Spasticity and spastic dystonia: the two faces of velocity-dependent hypertonia

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Abstract

***Background*:** spasticity and spastic dystonia are two separate phenomena of the upper motor neuron syndrome. Spasticity is clinically defined by velocity-dependent hypertonia and tendon jerk hyperreflexia due to the hyper-excitability of the stretch reflex. Spastic dystonia is the inability to relax a muscle leading to a spontaneous tonic contraction. Both spasticity and spastic dystonia are present in patients who are at rest; however, only patients with spasticity are actually able to kept their muscles relaxed prior to muscle stretch. The idea that has inspired the present work is that also in patients with spastic dystonia the stretch reflex is likely to be hyper-excitable. Therefore, velocity-dependent hypertonia could be mediated not only by spasticity, but also by spastic dystonia.

Methods: tonic stretch reflexes in the rectus femoris muscle were evoked in 30 patients with multiple sclerosis showing velocity-dependent hypertonia of leg extensors and the habituation of the reflex was studied. Moreover, the capability of relax the muscle prior to muscle stretch (spastic dystonia) was also investigated.

Results: A tonic stretch reflex was evoked in all the enrolled patients. 73% of the patients were able to relax their rectus femoris muscle prior to stretch (spasticity). In the overwhelming majority of these patients, the tonic stretch reflex decreased during repeated stretches. In the remaining 27% of the subjects, the muscle was tonically activated prior to muscle stretch (spastic dystonia). In the patients in whom spastic dystonia progressively increased over the subsequent stretches (50% of the subjects with spastic dystonia), the habituation of the reflex was replaced by a progressive reflex facilitation.

Discussion: this study shows for the first time that velocity-dependent hypertonia can be caused by two distinct phenomena: spasticity and spastic dystonia. The habituation of the tonic stretch reflex, which is a typical feature of spasticity, is replaced by a reflex facilitation in the half of the subject with spastic dystonia. These preliminary findings suggest that differentiating the two types of velocity-dependent muscle hypertonia (spasticity and spastic dystonia) could be clinically relevant.

Keywords: spasticity; spastic dystonia; repetitive muscle stretching; tonic stretch reflex; reflex habituation; multiple sclerosis; electromyography; upper motor neuron syndrome.

Introduction

Velocity-dependent muscle hypertonia is a frequent clinical sign in subjects affected by chronic Upper Motor Neuron Syndrome (UMNS). It is currently considered a synonym of spasticity, classically defined as the motor disorder characterized by a "velocity-dependent increase in tonic stretch reflexes (muscle tone) resulting from hyper-excitability of the stretch reflex" (Lance, 1980). While phasic stretch reflexes occur in response to very brief stretches as those produced by a tendon tap, tonic stretch reflexes are produced by stretches of longer duration, such as when testing the muscle tone clinically (Rothwell, 1994). In healthy subjects at rest, only phasic stretch reflexes can be evoked. In relaxed spastic patients, on the contrary, tonic stretch reflexes can be also elicited. Therefore, spasticity is viewed as a pathological stretch reflex, i.e. a tonic stretch reflex evoked at rest (Trompetto et al., 2014). In this scenario, velocity-dependent hypertonia, spasticity and tonic stretch reflex elicited at rest are all viewed as synonyms.

Although several previous works stressed that spastic muscles are quiescent at rest, prior to passive muscle stretch (Burke, 1975; Thilmann et al., 1991), some UMNS patients cannot relax their muscles, which are kept tonically activated without any voluntary command. This phenomenon, called spastic dystonia, can be described as the inability to relax the muscles (Gracies, 2005). Spastic dystonia can alter resting posture, thus contributing to the hemiplegic posture (Sheean and McGuire, 2009). Differently from spasticity, spastic dystonia is viewed as a form of efferent muscle hyperactivity, dependent upon continuous supraspinal drive to spinal motoneurones (Gracies, 2005).

