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Myoclonus–Dystonia Syndrome: Clinical Presentation, Disease Course, and Genetic Features in 11 Families

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Abstract: Myoclonus–dystonia syndrome (MDS) is an inherited movement disorder with clinical and genetic heterogeneity. The *epsilon sarcoglycan* (*SGCE*) gene is an important cause of MDS. We report the results of a clinical and genetic study of 20 patients from 11 families. We disclosed six novel and two previously described mutations in nine families. The majority of patients had a phenotype of myoclonus and dystonia in combination, but clinical findings considered atypical, such a very early onset, distal myoclonus, and legs involvement, were detected in a significant proportion of cases. The disease course was variable, from progression to spontaneous remission of the motor symptoms. There were no obvious differences between mutation-positive and -negative cases. © 2007 Movement Disorder Society

Key words: myoclonus–dystonia; pediatric; ε-sarcoglycan gene; clinical features; neurophysiology.

Myoclonus–dystonia syndrome (MDS) is an inherited movement disorder with onset in childhood or adolescence. It is characterized by myoclonic jerks and dystonia in variable combination, usually being myoclonus the predominant and most disabling symptom.[1] Mutations in the *epsilon-sarcoglycan* (*SGCE*) gene on chromosome 7q21 represent the most frequent genetic alteration disclosed in patients with MDS, but other genes and gene loci are known to be involved and still in a variable proportion of patients no genetic alteration can be disclosed, indicating that the disorder is genetically heterogeneous.[2–6]

We report the results of a clinical and genetic study in 20 patients from 11 unrelated families with MDS to further characterize the clinical spectrum.

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PATIENTS AND METHODS

Twenty patients (16 index cases and 4 affected family members) from 11 unrelated families affected by MDS are included in the study. Patients had been evaluated at the Fondazione IRCCS Istituto Neurologico "C. Besta" in Milano from January 1992 through 2006. The diagnosis of MDS was made in accordance with the diagnostic criteria established by Gasser et al.[7] All patients and available family members (N = 22) had given informed consent for clinical and genetic testing and the study was approved by the local ethic committee.

Clinical Study

All patients were interviewed to obtain family, medical and psychiatric history, and all underwent neurological examination by two specialists in movement disorders (NN and GZ). During the follow-up (mean: 4 years, range: 1–13 years) the patients regularly came for medical control once a year and were video recorded according to a standardized protocol. The videotapes at first and last follow-up have been reviewed in order to evaluate the disease course. Dystonic symptoms were assessed using the severity scale of the Burke, Fahn, and Marsden

Dystonia Rating Scale (BFMDRS).[8] Myoclonic symptoms were evaluated considering the distribution, the frequency of the jerks, and the circumstances of occurrence (at rest, with postural maintenance, on action) for each body segment (face, head, trunk, upper limbs, and lower limbs).

Electrophysiological Studies

Polymyographic study was carried out in 16 patients—at least 1 patient from each family. Electromyographic activity was recorded with surface electrodes from at least one pair of antagonist muscles, chosen on the basis of clinical features of the patient. The most studied pairs of muscles were wrist flexor/extensor, fingers flexor/extensor, and biceps/triceps. The study was performed at rest, in postural maintenance, during goal-directed movements, and during specific tasks (writing, drawing). When possible, stimuli sensitivity (sudden loud noise, touch) was also tested. In 12 (patients 1, 2, 3, 4, 5, 6, 7, 10, 12, 16, 17, 18) out of the 16 patients, the electrophysiological investigations included also EEG–EMG polygraph, jerk-locked back averaging of EEG–EMG; somatosensory evoked potentials, long loop reflex, transcranial magnetic stimulation.

