndrome and hypoglycaemia

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ABSTRACT

Congenital central hypoventilation syndrome (CCHS) is a rare genetic disorder typically presenting in infants with an impaired automatic control of breathing, particularly during sleep, and often associated with variable patterns of autonomic nervous system dysregulations. We studied three children who had CCHS associated with episodes of severe hypoglycaemia and hyperinsulinaemia; we discuss the possible relationship with impaired dopamine-beta-hydroxylase function.

Conclusion: Hypoglycaemia and hyperinsulinaemia might be suspected in children with CCHS presenting with seizures and hyperhydrosis; though, further studies are needed to confirm this association.

