Clinical phenotype heterogeneity in a family with ε-sarcoglycan gene mutation

Justyna Kaczyńska¹, Zygmunt Jamrozik¹, Michał Szubiga², Monika Rudzińska-Bar³, Piotr Janik¹

¹Department of Neurology, Medical University of Warsaw, Warsaw, Poland
²Department of Medical Genetics, Institute of Paediatrics, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland
³Department of Neurology, Andrzej Frycz Modrzewski Krakow University, Faculty of Medicine and Health Sciences, Krakow, Poland

ABSTRACT

Aim of the study. This paper describes six cases of patients with myoclonus-dystonia syndrome who are members of a family in which an SGCE gene mutation has been confirmed.

Clinical rationale for the study. Myoclonus-dystonia syndrome is a very rare disease, with an incidence in Europe of about 2 in every million. Due to the fact that only a few case reports of this illness are accessible in the literature, the material we collected seems to be valuable for clinical practice.

Materials and methods. A history was taken, and physical and genetic examinations of the patients were performed. Furthermore, the clinical examination of three patients was video-recorded.

Results. The clinical picture of the disease varied significantly between the described individuals, from a healthy carrier of the SGCE mutation to patients presenting mild to moderate symptoms. The differences concerned the age at onset of the disease, the initial symptoms, the intensity of involuntary movements, and the predominant symptoms. In addition to the typical movement disorders which are myoclonus and dystonia, in the described family there was also the coexistence of epilepsy, obsessive-compulsive behaviour, dyslexia, dysgraphia, non-harmonious development of cognitive processes, as well as mild phenotypic features of muscular dystrophy. The mutation (NM_001099401.2:c.806-809delACTG) found in the presented family has not been described elsewhere.

Conclusions and clinical implications. Our description of six cases of patients demonstrates the heterogeneity of the natural course of the disease, even in patients with the same mutation. It seems reasonable to regularly examine relatives of patients with myoclonus-dystonia syndrome, who should be observed for involuntary movements as well as non-motor symptoms.

Key words: myoclonus-dystonia syndrome, MDS, DYT11, SGCE

Introduction

Dystonia 11 (DYT11), or myoclonus-dystonia syndrome (MDS), is a genetically heterogeneous disorder inherited in an autosomal dominant manner with incomplete penetrance [1]. The gene associated with the development of the disease is the SGCE gene encoding ε-sarcoglycan, located on chromosome 7q. However, mutations in the SGCE gene are present only in 30–50% of patients with MDS [2, 3]. In the remaining cases, more than 50 different mutations have been identified, which demonstrates the genetic heterogeneity of the disease [4]. The incidence of DYT11 in Europe is about 2 in every million people [4, 5]. The disease usually appears in the first two decades of life. The symptoms include myoclonic jerking that co-occurs with dystonia. Myoclonus is the dominant symptom, which usually concerns the arms and axial muscles. Accompanying dystonia is usually mild, and often manifests itself as cervical dystonia or writer’s cramp [6] and occurs in more than 50% of patients [2].
Clinical rationale for the study

This study is a description of six affected patients in a family with genetically confirmed myoclonus-dystonia syndrome, in whom the clinical picture of the disease varied significantly between individuals. Due to the fact that there are only a few case reports of this illness in the literature, the material we collected seems to be valuable for clinical practice. To the best of our knowledge, there have been no descriptions of other such families in Poland.

Materials and methods

The authors (PJ, ZJ) personally examined three symptomatic patients (IV:1, IV:2, II:6), and one asymptomatic patient (III:2) and his spouse (III:1). Information about the other affected family members described here (II:1, II:3, III:7) was obtained from interviews with the examined patients and from the available medical documentation.

The patient’s genomic DNA was isolated from peripheral blood according to standard protocols (Epicentre, USA). Primers for eight exons of the SGCE gene and their flanking regions were designed using the online available programme FastPCR, based on the sequence of the SGCE-01 transcript in the ENSEMBL database, using previously described methodology [3]. Prior to subsequent analyses, the PCR products were checked by agarose gel electrophoresis. In order to avoid the background signal, the PCR products before direct sequencing were purified on Clean-Up columns (A & A Biotechnology, Poland). Although the SGCE gene consists of 13 exons, only eight exons were tested in this study. The following exons were excluded from testing: exons 1 and 10 (rare splicing variants); exon 11, because none of the known mutations have ever been detected in this exon; and exons 9b and 11b, as they are subject to alternative splicing [7].

Results

Symptoms of the disease occurred in six members of the described family; 13 other family members were healthy (Fig.1).