In a clinical setting, without surface electromyography (s-EMG), spastic dystonia is difficult to assess. It can be partially appreciated by evaluating the resting position of a joint, such as the pathological posture of elbow flexion, possibly due to spastic dystonia occurring in elbow flexor muscles. However, muscle contracture due to secondary tendon-muscle changes is another frequent cause of pathological postures (Gracies, 2005); furthermore, it is possible that spastic dystonia may occur in absence of pathological postures. Therefore, to assess spastic dystonia, just looking at the postures may be insufficient and misleading. The difficulty in the assessment of spastic dystonia is reflected by the lack in scientific literature of studies specifically investigating the prevalence of spastic dystonia in chronic UMNS patients.

Previous studies suggested that spastic dystonia is likely to be involved in velocity-dependent muscle hypertonia (Bakheit et al., 2011; Gracies, 2005). An active muscle, obviously, offers a greater resistance to stretch; moreover, the spinal motoneurons targeting a tonically activated muscle are likely to be more excited and, consequently, more easily activated by sensory inputs. As

a matter of fact, also in healthy subjects a tonic stretch reflex can be evoked in a tonically activated muscle (Rothwell, 1994). However, we found no studies in the literature investigating the role of spastic dystonia in velocity-dependent muscle hypertonia and, in the clinical practice, all forms of velocity-dependent hypertonia led to the diagnosis of spasticity.

This study, conducted on leg extensors of subjects affected by multiple sclerosis (MS), is the first attempt to investigate the role of spastic dystonia in velocity-dependent hypertonia.

The first aim of the study is to investigate the prevalence of spasticity and spastic dystonia among the patients with velocity-dependent hypertonia. The subjects were selected clinically, enrolling those showing velocity-depedent hypertonia of leg extensors. Then, using s-EMG we investigated whether the subjects were able to relax their leg extensors prior to muscle stretch (spasticity) or whether their leg extensors were tonically activated prior to stretch (spastic dystonia).

The second aim of this study was to investigate whether the features of the tonic stretch reflex can be different in patients with spasticity and spastic dystonia. In this attempt, we focused our attention on the habituation of the tonic stretch reflex. Several studies showed that tonic stretch reflex gradually decreases during repeated testing (Burke et al., 1970; Nuyens et al., 2002). This reflex habituation is an important feature as repetitive stretching is a common method in the management of hypertonia in UMNS patients (Smania et al., 2010). We focused the attention upon the habituation of the stretch reflex because it is a feature with a practical impact and because we previously observed that in some patients with velocity-dependent hypertonia this feature can be absent, suggesting a possible different behavior in subjects with spasticity and spastic dystonia.

Materials and methods

Subjects

Patients were enrolled at the Department of Neuroscience of the University of Genova, according to the following criteria: 1) multiple sclerosis diagnosed according to the revised McDonald's criteria (Polman et al., 2011); 2) velocity-dependent hypertonia of leg extensors with increased patellar reflex affecting one or both sides ranging from 1–3 according to the modified Ashworth scale (MAS); 3) no pain or discomfort during repetitive passive leg movements; 4) no clinical relapse and no use of botulinum toxin in the last 8 months; 5) no other diseases of the nervous system or any pathological condition interfering with the assessment of the stretch reflex on leg extensors; 6) no relevant cognitive impairment or other conditions preventing patients to understand study instructions such as the order to remain relaxed.

At the end of the evaluation, 30 subjects (16 women; age 51.3±7.3 years, mean±standard deviation) met the inclusion criteria and joined the study. Their demographic and disease-related variables are reported in Table 1. The recruited subjects represent a subsample of those involved in a recently published study (Marinelli et al., 2016).

The present study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; a written informed consent was obtained from all participants. The project was approved by the institutional review committee.

Experimental setup and s-EMG recordings

The patients were studied in the supine position, with the legs over the end of the couch so that they could be flexed at the knee. If velocity-dependent hypertonia was detected in both leg extensors muscles according to the inclusion criteria reported in the previous paragraph (points 2 and 3), the tested side was randomly chosen. Patients were asked to remain fully relaxed over the entire course of the s-EMG recordings.

First of all, to investigate spastic dystonia, s-EMG was recorded for 1 minute with the patient's leg fully extended, sustained at the heel by the examiner (starting position).