Genetic Studies

DNA was extracted from venous peripheral blood lymphocytes according to standard procedures. All 11 exons and flanking intron regions of the *SGCE* gene were tested for mutations by direct sequence analysis using an automated sequencing system (ABI Prism 3100 Genetic Analizer; Applied Biosystems), according to Valente et al. except for the primers of exon 3 (Table 1A).[9] In Patient 9 who had a novel mutation in a splicing site of the *SGCE* gene, we extracted mRNA from cultured fibroblasts and amplified the corresponding cDNA with specific primers (Table 1B).

Both positive and negative *SGCE* patients resulted negative for mutations in the *DYT1* gene (GAG and 18 base-pair deletion) in the *SGCE*-negative families the *CGH-1* gene was also screened, revealing no mutation.

RESULTS

Clinical Features

The detailed clinical features of the mutation-positive and -negative patients are reported in Table 2

Mutation-Positive Patients.

There were 16 *SGCE* mutation-positive patients from 9 unrelated families. All families were of Italian origin, except from one (Family 7) being from Morocco. Mode of inheritance appeared autosomal dominant in 7 families with reduced penetrance in 3 of them. One mutation-positive case was sporadic and in the remaining family (Family 1) the pedigree analysis suggested a recessive or dominant mode of inheritance from a nonpenetrant parent.

The mean onset of the disease was 4 years (range: 6 months to 20 years). Nine patients had a clinical phenotype of myoclonus and dystonia in combination. Myoclonus involved the upper part of the body (face, head, arms, and trunk) in all cases plus the involvement of legs in 2. Dystonia was represented by dystonic posturing of hands or writing dystonia in all, associated with axial dystonia (head or trunk) in half of them. In these 9 patients, myoclonus had been the presenting symptom of the disease except from one in which the disease had manifested with writing dystonia. Six patients had myoclonus only, involving the upper body parts (face, arms, neck, trunk); in one of them psychiatric symptoms preceded the onset of motor symptoms. The remaining patient had writing dystonia as the sole feature after 20-year disease course.

Alcohol sensitivity was reported in 4 families and denied in 2; for the remaining families this information was not known. Psychiatric symptoms were reported in 4 families and were characterized by obsessive-compulsive disorder, anxiety disorder and depression. Patient 16, now aged 28, suffered from anorexia during adolescenthood.

The course of the disease was variable. In 7 out of the 16 *SGCE*-positive patients from first to last follow-up, myoclonic jerks had progressed to involve other body regions and had became more frequent and intense. By

TABLE 1. *Primer sequence for (A) SGCE gene exon 3 sequence analysis and (b) SGCE mRNA analysis*

	Primer Fw	Primer Rw
A: SGCE gene exon 3 sequence analysis		
Ex 3-inn	3′-CCAAAGCAACATGTGTGAAAA-5′	3′-GATTGTTGGCTTCCCCACATT-5′
B: SGCE mRNA analysis		
Ex 1–11	3′-GAGGACGGACGGCCTAGC-5′	3′-CAACATGCATAACATATGCCAGA-5′
Ex 6–11	3′-ACATTGACTGGTGCAAAATTTCAT-5′	3′-CAACATGCATAACATATGCCAGA-5′

