

A Neurophysiological Study of Myoclonus in Patients with DYT11 Myoclonus-Dystonia Syndrome

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Abstract: Mutations in the ϵ -sarcoglycan (*SGCE*) gene have been associated with DYT11 myoclonus-dystonia syndrome (MDS). The aim of this study was to characterize myoclonus in 9 patients with DYT11-MDS presenting with predominant myoclonus and mild dystonia by means of neurophysiological techniques. Various severe multifocal myoclonus occurred in all of the patients, and included short (mean 89.1 ± 13.3 milliseconds) electromyographic bursts without any electroencephalographic correlate, sometimes presenting a pseudo-rhythmic course. Massive jerks could be evoked by sudden stimuli in 5 patients, showing a “startle-like” muscle spreading and latencies consistent with a brainstem origin. Somatosensory evoked potentials and long-loop reflexes were normal, as was silent period and long-term intracortical inhi-

bition evaluated by means of transcranial magnetic stimulation; however, short-term intracortical inhibition revealed subtle impairment, and event-related synchronization (ERS) in the beta band was delayed. Blink reflex recovery was strongly enhanced. Myoclonus in DYT11-MDS seems to be generated at subcortical level, and possibly involves basal ganglia and brainstem circuitries. Cortical impairment may depend from subcortical dysfunction, but it can also have a role in influencing the myoclonic presentation. The wide distribution of the defective *SGCE* in DYT11-MDS may justify the involvement of different brain areas. © 2008 Movement Disorder Society

Key words: myoclonus-dystonia syndrome; *SGCE* gene mutations; transcranial magnetic stimulation; ERD-ERS analysis; blink reflex; evoked potentials

The first attempt to characterize myoclonus-dystonia syndrome (MDS) clinically and neurophysiologically was made by studying patients presenting with a typi-

cal association of myoclonus and dystonia.¹ Since then, MDS has been the subject of considerable clinical debate aimed at its nosological classification,² variously given as essential myoclonus,³ inherited dystonia with lightning jerks responsive to alcohol,² primary dystonia with rapid jerks, and benign chorea.⁴

The advent of the “molecular era” has helped to identify genetically distinct diseases presenting with MDS, and made it possible to establish genotype–phenotype correlations. The finding that mutations in the ϵ -sarcoglycan (*SGCE*) gene are responsible for many patients with MDS⁵ has identified a specific disease called DYT11-MDS.

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TABLE 1. Clinical and genetic features of the patients

Patient	Age at onset/time of observation (years)	SGCE mutation	EMG burst* (ms)	Myoclonus severity at rest/action	Functional test	Dystonia	Pseudo-rhythmic jerks	Startle reactions
				UMRS-2/UMRS-4	UMRS-5			
1	2/18	I256fsX258	94 ± 46	63/60	14	+	—	—
2	2/18	R102X	79 ± 30	15/30	10	+	9 Hz	A
3	3/25	W270X	73 ± 28	51/65	14	+	8–9 Hz	A, F, SS
4	2/26	R237X	83 ± 25	3/38	10	—	6 Hz	A, F, SS
5 ^a	6/14	IVS2-1 G > T	104 ± 39	0/6	3	—	—	—
6 ^a	14/42	IVS2-1 G > T	112 ± 60	2/6	8	+	—	F, SS
7 ^a	6/33	IVS2-1 G > T	86 ± 39	NP/NP	NP	—	—	—
8 ^a	6/19	IVS2-1 G > T	75 ± 20	2/9	9	—	7–8 Hz	SS
9 ^a	2/9	IVS2-1 G > T	96 ± 24	29/46	11	+	7–9 Hz	—

*Mean ± SD EMG burst duration.

^aPatients belonging to the same family.

NP, not performed; +, present; —, absent; startle reaction to unexpected A, auditory; F, flash; SS, somato-sensory stimuli.

The aim of our study was to assess the neurophysiological profile of DYT11-MDS in order to explore its physiopathological basis.

