RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54, no. 1, pages: 33–38
DOI: 10.5603/PJNNS.a2020.0005

ISSN 0028–3843

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

Justyna Kaczyńska[1], Zygmunt Jamrozik[1], Michał Szubiga[2], Monika Rudzińska-Bar[3], Piotr Janik[1]

[1]Department of Neurology, Medical University of Warsaw, Warsaw, Poland

[2]Department of Medical Genetics, Institute of Paediatrics, Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland

[3]Department 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

(*Neurol Neurochir Pol 2020; 54 (1): 33–38*)

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].

Address for correspondence: Piotr Janik, Department of Neurology, Medical University of Warsaw, Warsaw, Poland, e-mail: piotr.janik@wum.edu.pl

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,

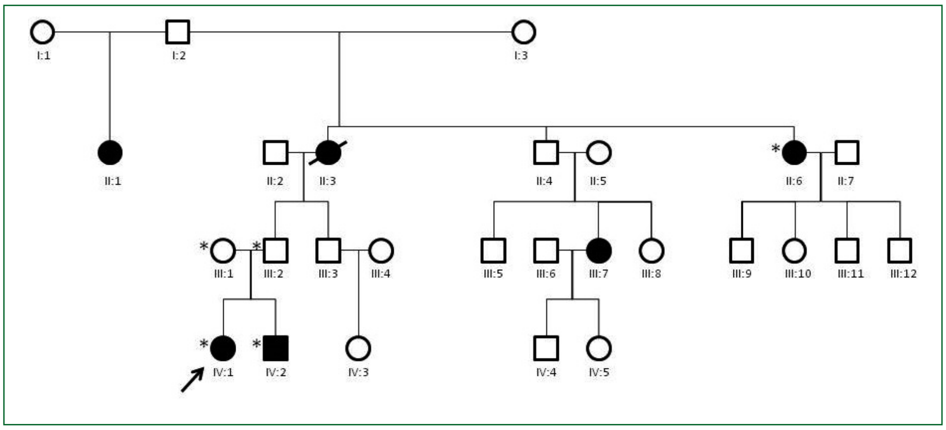

Figure 1. Pedigree. Women indicated by a circle, men indicated by a square; symbol with a slash indicates deceased individual. Filled symbols indicate clinically affected individuals, and unfilled symbols indicate unaffected individuals. Individuals marked with an asterisk were evaluated clinically and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

which was considered generalised epilepsy with absence seizures, due to observed generalised epileptic changes in the EEG increasing after hyperventilation and photostimulation. In EEG recordings performed on several occasions over her lifetime, a series of high-voltage slow waves, sharp waves, complexes of sharp and slow waves, as well as spikes and wave complexes had been revealed. No abnormalities were found during neuro-imaging. The patient was temporarily treated with clonazepam in doses of 0.5 mg twice a day. Treatment was withdrawn due to its negligible effect, quite mild movement symptoms, and the risk of addiction due to the long-term use of benzodiazepines. Based on genetic testing, a mutation in the *SGCE* gene was found in the patient.