TABLE 2. *Clinical and genetic findings of the 20 patients with MDS*

Fam. No.	No. of affected individuals	No. of examined patients	Pt. No	Age at onset	Present age	Presenting symptoms	Myoclonus distribution	Dystonia distribution	Disease course	Psychiatric symptoms	Alcohol sensitivity	*SGCE* mutation
1	3	3	Pt. 1	6 mo	21 yrs	Myoclonus	Head, trunk, arms	Head, hands	Nonprogressive	−	n.k.	*G112R
			Pt. 2	6 mo	18 yrs	Myoclonus	Head, trunk, arms	Head, hands	Nonprogressive			
			Pt. 3	6 mo	25 yrs	Myoclonus	Head, trunk, arms	−	Remission			
2	4	2	Pt. 4	2 yrs	19 yrs	Myoclonus	Face, head, trunk, arms, legs	−	Progressive	−	+	R102X
			Pt. 5	6 yrs	48 yrs	Myoclonus	Right arm	−	Nonprogressive			
3	3	3	Pt. 6	3 yrs	13 yrs	Myoclonus	Head, arms	Hands	Improved	−	n.k.	None
			Pt. 7	3 yrs	13 yrs	Myoclonus	Face, head, arms	Head, hands	Improved			
			Pt. 8	3yrs	7 yrs	Myoclonus	Face, head, arms	Hands	Nonprogressive			
4	1	1	Pt. 9	2 yrs	8 yrs	Myoclonus	Head, arms	Hands	Nonprogressive	−	n.k	*IVS6–1 G>A
5	3	3	Pt. 10	6 yrs	19 yrs	Myoclonus	Face, head, trunk, arms, legs	Head, trunk, hands	Progressive	−	+	*I256fsX258
			Pt. 11	10 mo	3 yrs	Myoclonus	Head, arms	−	Nonprogressive			
6	2	2	Pt. 12	3 yrs	8 yrs	Myoclonus	Face, head, trunk, arms	Writing dystonia	Progressive	+	−	*IVS5–1G>A
			Pt. 13	6 yrs	47 yrs	Dystonia	−	Writing dystonia	Nonprogressive			
7	2	2	Pt. 14	4 yrs	15 yrs	Myoclonus	Head, trunk, arms	Writing dystonia	Progressive	+	n.k.	* Y134X
			Pt. 15	20 yrs	44 yrs	Dystonia	Right hand	Writing dystonia	Nonprogressive			
8	4	1	Pt. 16	5 yrs	28 yrs	Myoclonus	Face, head trunk, arms, legs	Head, trunk, hands	Progressive	+	+	* W270X
9	5	1	Pt. 17	8 mo	5 yrs	Myoclonus	Head, trunk, arms	Hands	Nonprogressive	−	+	None
10	5	2	Pt. 18	6 yrs	14 yrs	Myoclonus	Head, upper limbs	−	Progressive	+	n.k.	IVS2–1G>T
			Pt. 19	12 yrs	41 yrs	OCD	Face, head, upper limbs	−	Progressive			
11	3	1	Pt. 20	2 yrs	6 yrs	Myoclonus	Head, trunk, arms	Hands	Nonprogressive	−	−	R102X

*Novel mutation; n.k.: not known; OCD: obsessive-compulsive disorder.

contrast, in none of these patients a worsening of dystonia was observed. The progression of myoclonus caused a disability in performing daily activities and these patients were therefore given medication with different drugs (clonazepam, valproic acid, levitiracetam), with no or only mild improvement. Noticeably, in Patient 10 benzodiazepines (diazepam and clonazepam) caused a severe worsening of the myoclonic jerks. No patients received any treatment for dystonia.

In 8 patients, the disease course was nonprogressive: no modification of distribution or severity of myoclonus and dystonia was observed.

In one case (Patient 3) a complete spontaneous remission of myoclonus was observed by age 12.

Mutation-Negative Patients.

There were 4 patients from 2 unrelated families. In one family (Family 9) the pedigree analysis indicated an autosomal dominant mode of inheritance with reduced penetrance consistent with maternal imprinting.

The mean age at onset of the disease was 2 years and 4 months (range: 8 months to 3 years). All patients had a clinical phenotype of myoclonus combined with dystonia, involving the upper body part and being myoclonus the predominant movement disorder. None of the patients had an involvement of lower limbs. In one family alcohol sensitivity and psychiatric symptoms, described as anxiety disorder were also reported. In both families there was a history of epilepsy, which did not cooccurred in the subjects affected by MDS, with characteristics of generalized primary epilepsy.

None of the patients experienced a progression of the motor symptoms and no treatment had been given. The movement disorder spontaneously improved in the two older siblings of Family 3 after age 10.