Soon after, tonic stretch reflex was elicited by flexing the investigated patient's leg from the starting position until a 90° angle between the leg and thigh was reached (final position). The movements of leg flexion were performed by the examiner, while the patient was asked not to help or resist the movements (passive movements). In each patient, 40 passive discontinuous movements of the leg (from starting position to final position) were collected. The examiner randomly interposed a few metronome tones so that the interval between the beginning of two successive movements ranged from 3 to 10 seconds. This variable time interval prevented subjects from anticipating the subsequent displacement, thus minimizing paratonic muscle activity (Marinelli et al., 2017). To evaluate spastic dystonia changes during repetitive movements, s-EMG was also recorded in the 1000ms preceding each muscle stretch, with the patient in the starting position.

Both spastic dystonia and tonic stretch reflex were measured recording the EMG activity from the rectus femoris muscle through surface electrodes (TSD150B, Biopac Systems Inc, USA). The bipolar surface electrode was composed of two stainless steel pads with a diameter of 11.4 mm each and an inter-electrode distance of 20 mm. The electrode had a 330 gain, input impedance of 100 MΩ, common mode rejection ratio of 95 dB, noise voltage 2μV rms. The skin above the muscle belly was cleansed with 0.5% chlorexidine gluconate/ethanol and conductive paste was carefully placed on each pad in order to minimize impedance, avoiding contact between the two pads. The

electrode was placed at 50% on the line from the anterior spina iliaca superior to the superior part of the patella, parallel to this line (Hermens and Roessingh Research and Development BV, 1999). A reference electrode was fitted around the wrist. The signal was acquired by a MP150 unit (Biopac Systems Inc, USA) with a 2 KHz sampling rate and underwent a Blackman -61 dB 10-350 Hz band-pass filter for off line processing (AcqKnowledge 3.8.1 software by Biopac Systems Inc, USA). For the kinematic recording of the passive movements, we used a TSD130B twin-axis electronic goniometer (Biopac Systems Inc, USA) connected to the Biopac MP150 data acquisition system. The goniometer was placed across the knee joint in order to optimally record the angle during the joint displacements.

To control the velocity of leg displacement and to ensure that, within each single subject, the leg was flexed at the same speed in the course of the 40 movements, we used a method recently developed in our laboratory, which is based on the synchronization of the movements with the tones produced by a software emulated metronome. The tones are perceived by the examiner through earphones. This method has been described in detail elsewhere (Marinelli et al., 2013) and can be briefly summarized as follows. The examiner is required to move the leg from the starting position to the final position in a time corresponding to the interval between two consecutive tones. In this way, the movement velocity increases linearly with the tone frequency set on the metronome (beats per minute – BPM). At first, in each subject, the optimal BPM to evoke a stretch reflex is chosen, taking into account that low values could not be able to elicit the reflex or could elicit a reflex too small to be investigated (especially in subjects with a low degree of velocity-dependent hypertonia). Furthermore, in order to remain in the range of velocities used during muscle tone assessment, the maximal possible value is set at 120 BPM (180 ° per second). Once the optimal BPM has been set, the examiner starts performing consecutive flexion and extension movements following the rhythm of the metronome, moving from the starting position to the final position and *vice-versa* in synchrony with consecutive tones. Performing a few of these continuous (or "sinusoidal") movements (less than 6) allows the examiner to learn the appropriate velocity and therefore to perform the movements also interposing an interval of few tones between them, thus obtaining discontinuous movements.

Data analysis

Single subject analysis

In each subject, spastic dystonia was considered present if tonic muscle activity was detected during the initial 1 minute s-EMG recording.

For each discontinuous passive movement (from 1 to 40), the angle values detected by the

electronic goniometer were used to calculate the onset of the movement (onset time) and the termination of the movement (termination time). Onset and termination times were visually detected on the goniometer trace displayed on the computer screen, using a display gain of 20°/cm and a temporal window of 340ms/cm. Tonic stretch reflex amplitude was measured as the average rectified value of the EMG during each movement (from onset time to termination time).

Spastic dystonia was measured as the rectified value of the s-EMG in the 1000ms preceding each passive movement.

To analyze the course of tonic stretch reflex amplitude along the 40 movements, we performed a linear regression analysis. The slopes of the regression lines (*a* coefficient of function y=*a*x+b) were calculated (tonic stretch reflex slope). The p values of the regression analysis allowed to understand if positive or negative slopes actually reflected a significant increasing or decreasing trend respectively. A similar analysis was performed for spastic dystonia (where present), by measuring spastic dystonia slopes and the corresponding p values (spastic dystonia slope).