METHODS

Study Population

The study involved 9 patients with DYT11-MDS (6 females), who were diagnosed and followed up at our Institute. Five patients belonged to the same family. All of the patients inherited the disease paternally. The *SGCE* gene was analyzed by means of direct sequence analysis using an automated sequencing system (ABI Prism 3100 Genetic Analyzer; Applied Biosystems) as previously described⁶ (Table 1).

The severity of the myoclonus was characterized on the basis of the scores obtained for sections 4 (action myoclonus), 5 (functional disability), and 2 (myoclonus at rest) of the Unified Myoclonus Rating Scale (UMRS).⁷ The scores are given as the mean values of the independent assessments made by three expert neurologists or neuropsychiatrists.

Neurophysiological Protocol

The EEG-electromyographic (EMG) signals were recorded using surface electrodes, and digitally acquired using a computerized system (sampling frequency 512 Hz; band pass filters 1.6–120 Hz for EEG and 5–250 Hz for EMG; Micromed, Italy). Nineteen electrodes were placed on the scalp according to the 10–20 International System. The EMG recordings included the distal muscles of the upper limbs (flexor and extensor carpi); moreover, the proximal upper limb muscles were recorded in 8 patients, the neck and

shoulder muscles in three, the orbicularis oris in one, and the proximal lower limb muscles in one. Intermittent photic stimulation (IPS) was performed with 10 seconds flash trains at 1, 3, 5, 10, 14, and 20 Hz, intermingled with stimulus free intervals of 10 seconds, while subjects kept the eyes closed.

Jerk-locked back-averaging (JLBA) was carried out using isolated positive EMG bursts. The time window for averaging included 500 milliseconds before and after the point where the rectified EMG, recorded on the wrist flexor, diverged from baseline; at least 50 artifact-free epochs were included.

Event-related synchronization (ERS) and desynchronization (ERD)⁸ task was properly performed in 7 patients. The patients were asked to perform at least 100 brisk (lasting less than 1 second) self-paced extensions of the right index, with a time interval of about 10 seconds. EEG data were analyzed 4 seconds before and 3 seconds after the movement onset. A reference period at rest, from 3,500 to 2,500 milliseconds before the movement onset, was chosen. The ERD/ERS pattern was calculated using a previously described procedure.⁹

In 2 of the 3 patients showing myoclonus in response to a sudden noise, the sequence of muscle activation was evaluated polymyographically (Dantec Counterpoint, Denmark; band pass filters: 20 Hz–1 kHz) including the cervical muscles (orbicularis oculi, masseter, and sternocleidomastoid muscle) and the proximal and distal limb muscles. The patients were sitting with eyes closed, when an unexpected loud sound was generated by discharging the magnetic coil from the magnetic stimulator over a metallic platform.

Transcranial magnetic stimulation (TMS) (Mag-ProX100, Medtronic, Denmark) was performed using a

parabolic coil (140 mm diameter), positioned on the vertex. Total (TMCT) and central motor conduction times (CMCT) were measured as previously described.¹⁰ The resting motor threshold (RMT), defined as the minimum stimulation intensity required to produce motor evoked potentials (MEPs) of about 50 to 100 μ V in at least five of 10 trials, was identified following standard procedures.¹¹ In 7 patients, the silent period (SP) was recorded from the thenar muscles after magnetic stimulation at an intensity of 120% RMT, and calculated as the mean of five responses, each of which was obtained by measuring the interval from MEP onset to the reappearance of EMG activity, while the subject maintained a submaximal tonic contraction.¹²