Electrophysiological Results

The data of EMG recordings are summarized in Table 3. The EMG correlates of the myoclonic jerks demonstrated bursts with a wide range of duration, from 60 to 500 ms. The myoclonic jerks were evident at rest in 6 patients, and in this circumstance the bursts occurred on a silent background (Fig. 2A). In all patients, voluntary muscle activation produced or aggravated the myoclonic jerks, which became repetitive with always an arrhythmic pattern. In 5 patients, there were also polymyographic features consistent with dystonia (cocontraction of agonist and antagonist muscles during voluntary movements), and in these patients the myoclonic jerks were superimposed to the abnormal prolonged tonic activity (Fig. 2B). Each patient showing both very short and very long bursts (Fig. 2C,D). The burst occurred mainly synchronous on antagonist muscles (Fig. 2C) but sometimes they were also asynchronous. Other electrophysiological investigations (somatosensory and central motor evoked potentials, long-loop reflex study, EEG–EMG and jerked locked potentials) resulted normal in *SGCE*-positive and -negative patients. In one mutation-negative patient (Patient 17), epileptic abnormalities characterized by high amplitude spike and waves on temporal regions were transiently recorded on EEG during sleep.

TABLE 3. *Polymyographic aspects of myoclonus*

Fam. No.	Pt. No	*SGCE* mutation	Duration of bursts (ms)	Other characteristics	Distribution	Presence at rest	Presence with postural maintenance	Presence with voluntary movements	Stimuli sensitivity
1	Pt. 1	+	100–500	Synchr, isol	Proximal and distal	No	Yes	Yes	No
	Pt. 2	+	60–250	Synchr, arrhyt	Proximal and distal	No	Yes	Yes	No
	Pt. 3	+	100	Synchr, isol	Proximal and distal	No	No	Yes	Yes
2	Pt. 4	+	50–300	Synchr, arrhyt	Proximal and distal	No	No	Yes	Yes
	Pt. 5	+	80–150	Synchr, isol	Proximal and distal	No	No	Yes	No
3	Pt. 6	−	80–200	Synchr, isol	Proximal and distal	Yes	Yes	Yes	n.t
	Pt. 8	−	100–15	Synchr, isol	Proximal	No	No	Yes	n.t
	Pt. 7	−	60–250	Synchr and asynchr, isol	Proximal	No	Yes	Yes	n.t
4	Pt. 9	+	100–200	Synchr, arrhyt	Proximal and distal	No	No	Yes	n.t.
5	Pt. 10	+	50–400	Synchr, arrhyt	Proximal and distal	Yes	Yes	Yes	Yes
6	Pt. 12	+	100–150	Synchr and asynchr, arrhyt	Proximal and distal	Yes	Yes	Yes	n.t.
7	Pt. 14	+	150–400	Synch, arrhyt	Proximal and distal	Yes	Yes	Yes	n.t.
8	Pt. 16	+	100–300	Synchr, arrhyt	Proximal and distal	No	Yes	Yes	Yes
9	Pt. 17	−	100–200	Synch, arrhyt	Distal	Yes	Yes	Yes	n.t
10	Pt. 18	+	100–300	Synchr and asynchr,, arrhyt	Proximal and distal	No	Yes	Yes	No
11	Pt. 20	+	100–150	Synch, arrhyt	Proximal and distal	Yes	Yes	Yes	n.t

n.t.: not tested; synchr: synchronous; asynchr: asynchronous; isol: isolated; arrhyt: arrhythmic.

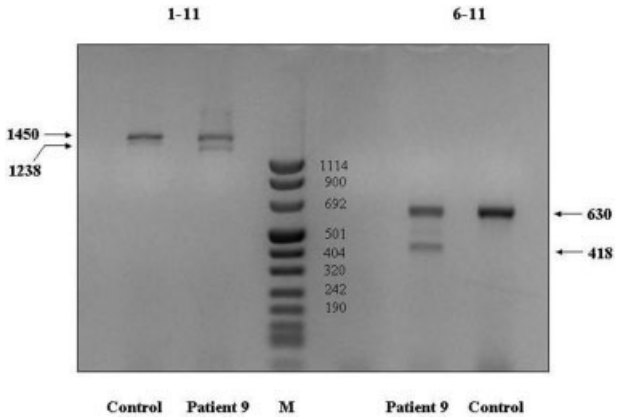

FIG. 1. cDNA from cultured fibroblasts. At the left side cDNA amplification with primers located in exons1 and 11. M: markers. At the right side cDNA amplification with primers located in exons 6 and 11.