Case 2 (IV:2, video) is a 15 year-old boy who developed the first symptoms of the disease at the age of 2 years 6 months. He was a child of a second, normal pregnancy, born at 40 weeks, receiving 7/9/9 points on the Apgar scale. The first symptom of the disease was hand myoclonus. A few years later, symptoms of dystonia occurred. At the time of examination, the dominant symptom was hand myoclonus. Moreover, there was cervical dystonia, moderate writer's cramp which caused objects to occasionally fall out of the hand, a dystonic hand position, as well as myoclonus of the head, arms and hands. Due to the young age of the patient, a reaction to alcohol was not established. Motor symptoms were moderate, and the course of the disease was initially progressive, and subsequently stable. In addition, the patient had developed mild obsessive-compulsive symptoms and specific abnormalities of school skills in writing (dysgraphia) and reading (dyslexia). At the age of 14, the patient underwent a psychological examination. Intellectual abilities were assessed as below average, but within the normal range, with an IQ score of 80. Generalised epilepsy with absence seizures was also diagnosed. In the PET-CT scan of the brain, a slightly increased FDG metabolism was found in deep structures on the left side. Furthermore, a symmetrically reduced metabolism was found in the medial parts of both temporal lobes. On physical examination, a supraclavicular triangle, gothic palate, a lower right palatal arch, with the tongue slightly turned to the left, were noticed. The patient choked from time to time. The diagnostics were extended to include an electromyographic examination, obtaining a record of the muscles under investigation, which may suggest discrete myogenic changes. Creatine kinase activity was 83 U/L. Subsequently, a biopsy of the left quadriceps muscle was performed in which myopathic lesions were not confirmed. The patient was temporarily treated with clonazepam in doses of 0.5mg twice a day. Treatment was withdrawn due to its negligible effect, moderate movement symptoms, and the risk of addiction due to the long-term use of benzodiazepines. Based on genetic testing, a mutation in the *SGCE* gene was found in the patient.

Case 3 (II:6, video) is a 79 year-old woman, in whom at the age of about 35 the first symptoms of the disease had appeared in the form of involuntary movements of the head and lower limbs. The dominant symptom at the time of evaluation was irregular head tremor varying in amplitude and frequency which was assessed as dystonic tremor. Moreover, there was cervical dystonia (retrocollis), positional and kinetic hand tremor, as well as a trembling mouth and voice. On examination, there was noticeable slowness of movements, which however did not meet the criteria of bradykinesia. Based on genetic testing, a mutation in the *SGCE* gene was found in the patient.

Case 4 (II:1) is a woman in whom at the age of about seven years the first symptoms of the disease appeared. The predominant symptom in this patient was limb myoclonus.

Case 5 (II:3) is a woman in whom the first symptoms of the disease appeared at the age of about 30. These included head and upper limb myoclonus.

Case 6 (III:7) is a woman in whom the first signs of the disease in the form of hand myoclonus appeared at the age of about 15.

A summary of the clinical and genetic findings is set out in Table 1.

Five patients (II:6; III:1; III:2; IV:1; IV:2) were tested for mutations in the SGCE gene (ENSG00000127990). In four patients (II:6; III:2; IV:1; IV:2), a novel mutation was found: according to HGVS nomenclature NM_001099401.2:c.806--809delACTG, according to Ensembl nomenclature c.806--809del (Transcript ID: ENST00000445866.7). This mutation leads to the deletion of codons encoding aspartic acid and tryptophan and reading frame shift. A so-called frameshift mutation means that triplets of nucleotides (codons), after the mutation, code different amino acids. In this case, the mutation altered the STOP codon in the sequence, leading to the creation of an abnormally short SGCE polypeptide.