Case 1 (IV:1, video) is a 22 year-old woman who developed the first symptoms of the disease at 18 months. She was a child of a first, normal pregnancy, born at 40 weeks, receiving 9 points on the Apgar scale after birth. The presenting symptom of the disease was myoclonus of the hand. A few years later, the symptoms of dystonia occurred. At the time of examination, the dominant symptom was head myoclonus. Moreover, we also noticed neck myoclonus, sporadic trunk myoclonus that involved the axial muscles, as well as cervical dystonia and mild writer’s cramp. There was a remarkable reaction to alcohol — its consumption caused transient relief of myoclonus. Motor symptoms were quite mild and the course of the disease was initially progressive, then stationary. Difficulties in writing and performing manual work had been observed from childhood. At the age of six, the patient underwent a psychological examination and was diagnosed as having normal mental development. At the age of eight, her intellectual abilities were assessed as average and within the normal range. At the age of 15, a psychological and pedagogical opinion was issued due to school difficulties. In this evaluation, average intellectual abilities were found with a very non-harmonious development of cognitive processes — cause-and-effect thinking and graphomotor skills were well formed, verbal functions had developed at an average level, but arithmetic reasoning was at a decreased level, as was the range and durability of long-term memory processes and direct auditory memory. The examination also revealed specific difficulties in reading and writing, which at the average level of intellectual development was diagnosed as developmental dyslexia. In addition, mild obsessive-compulsive behaviour was diagnosed. In the past, there had been also one episode of a loss of consciousness,

Figure 1. Pedigree. Women indicated by a circle, men indicated by a square; symbol with a slash indicates deceased individual. Filled symbols indicate clinically affected individuals, and unfilled symbols indicate unaffected individuals. Individuals marked with an asterisk were evaluated clinically and genetically tested. Arrow points to the proband.
Discussion

This paper describes cases of MDS in patients who are related to each other. The same mutation of the SGCE gene being the cause of myoclonus-dystonia syndrome has been identified in all family members who have been genetically tested. Patients exhibited significant variations in their clinical picture. Differences concerned the age at disease onset, as well as the type and severity of symptoms, from a healthy carrier of the mutation to patients presenting with mild to moderate symptoms. Motor symptoms in all six patients were typical for MDS, but each presented with different distributions and severity. Although the mutations in the SGCE gene are inherited in an autosomal dominant manner [8, 9], one (III:2) of the carriers of the mutation did not have any symptoms of myoclonus-dystonia syndrome. The probable explanation is the phenomenon of so-called maternal imprinting, which has been observed in some families with MDS. According to the data in the literature, almost all children who inherit the mutation from their father develop symptoms. However, if inheritance is from the mother, the development of symptoms is observed in only about 5%
Table 1. A summary of the clinical and genetic findings

<table>
<thead>
<tr>
<th>Case/sex</th>
<th>Age at onset [years]</th>
<th>Type of involuntary movement</th>
<th>Distribution of myoclonus</th>
<th>Distribution of dystonia</th>
<th>Course of disease</th>
<th>SGCE gene mutation</th>
<th>Accompanying symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F (IV:1)</td>
<td>1.5</td>
<td>myoclonus, dystonia</td>
<td>hand, head, neck, trunk, axial muscles</td>
<td>neck, hand</td>
<td>stationary</td>
<td>+</td>
<td>developmental dyslexia, OCB, generalised epilepsy with absence seizures</td>
</tr>
<tr>
<td>2/M (IV:2)</td>
<td>2.5</td>
<td>myoclonus, dystonia</td>
<td>hands, head, shoulders</td>
<td>neck, hand</td>
<td>stationary</td>
<td>+</td>
<td>dyslexia, dysgraphia, OCB, generalised epilepsy with absence seizures, some features of muscle dystrophy</td>
</tr>
<tr>
<td>3/F (II:6)</td>
<td>35</td>
<td>dystonia, tremor</td>
<td>–</td>
<td>head, neck</td>
<td>stationary</td>
<td>+</td>
<td>slowness of movements</td>
</tr>
<tr>
<td>4/F (II:1)</td>
<td>7</td>
<td>myoclonus</td>
<td>limbs</td>
<td>not known</td>
<td>not known</td>
<td>not known</td>
<td>not known</td>
</tr>
<tr>
<td>5/F (II:3)</td>
<td>30</td>
<td>myoclonus</td>
<td>head, upper limbs</td>
<td>not known</td>
<td>not known</td>
<td>not known</td>
<td>not known</td>
</tr>
<tr>
<td>6/F (III:7)</td>
<td>15</td>
<td>myoclonus</td>
<td>hands</td>
<td>not known</td>
<td>not known</td>
<td>not known</td>
<td>not known</td>
</tr>
</tbody>
</table>

F — female; M — male; OCB — obsessive-compulsive behaviour

Figure 2. Results of direct sequencing (fluorogram); A — patient with mutation of SGCE gene; B — healthy control

of children [10]. Patient III:2 inherited the mutation from the sick mother and did not present the phenotype of the disease. Due to probable maternal imprinting, his mutant SGCE gene allele is probably methylated (inactive), hence he did not develop the symptoms of the disease. The patient's children, however, both have the NM_001099401.2:c.806-809delACTG mutation and developed symptoms of the disease, which may indicate that the mutant alleles were no longer methylated.