Analysis across subjects

To reduce inter-subject variability, in each subject the amplitudes of the tonic stretch reflexes obtained during each movement from number 2 to number 40 were normalized with respect to the amplitude of the tonic stretch reflex obtained during movement 1. Similarly, the amplitudes of spastic dystonia detected before each movement from number 2 to number 40 were normalized with respect to the value obtained before movement 1.

Such normalization was required in order to perform a pooled analysis for subjects without spastic dystonia, in those with increasing spastic dystonia, as well as in those with decreasing spastic dystonia.

As for single subjects, a linear regression analysis between movement number and the normalized tonic stretch reflex amplitude (normalized tonic stretch reflex slope) or spastic dystonia amplitudes (normalized spastic dystonia slope) was performed. Finally, in subjects with spastic dystonia, a linear regression analysis of the relation between normalized stretch reflex slope and normalized spastic dystonia slope was calculated.

The consistency of the range of motion and mean velocity during all movements was confirmed by a subsequent analysis. All analyses were considered significant for $p<0.05$. All the measures of variability are expressed as standard deviation.

Results

Single subjects analysis

In 22 patients (1-22; 73%) spastic dystonia was absent, while in the remaining 8 patients (23-30; 27%) spastic dystonia was present. A tonic stretch reflex was evoked in all 30 enrolled patients. Duration and mean velocity of the repeated passive movements were reproducible and consistent with the selected BPM rate. For each patient, table 2 shows tonic stretch reflex slopes and spastic dystonia slopes with the p values of the corresponding linear regressions.

Among patients without spastic dystonia, the vast majority (1-19) had negative tonic stretch reflex slopes (12 with significant p values) while the remaining 3 patients (20-22) had positive slopes (1 with a significant p value).

In patients with spastic dystonia, the slopes of both spastic dystonia and tonic stretch reflex were negative in 4 patients (23-26); the p values of regression analyses were significant in 2 subjects for tonic stretch reflexes (23-24) and in 1 subject for spastic dystonia (24). In the remaining 4 patients (27-30) both spastic dystonia and tonic stretch reflex slopes were positive; the p values were significant in 2 patients (28,30) for tonic stretch reflexes and in 2 patients (29-30) for spastic dystonia (Table 2).

Figure 1 shows the raw data of 3 representative subjects (see figure legend).

Analysis across subjects

Subjects were pooled together based on the behavior of spastic dystonia (absent/decreasing/increasing).

In the patients without spastic dystonia (1-22), normalized tonic stretch reflex amplitude decreased with the increase of movement number ($p<0.0001$) (Figure 2).

In the patients with negative spastic dystonia slopes (23-26), both normalized tonic stretch reflex amplitude ($p=0.0003$) and normalized spastic dystonia amplitude ($p=0.019$) decreased during repeated movements (Figure 3).

In the 4 patients (27-30) with positive spastic dystonia slopes (27-30), normalized tonic stretch reflex amplitude ($p<0.0001$) and normalized spastic dystonia amplitude ($p<0.0001$) increased with the increase of movement number (Figure 4).

The relation between spastic dystonia and tonic stretch reflex is further supported by the finding of a significant positive correlation between normalized spastic dystonia and tonic stretch reflex slopes (Figure 5).

Discussion

A tonic stretch reflex was evoked (in the absence of any volitional command, i.e. with the subjects at rest) in all the patients with velocity-dependent hypertonia. This result fits with previous demonstration that tonic stretch reflex is the cause of velocity-dependent hypertonia (Thilmann et al., 1991). The new fact here is that tonic stretch reflex was present not only in patients able to relax their muscle prior to stretch (subjects with spasticity), but also in those which have lost this capability (subjects affected by spastic dystonia). This finding was largely expected since α-motoneurons excitability is known to be increased either in patients with spasticity and in those with spastic dystonia. In spasticity, hyper-excitability of the α-motoneurons remains sub-threshold: they discharge (in the absence of any volitional motor inputs) only when they are activated by inputs from the muscle spindles. On the contrary, in spastic dystonia, the increased excitability of the α-motoneurons is sufficient to trigger their firing without volitional inputs and without inputs from the periphery. In this sense, spasticity is a reflex phenomenon, while spastic dystonia is an efferent phenomenon. However, as the α-motoneuron is the efferent part of the stretch reflex, in both conditions the stretch reflex excitability is exaggerated, thus leading to a pathological tonic stretch reflex (i.e. a tonic stretch reflex evoked in a subject at rest).