Molecular Results

We disclosed mutations in the *SGCE* gene in 9 out of the 11 families: six novel (G112R, IVS6–1 G>A, I256fsX258, IVS5–1 G>A, Y134X, W270X) and two previously described (R102X and IVS2–1 G>T) mutations.[2,10]

The novel missense mutation G112R in exon 3 (Family 1) was found in three affected siblings; the DNA's mother was negative, while the DNA of the asymptomatic father was not available for the analysis. The mutation was present in a highly conserved region of the gene and was absent in 160 control alleles.

In the only affected patient (Patient 9) of Family 4, we found a mutation in a splice site of the gene: a substitution G>A in the first intronic nucleotide before exon 7. In order to identify a possible abnormal transcript, we amplified cDNA from patient's cultured fibroblasts. The amplification revealed the presence of two bands: one corresponding to the size of the wild-type transcript and a smaller one with a molecular weight corresponding to the deletion of exon 7 (see Fig. 1), which was confirmed also by sequence analysis. The mutation was not found in the asymptomatic parents, suggesting that a "de novo" mutation occurred in the patient.

The I256fsX258 mutation in exon 6 was found in the two siblings (Patients 10 and 11) of Family 5, in the asymptomatic father and in other two affected family members. The deletion caused a frameshift with a stop codon at position 258.

In Family 6, we found a heterozygous substitution G>A in the first intronic nucleotide before exon 6. The mutation should cause the skipping of exon 6 in one allele but the cDNA was not available for the analysis.

In the index case (Patient 14) of Family 7, a novel mutation Y134X in exon 4 was detected. The DNA of the father (Patient 15) and of the asymptomatic mother was not available for genetic testing.

The novel W270X mutation in exon 6 was found in the index case of Family 8, in the asymptomatic father and sister, while it was absent in the mother.

The R102 mutation, described previously in German and French pedigrees, was found in 2 unrelated families of our series. In Family 2 it was disclosed in the index case (Patient 4), in her symptomatic father (Patient 5) and in asymptomatic sister; we were not able to obtain the DNA of the other family members reported to be affected. In Family 11 the R102X mutation was disclosed in the index case (Patient 20), and in the asymptomatic father; the paternal grandmother and his brother were reported to be affected but DNA was not available for genetic testing.

The IVS2–1 G>T mutation found in the 2 patients of Family 10 has been already described in one French family.[10]

DISCUSSION

Our study confirms that the *SGCE* gene plays a major role in the pathogenesis of MDS: we disclosed mutations in a high proportion of families (9 of 11, 80%) while the screening of other genes known to be associated to MDS, such as *DYT1*[3] and *GCH-1*,[4] resulted negative. The data in the literature regarding the prevalence of *SGCE* mutations in the different series are variable. Considering patients with MDS as defined according to the established criteria,[1] recent studies on large series of patients reported a proportion of positive patients of 20%,[9] 29%,[10] and 22%.[11] The higher proportion of *SGCE*-positive patients in our series is due to the fact that all but one of our patients were familial cases, and it is well known that *SGCE* mutations are more common in patients with a positive family history.[5,7,12] Interestingly, the only sporadic patient of our series was mutated, indicating that the absence of family history does not exclude the possibility of mutation in the *SGCE* gene, due to the reduced penetrance of the mutated genotype and the possible occurrence of de novo mutation as in our case.[13] In our *SGCE*-positive families the reduced penetrance was due to the maternal imprinting of the mutated allele, even if some family members did not follow this imprinting pattern. The autosomal dominant paternal inheritance of the *SGCE* gene is a very is another very important factor that may help to predict the genetic status in MDS families, however this pattern of inheritance may also be seen in negative families, as in Family 9 of our series.[9,11] In this family, like in other