Paired-pulse TMS was performed in 8 patients. A figure-of-eight coil (55 mm outer diameter of each winding) was placed over the optimal scalp position.¹³ RMT was calculated as described earlier. The active motor threshold (AMT) was defined as the minimum stimulation intensity that could elicit visible MEPs in five trials during moderate tonic contraction of the target muscle.¹⁴ Short intracortical inhibition (SICI) and facilitation (SICF) were determined according to a previously published protocol.¹⁴ MEPs were recorded from the resting thenar muscle (Keypoint; Medtronic, Denmark; band pass filters 20 Hz–10 kHz). The conditioning stimulus was set at 90% AMT, and the test stimulus at 120% RMT. The subjects randomly received either 40 individual test or paired stimuli at interstimulus intervals (ISIs) of 1, 2, 3, 4, 5, 6, 10, and 15 milliseconds. Long-term intracortical inhibition (LICI) was investigated as described.¹⁵ Both the conditioning and test stimuli were set at an intensity of 120% RMT, and paired stimuli were randomly delivered at ISIs of 20, 30, 40, 60, 80, and 100 milliseconds (five trials for each ISI). At each ISI, was calculated the ratio between the average amplitude of the conditioned MEPs and the mean unconditioned responses.

Long-loop reflexes (LLRs) were recorded from the thenar muscles, according to a previously illustrated procedure,¹⁰ at rest and during moderate isometric contraction to calculate the ratio between the short-loop reflex (SLR) and LLR.

Somatosensory evoked potentials (SSEPs) were obtained in 6 patients by 1 Hz electrical stimulation of the median nerve at the wrist. The N20-P25 and P25-N33 amplitudes were calculated on the C3'-A1+A2 derivation.¹⁰ Visual evoked potentials (f-VEPs) were obtained in 3 patients by 1 Hz white flashes for 100 to 120 seconds. The latency of the main positive wave (P2) and N1-P2 amplitude were measured on Oz-Fz derivation.

The recovery cycle of the R2 component of the blink reflex was studied in 7 patients according to a previously illustrated procedure,¹⁶ at various ISIs (100, 200, 400, 600, 800 milliseconds). The mean R2 area following the test stimulus was expressed as a percentage of the mean R2 evoked by the first conditioning pulse.

All of the subjects gave their written informed consent to participate to the study, which was approved by the Ethics Committee of our Institute.

The measures obtained in the patients were statistically compared with those obtained in healthy subjects using the Mann-Whitney U test; the UMRS-4 scores and the results of the neurophysiological tests were evaluated using Pearson's simple correlation test.

RESULTS

At the time of data collection, the mean patients' disease duration was 17.8 (± 7.8) years (Table 1).

Action myoclonus was the main symptom in all of the patients, and asymmetrically or asynchronously involved the upper limbs (8 patients), neck (8 patients), trunk (4 patients), face and cranial muscles (3 patients), and lower limbs (3 patients). Jerks were obvious during posture maintenance and in reaching goals.

Seven patients had myoclonus at rest, which was less frequent and of smaller amplitude than action myoclonus in five cases. Multifocal myoclonus was enhanced by emotional distress in all of the patients; in five, sudden stimuli were capable of evoking massive jerks that bilaterally involved the face and upper limbs (Table 1).

Mild dystonia occurred inconsistently in 5 patients only during action or posture maintenance (Table 1).

The mean UMRS-4 scores were 32.5 (± 23.8), and the mean UMRS-5 scores 9.8 (± 3.1). On the basis of these scores, the severity of the myoclonus was classified as moderate in 2 patients, intermediate in 3, and very mild in the others. The mean UMRS-2 scores were 20.6 (± 24.6), being moderate in 2 patients, intermediate in 2, and very mild or absent in the others (Table 1).

EEG and EMG Findings

EEGs were normal in all of the patients, and JLBA did not reveal any EEG correlate of the myoclonus.

The features of action and spontaneous myoclonus were similar in all of the patients and apparently inde-