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

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

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

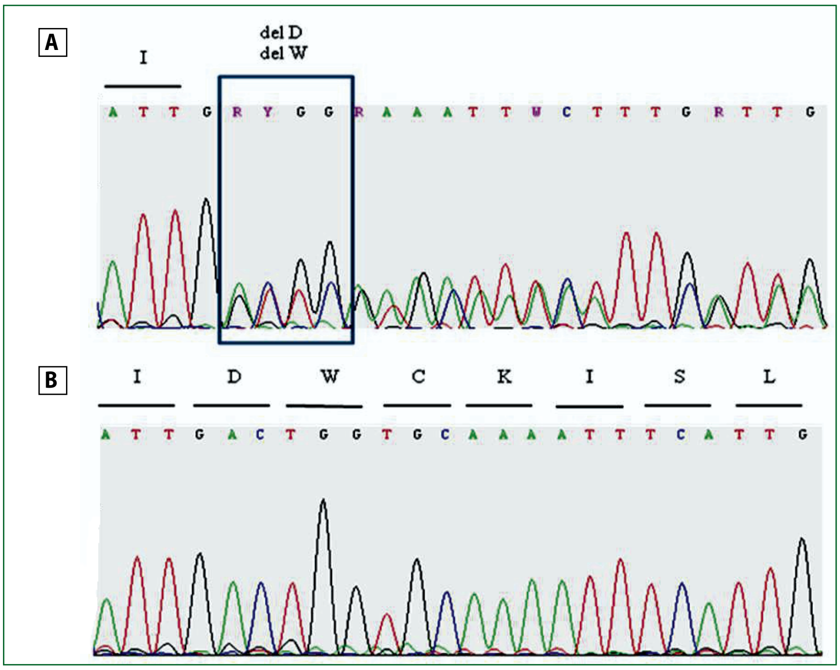

Figure 2. Results of direct sequencing (fluorogram); **A** — patient with mutation of *SGCE* gene; **B** — healthy control

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 two persons it was the dominant symptom. Head myoclonus occurred in three people, and in one of them it was the main symptom of the disease. One patient presented myoclonus of the neck, trunk and axial muscles, one patient had myoclonus of the shoulders, and two patients had limb myoclonus. One patient presented a remarkable reaction to alcohol in the form of the resolution of myoclonus, which is characteristic of MDS: in most cases, alcohol consumption lessens the symptoms [6]. In the other five cases, the reaction to alcohol was unknown.

Dystonia was diagnosed in three patients; the other three did not undergo a personal neurological examination, which makes it impossible to be certain whether they had this movement disorder. In two patients, dystonia appeared only several years after the onset of the disease, but in one patient it was one of the first symptoms. All three patients had cervical dystonia. One patient presented additionally with mild writer's cramp; in one patient this focal dystonia was more severe and was accompanied by occasional dropping of objects from the hands and dystonic positioning of the hand. One person suffered from significant dystonic head tremor.

Tremor was found in one of the six patients. Dystonic head tremor was the predominant symptom of the disease in this patient, and there was also a positional and kinetic tremor of the hands, and a mouth and voice tremor.

In addition to the typical movement disorders in the described family, the coexistence of additional symptoms was noted. Two of the six patients were diagnosed with generalised epilepsy with absence seizures. In the literature there are single descriptions of families, members of whom had not only the typical movement symptoms of MDS but were also diagnosed with epilepsy. Such a family was described by Foncke et al. [12]. They observed the symptoms of epilepsy and/or EEG abnormalities associated with the movement symptoms of the disease in three out of five patients with confirmed mutations of the *SGCE* gene. Members of this family presented various types of seizures. One person had episodes of amnesia lasting for a few seconds, several times a day. A second person suffered from epilepsy in the form of a strange odour sensation with a subsequent panic attack. This patient had episodes of evolution to complex partial seizures with reduced consciousness (according to ILAE 2017 Classification: focal impaired awareness seizures) and several times secondary generalisation (according to ILAE 2017 Classification: focal to bilateral tonic-clonic seizures). The presentation of epilepsy in a third member of this family was reduced consciousness, consisting of staring and lack of communication. Seizures in this patient were similar to those presented by the patients described in our paper [14].

Two patients were diagnosed with obsessive-compulsive behaviour. There are cases in the literature concerning the coexistence in MDS of movement disorders with psychiatric disorders i.e. depression, anxiety disorders, obsessive-compulsive disorder, personality disorders, addictions, and attention deficit hyperactivity disorder (ADHD) [6].

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 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.

Financial support: *This publication was prepared without any external source of funding.*