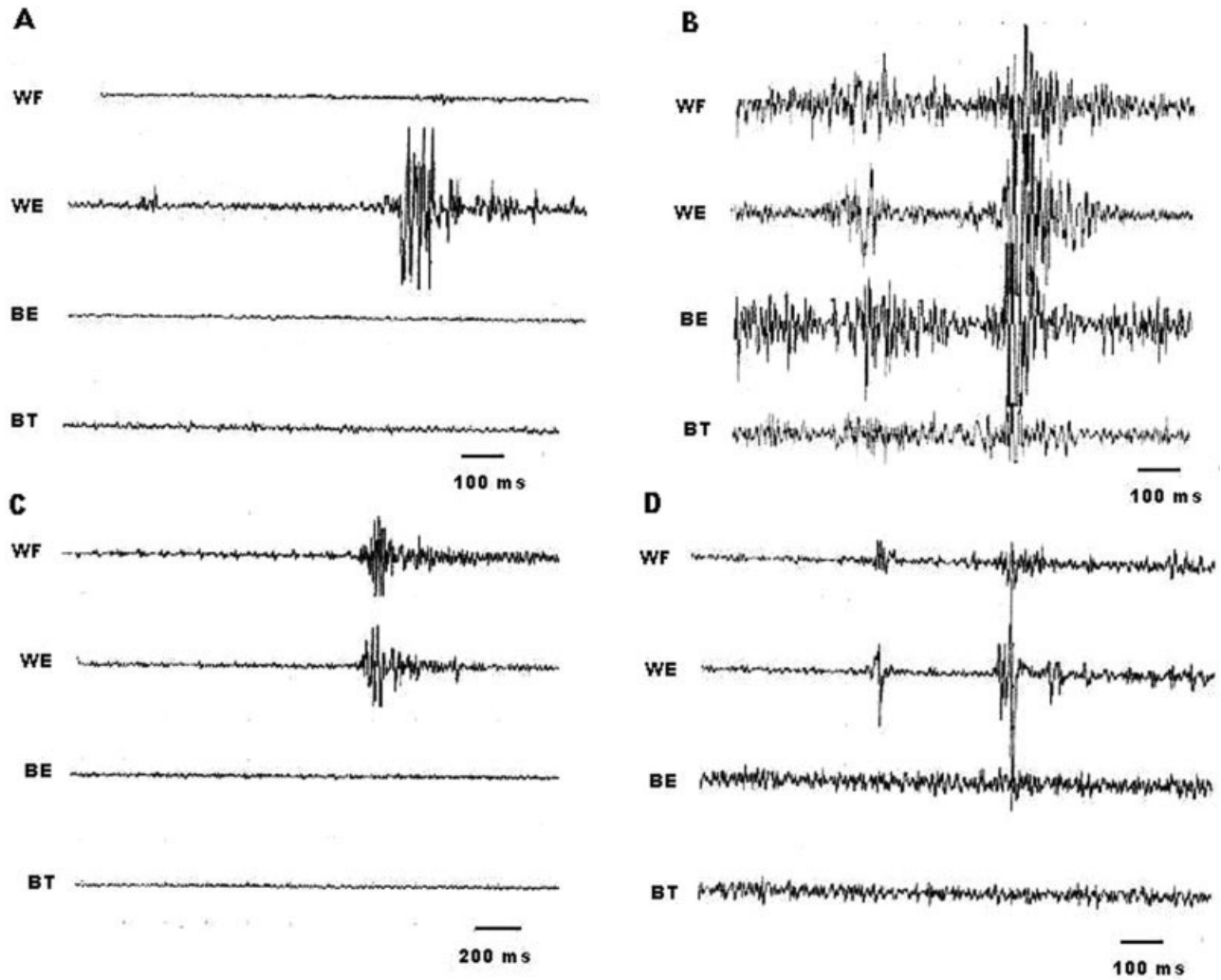

FIG. 2. EMG activity from Patient 4 (A, C, and D) and Patient 10 recorded with surface electrodes from upper right limb. Muscles are from top downwards: wrist flexors (WF), wrist extensors (WE), brachial biceps (BB) brachial triceps (BT). **A**: at rest on distal muscles isolated burst lasting 150 ms. **B**: prolonged tonic activity with superimposed repetitive EMG bursts lasting 200–400 ms during voluntary movements. **C**: synchronous bursts lasting 300 ms at rest on distal muscles. **D**. brief bursts (60–80 ms) on distal muscles during postural maintenance.

similar reported, undetectable mutations in the *SGCE* gene may be postulated.[7]

We found 8 different *SGCE* mutations, six novel and two previously described. Five of the 6 new mutations are "loss of function" mutations, causing an abnormal or truncating protein, like the majority reported in patients with MDS,[10] while the remaining one was a missense mutation. Missense mutations are much rarer. Recently, it has been shown that three missense mutants (H60R, H60P, L1196) produce proteins that are not correctly localized to the plasma membrane and therefore degraded by the proteasome.[14]

The R102X mutation appears to be one of the most common recurrent mutations, being already described in 10 families including ours from different countries.[10] The IVS2–1 mutation described in a French family has been proved to be causative by determining an alternative splicing of exon 2.

The clinical presentation of our MDS patients is overall similar to previously described patients[1] with no clear difference between *SGCE* mutation-positive and -negative cases, but some aspects of the clinical presentation are worthy to be underlined. In 4 patients the symptoms began before 1 year of age; such very early onset has been rarely described, but it may be not exceptional and MDS should be considered in the differential diagnosis of myoclonic conditions in the first year of life. Lightning myoclonic jerks with segmental distribution, in-