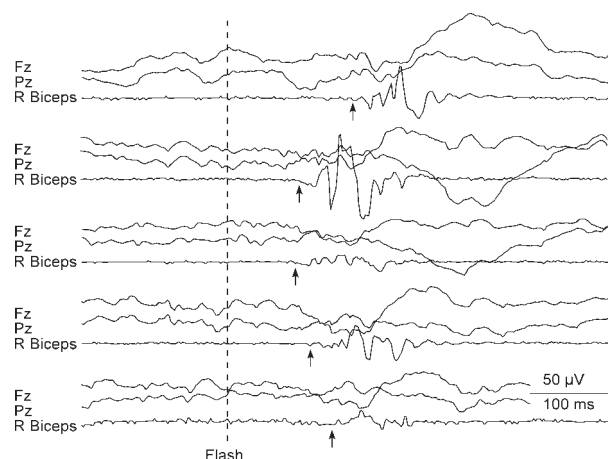


FIG. 1. EEG-EMG traces of five consecutive reflex jerks (top to bottom) during 1 Hz IPS in patient no. 4. Each recording includes 200 milliseconds before and 500 milliseconds after the flash stimulus; the traces are aligned with respect to the flash stimulus. The arrows indicate the onset of the EMG bursts. Note the variable EMG latencies following flash stimuli; wide oscillations on the EEG traces cannot be considered as evoked potentials but as blink or jerk-related artifacts. Indeed, they are consistently time-related with the jerks, but they occur with variable latency with respect to the stimulus.

pendent from the concomitant occurrence of stimulus-evoked myoclonus.

Action and Spontaneous Myoclonus

The EMG recordings showed myoclonic bursts of variable durations lasting on average 89.1 (± 13.3) milliseconds (Table 1). Most bursts were synchronous on antagonist muscles, and asynchronous on the two body sides. When evaluated during posture maintenance or action, myoclonus could occur with a repetitive pseudo-rhythmic course (Table 1).

Stimulus-Evoked Myoclonus

Three patients experienced flash-induced jerks involving the face, neck, and proximal upper limbs bilaterally. Upon 1 Hz IPS, reflex myoclonus occurred after each flash five times in 1 patient (no. 4); in the others, it occurred after the first flash of the train. The recorded proximal limb muscle jerks occurred at a latency of 84 to 144 milliseconds from flash (see Fig. 1). The EEG did not show any significant change during IPS.

EMG responses were analyzed in detail in 2 of the 3 patients with auditory reflex myoclonus. Each stimulus-induced EMG burst first involved the orbicularis oculi muscle (with a delay of 35–45 milliseconds with respect to the stimulus); the sternocleidomastoid was

activated before the masseter (with an interval of 2–5 milliseconds), thus suggesting upstream activation of the cranial muscles; the subsequent activation of the skeletal muscles revealed long latencies between proximal and distal limb muscle involvement (15–25 milliseconds from the biceps to the opponens pollicis) (see Fig. 2).

Movement-Related ERD-ERS

The patients and healthy subjects showed desynchronization in the specific movement-reactive EEG α band, which was prominent on the central derivation contralateral to the movement (C3). Maximum α -ERD was similar in the two groups (Table 2, Fig. 3A). Both groups showed desynchronization and synchronization in the specific movement-reactive β band, with maxi-