References

1. Asmus F, Zimprich A, Tezenas Du Montcel S, et al. Myoclonus-dystonia syndrome: epsilon-sarcoglycan mutations and phenotype. Ann Neurol. 2002; 52(4): 489–492, doi: 10.1002/ana.10325, indexed in Pubmed: 12325078.
2. Rachad L, El Kadmiri N, Slassi I, et al. Genetic Aspects of Myoclonus-Dystonia Syndrome (MDS). Mol Neurobiol. 2017; 54(2): 939–942, doi: 10.1007/s12035-016-9712-x, indexed in Pubmed: 26790671.
3. Szubiga M, Rudzińska M, Bik-Multanowski M, et al. A novel conserved mutation in SGCE gene in 3 unrelated patients with classical phenotype myoclonus-dystonia syndrome. Neurol Res. 2013; 35(6): 659–662, doi: 10.1179/1743132812Y.0000000146, indexed in Pubmed: 23561547.
4. Charlesworth G, Bhatia KP, Wood NW. The genetics of dystonia: new twists in an old tale. Brain. 2013; 136(Pt 7): 2017–2037, doi: 10.1093/brain/awt138, indexed in Pubmed: 23775978.
5. Asmus F, Devlin A, Munz M, et al. Clinical differentiation of genetically proven benign hereditary chorea and myoclonus-dystonia. Mov Disord. 2007; 22(14): 2104–2109, doi: 10.1002/mds.21692, indexed in Pubmed: 17702043.
6. Kinugawa K, Vidailhet M, Clot F, et al. Myoclonus-dystonia: an update. Mov Disord. 2009; 24(4): 479–489, doi: 10.1002/mds.22425, indexed in Pubmed: 19117361.
7. Asmus F, Gasser T. Dystonia-plus syndromes. Eur J Neurol. 2010; 17 Suppl 1: 37–45, doi: 10.1111/j.1468-1331.2010.03049.x, indexed in Pubmed: 20590807.
8. Bressman SB. Genetics of dystonia: an overview. Parkinsonism Relat Disord. 2007; 13 Suppl 3: S347–S355, doi: 10.1016/S1353-8020(08)70029-4, indexed in Pubmed: 18267263.
9. Thümmler S, Giuliano F, Pincemaille O, et al. Myoclonus in fraternal twin toddlers: a French family with a novel mutation in the SGCE gene. Eur J Paediatr Neurol. 2009; 13(6): 559–561, doi: 10.1016/j.ejpn.2008.11.009, indexed in Pubmed: 19147379.
10. Raymond D, Ozelius L. Myoclonus-Dystonia. 2003 May 21 [Updated 2012 Jan 26]. In: Adam MP, Ardinger HH, Pagon RA, et al., ed. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2019. https://www-1ncbi-1nlm-1nih-1gov-100001aq53486.han3.wum.edu.pl/books/NBK1414/.
11. Roze E, Apartis E, Clot F, et al. Myoclonus-dystonia: clinical and electrophysiologic pattern related to SGCE mutations. Neurology. 2008; 70(13): 1010–1016, doi: 10.1212/01.wnl.0000297516.98574.c0, indexed in Pubmed: 18362280.
12. Foncke EMJ, Gerrits MCF, van Ruissen F, et al. Distal myoclonus and late onset in a large Dutch family with myoclonus-dystonia. Neurology. 2006; 67(9): 1677–1680, doi: 10.1212/01.wnl.0000242880.49051.1f, indexed in Pubmed: 17101905.
13. Raymond D, Saunders-Pullman R, de Carvalho Aguiar P, et al. Phenotypic spectrum and sex effects in eleven myoclonus-dystonia families with epsilon-sarcoglycan mutations. Mov Disord. 2008; 23(4): 588–592, doi: 10.1002/mds.21785, indexed in Pubmed: 18175340.
14. Foncke EMJ, Klein C, Koelman JH, et al. Hereditary myoclonus-dystonia associated with epilepsy. Neurology. 2003; 60(12): 1988–1990, doi: 10.1212/01.wnl.0000066020.99191.76, indexed in Pubmed: 12821748.
15. Coughlin DG, Bardakjian TM, Spindler M, et al. Hereditary Myoclonus Dystonia: A Novel Variant and Phenotype Including Intellectual Disability. Tremor Other Hyperkinet Mov (N Y). 2018; 8: 547, doi: 10.7916/D8J11FRZ, indexed in Pubmed: 29607243.
16. Nigro V, Savarese M. Genetic basis of limb-girdle muscular dystrophies: the 2014 update. Acta Myol. 2014; 33(1): 1–12, indexed in Pubmed: 24843229.