volving mainly the upper body part with a predominant proximal distribution, alone or combined with dystonia, is reported to be the typical MDS presentation.[7] In our series, distal myoclonus in the upper limbs was also detected in the great majority of patients, and a similar observation has been reported in a large Dutch family.[15] Moreover, in 3 patients of our series we have observed an involvement of lower limbs, considered to be a rare feature of MDS.[1] One patient of our series had a focal dystonia as the only manifestation of the disease; the phenotype of pure dystonia in MDS, usually a focal dystonia such as writer cramp or cervical dystonia, has been described in very few patients[9,16,17] and may suggest a wrong diagnosis of primary dystonia.

The course of the disease was variable, from patients with a progressive course to patients in which the disease had improved or completely disappeared. Progression of the symptoms was observed in less than half of the patients, and in all cases correlated with a worsening of myoclonus only; when present dystonia remained unchanged in terms of distribution and severity. In 1 *SGCE* mutation-positive patient, with clinical phenotype of myoclonus only, a spontaneous remission of symptoms was observed, as already reported.[18,19] Two *SGCE* mutation-negative patients with onset of symptoms at age 3, showed a marked spontaneous improvement of myoclonus after age 10; the mild dystonic symptom had remained unchanged.

In some families, we observed a striking intrafamilial variability of the clinical presentation (age at onset and clinical features) and the disease course, adding evidence to the absence of genotype–phenotype correlation in *SGCE* patients.[10]

The EMG patterns of myoclonus are similar to those reported by other authors, in terms of duration of bursts, temporal profile, circumstances of occurrence and their possible combination with a dystonic activity.[7,20] The electrophysiological results provided in this study are in accordance with a subcortical origin of the myoclonus[20,21] and no difference between mutation-positive and -negative patients were found but extensive neurophysiologic investigations on larger series of mutation-positive and -negative patients may disclose aspects that would help in predicting the genetic status in the single patient and hopefully provide new insights about the pathophysiology of this disorder.

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