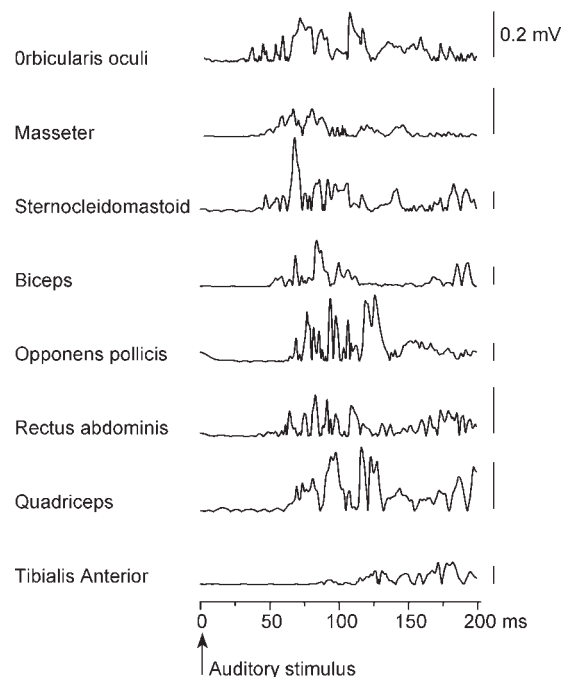


FIG. 2. Reflex EMG response to auditory stimulus in patient no. 4. The traces are the average of five trials. An unexpected loud sound was obtained by discharging the magnetic coil from the magnetic stimulator over a metallic platform, triggering the acquisition of the traces. The median of the poststimulus activation latencies were 41.5 milliseconds (range 33.4–45.0) for the orbicularis oculi; 51.0 milliseconds (range 42.2–53.4) for the masseter; 47.8 milliseconds (range 38.3–51) for the sternocleidomastoid; 51.7 milliseconds (range 49.5–59.8) for the brachial biceps; 70.3 milliseconds (range 68.0–80.5) for the opponens pollicis; 52.7 milliseconds (range 51.0–59.1) for the rectus abdominis; 68.6 milliseconds (range 61.5–76.6 milliseconds) for the quadriceps, and 91.0 milliseconds (range 86.1–119.1) for the tibialis anterior. These latencies were consistent with startle reactions. The earliest activation of the orbicularis oculi represents the audio-genic blink, partially merged with the following generalized reflex response.

TABLE 2. Neurophysiologic measures

		Patients	Controls
Event related desynchronization (ERD) synchronization (ERS)	Index extension (ms)	467.2 ± 98.3	432.9 ± 202.2
	Max α -ERD value on C3 (%)	-52.4 ± 15.5	-49.8 ± 14.9
	Max β -ERS value on C3 (%)	104.4 ± 77.7	153.9 ± 99.8
	Max β -ERS latency on C3 (ms)	1305.3 ± 406.8 ^a	848.2 ± 336.1
Motor conduction times and cortical motor excitability	TMCT (ms)	17.1 ± 1.6	19.2 ± 1.4
	CMCT (ms)	5.4 ± 0.5	4.7 ± 1.7
	RMT ^b (%)	44 ± 10.2	46 ± 11.3
	SP (ms)	138.1 ± 44.1	148.1 ± 33.4
	RMT ^c (%)	66.4 ± 11.8	65.6 ± 13.5
	AMT ^c (%)	49.2 ± 6.9	49.5 ± 8.6
Somatosensory evoked potentials (SSEPs), flash evoked potentials (f-VEPs), and long-loop reflexes (LLR)	N9 (ms)	9.0 ± 0.7	9.5 ± 0.9
	N13 (ms)	11.8 ± 1.5	12.9 ± 1.0
	N20 (ms)	18.4 ± 0.7	18.7 ± 1.1
	N13-N20 (ms)	6.5 ± 0.9	5.9 ± 0.7
	N20-P25 (μ V)	3.8 ± 2.9	4.3 ± 2.7
	P25-N33 (μ V)	2.6 ± 2.7	3.1 ± 2.4
	P2 (ms)	109.6 ± 14	104.4 ± 10.7
	N1-P2 (μ V)	5.7 ± 3.6	13.5 ± 3.5
	SLR-LLR amplitude ratio	4.3 ± 1.9	4.8 ± 2.3

^a $P \leq 0.01$.^bParabolic coil.^cFigure-of-eight coil.

TMCT, total motor conduction times; CMCT, central motor conduction times; SP, silent period; RMT, resting motor threshold; AMT, active motor threshold.