In six affected family members, the age at onset varied from 1.5 to 35 years with the mean onset of symptoms at 15.2 years. In two patients, the first symptoms of the disease appeared after the age of 30, which is rare in MDS, because the disease appears typically in childhood with average onset of symptoms at 6 years [11]. Foncke et al., among 20 symptomatic patients, observed the late onset of the disease in only three patients (aged 43, 60, and 75 years) [12]. In the siblings described in our paper (IV:1, IV:2), the sister’s symptoms developed earlier, which is a typical phenomenon — the symptoms appear earlier in girls [13].

Myoclonus occurred in five patients, and one did not present this kind of involuntary movement (Tab. 1). Hand myoclonus occurred in three patients, in two of them it was the first symptom of the disease, and in one of these
deficit hyperactivity disorder (ADHD) [6].

Somatic disorder, personality disorders, addictions, and attention disorders i.e. depression, anxiety disorders, obsessive-compulsive disorder, personality disorders, addictions, and attention deficit hyperactivity disorder (ADHD) [6].

In the other five cases, the reaction to alcohol was unknown. In most cases, alcohol consumption lessens the symptoms [6]. There are different reports on the occurrence of cognitive impairment in patients with myoclonus-dystonia syndrome. Some authors do not recognise cognitive impairment in this group of patients. However, there have been reports of cases of above-average verbal functioning with the simultaneous impairment of memory and executive functions. Coughlin et al. described the case of a 21 year-old woman with a documented mutation in the SGCE gene in which the clinical presentation of the disease consisted of generalised myoclonus, cervical dystonia and writer’s cramp, and in which the symptoms were accompanied by intellectual disability [15].

Two patients presented specific disorders in terms of school skills: one was diagnosed with developmental dyslexia, the other with dyslexia and dysgraphia. To the best of our knowledge, there have been no reports in the literature to date regarding incidences of dyslexia and dysgraphia in patients with myoclonus-dystonia syndrome.

One patient had undergone a psychological examination several times during her life, while another had undergone a psychological examination only once. The other patients were not assessed by a psychologist. The intellectual abilities of one evaluated patient (IV:1) were at an average level, with a very non-harmonious development of cognitive processes, whereas the intellectual abilities of another patient (IV:2) were below average, but within the normal range. There are different reports on the occurrence of cognitive impairment in patients with myoclonus-dystonia syndrome. Some authors do not recognise cognitive impairment in this group of patients. However, there have been reports of cases of above-average verbal functioning with the simultaneous impairment of memory and executive functions. Coughlin et al. described the case of a 21 year-old woman with a documented mutation in the SGCE gene in which the clinical presentation of the disease consisted of generalised myoclonus, cervical dystonia and writer’s cramp, and in which the symptoms were accompanied by intellectual disability [15].

One patient (IV:2) from our described family presented mild phenotypic features of myopathy: supraclavicular triangle, gothic palate, and periodic choking. The patient has a mutation in the SGCE gene, which is located in the chromosomal region 7q21-q31 [2]. It is interesting that there is a locus nearby for the genes responsible for the formation of two forms of autosomal dominant inherited limb-girdle muscular dystrophy: LGMD 1D in locus 7q36 and LGMD 1F in locus 7q32 [16]. The SGCE gene encodes the ε-sarcoglycan protein, which is one of the six isoforms of the transmembrane glycoprotein, while mutations of the genes encoding the other four isoforms of this protein (α-, β-, γ- and δ-sarcoglycan) are associated with the occurrence of limb-girdle muscular dystrophies [2]. Although some mild myopathic changes were found on electromyography, muscle biopsy did not confirm dystrophic or myopathic changes. Genetic testing of LGMD was not performed.

Clinical implications

Our description of six cases of patients with myoclonus-dystonia syndrome demonstrates the heterogeneity of the natural course of the disease, even in patients with the same mutation. To the best of our knowledge, the mutation which was found in the described family has not been reported previously. It seems reasonable to regularly examine relatives of patients with MDS, who should be observed for involuntary movements as well as non-motor symptoms.
Ethical approval was not necessary for the preparation of this article. We obtained patients’ written consent to video recordings of clinical examinations, and its use for didactic and scientific purposes.

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References