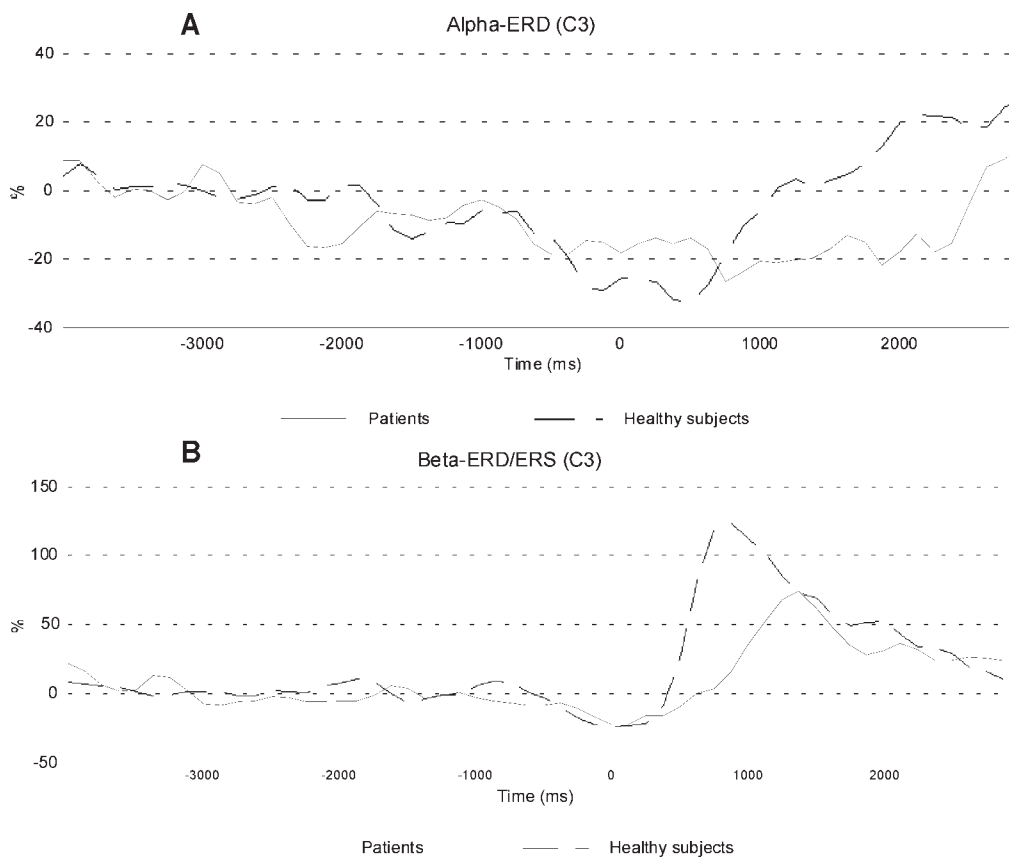


FIG. 3. Grand averages of α -ERD (A) and β -ERD/ERS (B) on the contralateral central electrode (C3) in the patients (continuous lines) and controls (dashed lines). Movement onset corresponds to time zero.

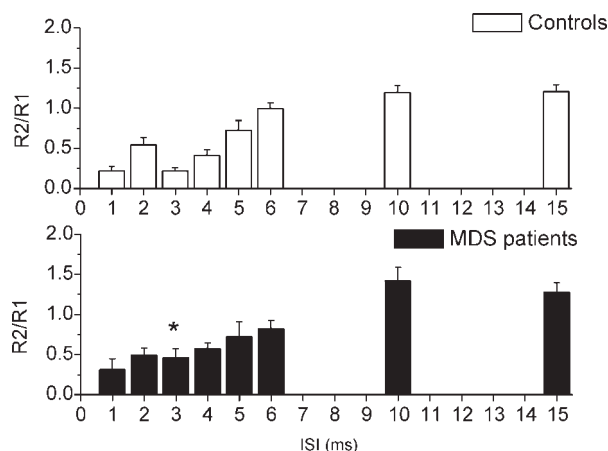


FIG. 4. Short interval intracortical inhibition (SICI) and short interval intracortical facilitation (SICF): mean R2 (conditioned responses), R1 (basal responses) amplitude ratio in MDS patients (black) and healthy subjects (white) at various interstimulus intervals (ISIs). **P*: between 0.05 and 0.01.

mum ERS amplitude occurring on C3; however, the ERS maximum latency was significantly longer in the patients (Table 2, Fig. 3B).

Transcranial Magnetic Stimulation

Conduction times and cortical motor threshold were similar, although the SP was slightly but not significantly shorter in the patients with respect to the healthy subjects (Table 2).

Upon paired-pulse stimulation, inhibition of the test responses at short ISIs (1–6 milliseconds) and facilitation at longer ISIs (10 and 15 milliseconds) occurred in all of the subjects, but inhibition at an ISI of 3 milliseconds was significantly less in the patients than in the healthy subjects (see Fig. 4). The mean LICI curves indicated similar facilitation of test responses (ISIs 20–60 milliseconds) with inhibition at longer ISIs (80 and 100 milliseconds).

SSEPs, f-VEPs, and Reflex Responses

SSEPs and f-VEPs were normal (Table 2).

LLRs were consistently absent at rest, and the mean SLR-LLR amplitude ratio was similar in the patients and healthy subjects during muscle contraction (Table 2).

The R2 component of the blink reflex was inhibited at all ISIs. Mean recovery was greater in the patients than in the healthy subjects at ISIs of 100, 200, 600, and 800 milliseconds (see Fig. 5).

Relationship Between the UMRS Scores and Neurophysiological Measures

The simple correlation function used to evaluate possible relationships between the UMRS scores and the results of the various neurophysiological tests did not identify any correlations.

DISCUSSION

The clinical features of our DYT11-MDS patients were in line with those previously described.^{7,17} Our patients presented with a movement disorder including mild nondisabling dystonia and predominant multifocal myoclonus. Previous descriptions of polymyographic findings in MDS, referring to patients with unspecified and probably heterogeneous genetic backgrounds, revealed EMG bursts of variable duration, with the inconsistent involvement of antagonist muscles, the presence of negative myoclonus and long repetitive jerks defined as myorhythmia.^{1,2} A recent study of DYT11-MDS patients¹⁸ described more homogeneous polymyographic features, including isolated and quasi-rhythmic jerks with a mean duration of about 100 milliseconds and isolated negative myoclonus. In agreement with this observation, we found that the EMG bursts lasted from 73 to 112 milliseconds, sometimes presenting with a pseudo-rhythmic course, but we also noticed stimulus-sensitive myoclonus in response to unexpected stimuli, which was never described before. This partial inconsistency could be explained by differences in the neurophysiological set-

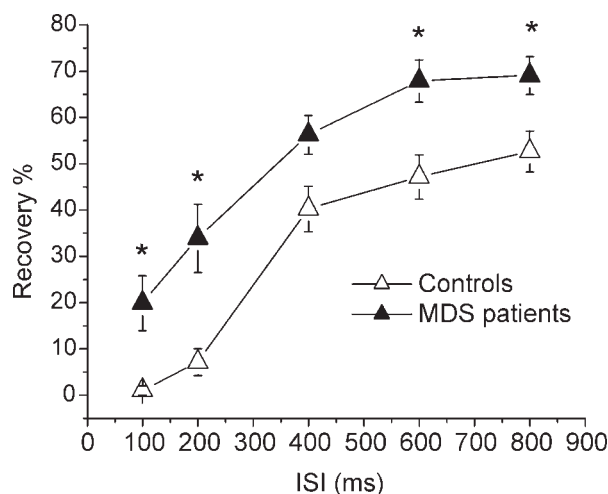


FIG. 5. Blink recovery curves in MDS patients (black) and healthy subjects (white) at various interstimulus intervals (ISIs). **P*: between 0.05 and 0.01.

ting and by the wide evaluation (e.g. including auditory and photic stimuli) performed in our patients.

In agreement with previous studies,^{1,2,18} our DYT11-MD patients never showed the consistently brief myoclonic bursts or the classical signs of cortical hyperexcitability (such as enlarged SSEPs and enhanced LLRs¹⁹) characterizing cortical myoclonus; as well, JLBA consistently ruled out the presence of associated EEG transients. These characteristics undoubtedly support a subcortical origin of the myoclonus, but they do not indicate any specific generator and do not rule out a possible cortical participation in the pathophysiology of DYT11-MDS. To further clarify this point, we investigated cortical motor function by TMS and we evaluated the ERD-ERS patterns associated with voluntary movements.

Paired-pulse TMS revealed the presence of a subtle SICI impairment, a finding that has not been previously reported in patients with DYT11-MDS; moreover, a recent paper reported normal SICI values in 5 patients with DYT11-MDS examined with a different protocol.²⁰ However, our findings are similar to those reported in patients with focal or generalized dystonia,^{21–23} and with paroxysmal kinesigenic dyskinesia,²⁴ as well in patients with cortical myoclonus.^{13,25,26} The impaired SICI observed in dystonic patients has been attributed to a reduction in the power of GABA_A circuitry in the motor cortex because of primary dysregulation of the striato-pallido-thalamo-cortical loop,²⁷ and so we can assume that DYT11-MDS involves a similar functional abnormality of the thalamo-cortical drive. Contrasting with their SICI impairment, our DYT11-MDS patients had normal SP durations and LICI. However, this is not surprising as it has been found that long-lasting inhibition is also inconsistently affected in other forms of dystonia.^{24,27,28}

In line with SICI impairment, the ERD-ERS patterns also suggested a subtle involvement of motor cortex interneuronal function. Indeed, the finding of delayed β -ERS suggests defective post-excitatory inhibition in the motor cortex at the end of the movement,⁹ which may reflect a lack of physiological synchronization of the GABAergic interneuron network.²⁹

The consistent finding of an enhanced recovery of the mean R2 component of the blink reflex in our patients may also suggest the presence of a hyperexcitable brainstem interneuronal pool³⁰ in DYT11-MDS. Enhanced recovery of the blink reflex has also been reported in dystonic disorders,^{30,31} and interpreted as a consequence of defective suprasegmental control mechanisms.³¹ It is possible that a similar mechanism should also be considered in DYT11-MDS patients,

although the relatively frequent observation of a strong startle reaction could also indicate direct brainstem involvement. We found that the jerks evoked by auditory stimuli followed a pathway that was consistent with a startle response.³² Furthermore, although we did not evaluate the sequence of muscle invasion in flash-induced myoclonus in detail, we can hypothesize a subcortical mechanism mediating the reflex because it was not associated with any of those EEG changes that typically characterize photic cortical myoclonus³³; in addition, the post-flash latency of the reflex myoclonus varied, as has been described in startle reactions.³² In this study, we did not formally perform the habituation test needed to properly define a startle syndrome, and a specific study will better precise this aspect. However, we believe that the recognition of a startle-like myoclonus is an important feature in our patients, further indicating the peculiarity of DYT11-MDS among the dystonic syndromes. The observed reflex myoclonus recalled that described in some patients with multiple system atrophy, who show exaggerated startle reactions associated with action myoclonus.^{34–36} Under these conditions, the latencies of the startle responses suggest the presence a brainstem generator. Similarly, in the prototype Papio-papio baboon model, reflex myoclonic seizures and brainstem-generated jerks may simultaneously occur in response to various types of stimuli or stressing situations.^{37,38}

In conclusion, in patients with DYT11-MDS, we found neurophysiological signs suggesting the dysfunction of different systems, including brainstem and neo-cortex. We could hypothesize that stimulus-evoked myoclonus is generated by a brainstem dysfunction, as suggested by the neurophysiological data. Action and spontaneous myoclonus should arise from different dysfunctional circuitry, possibly involving the basal ganglia. The finding of a cortical dysfunction is not strictly specific for DYT11-MDS, because it was reported also in other types of dystonia. The role of the motor cortex in the generation of myoclonus is questionable, indeed the cortical impairment may be a result of subcortical dysfunction; however, it can have a role in modulating the myoclonic presentation. Neuronal dysfunction occurring at multiple brain levels may occur in DYT11-MDS because *SGCE* protein is widely localized in various brain regions, including the cortex and brainstem.³⁹ The finding that it has a subcellular localization in neuronal membranes^{39,40} suggests that it may play a role in synaptic functions, thus leading to an interneuronal system imbalance that sustains physiological inhibition in multiple brain areas.

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