The first aim of this study was to investigate the prevalence of spasticity and spastic dystonia among MS patients with velocity-dependent hypertonia of leg extensors. We found that 73% of the patients were able to relax their muscle prior to stretch. These subjects represent those actually affected by spasticity. In the remaining 27% of the subjects, RF was tonically activated prior to muscle stretch. These are the subjects affected by spastic dystonia. In a clinical setting, all the enrolled subjects would have been considered affected by spasticity. Therefore, this study reveals for the first time that there are two types of velocity-dependent hypertonia: that mediated by spasticity and that mediated by spastic dystonia. Using clinical rating scales with a better standardization of velocity in providing muscle elongation, such as the Modified Tardieu Scale, would have not helped in the distinction of the two types of velocity-depend hypertonia, while s-EMG was crucial in detecting spastic dystonia and its variation during repetitive stretches.

The present study represents just the first attempt to investigate the prevalence of spasticity and spastic dystonia in UMNS patient. These data are largely preliminary. First, they refer only to RF; second, they were collected only in MS patients. The prevalence of spastic dystonia should be investigated in all the muscle groups affected by muscle hypertonia (i.e. foot extensors, leg flexors, elbow, wrist and fingers flexors, elbow extensors) and in all the diseases causing UMNS (i.e. MS,

stroke, traumatic lesions, cerebral palsy, etc.). Following the experimental protocol used in the present study (clinical assessment of velocity-dependent hypertonia and subsequent s-EMG detection of spasticity and spastic dystonia), we will be able to investigate the true prevalence of spasticity, which probably is now overestimated, and that of spastic dystonia, which is likely underestimated.

The second aim of this study was to investigate the habituation of the tonic stretch reflex in patients with spasticity and in those with spastic dystonia. We found that during repetitive passive stretches the magnitude of tonic stretch reflex decreased in the overwhelming majority of the patients who were able to maintain their RF relaxed before muscle stretching (patients with spasticity). On the contrary, in each patient unable to relax RF completely prior to stretch (patients with spastic dystonia), tonic stretch reflex and spastic dystonia showed the same trend during stretches repetition, i.e. their amplitudes decreased or increased from movement 1 to 40. Therefore, spastic dystonia drives the behavior of tonic stretch reflex during repetitive stretching. This effect is likely to be mediated by excitability changes of the α-motoneurons. If spastic dystonia increases along the trials, also the excitability of spinal motoneurons will probably increase and, as a consequence, tonic stretch reflex amplitude becomes larger, despite the action of those mechanisms that are supposed to reduce the amplitude of tonic stretch reflex when repeatedly activated. We are tempting to suggest that also in the 3 patients (subjects 20-22) without spastic dystonia in whom tonic stretch reflex increased over the stretches, this finding could have been caused by a progressive enhancement in spinal motor neuron excitability, which however did not reach the threshold for motor neurons firing.

These data state that the clinical features of velocity-dependent hypertonia may be different depending on whether the cause of the hypertonia is spasticity or spastic dystonia. This point is very important, since it suggests that separating the two forms of muscle hypertonia could be clinically relevant. These preliminary results warrant further studies aimed at investigating these two forms of velocity dependent-hypertonia.

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Table 1

Patient	Sex	Age	EDSS	MAS	Disease duration	Clinical course	Antispastic medication
1	F	50	6	1	24	SP	none
2	M	40	7	2	18	SP	none
3	M	42	6.5	1.5	22	SP	baclofen
4	F	48	6.5	3	10	SP	baclofen
5	F	43	7	3	16	SP	none
6	M	53	6.5	1	15	SP	none
7	M	43	6.5	2	4	SP	none
8	F	61	6.5	1.5	23	SP	none
9	F	42	7.5	2	8	SP	tizanidine
10	F	45	6.5	3	19	PP	none
11	F	53	6.5	3	38	SP	baclofen
12	M	54	6	3	16	SP	none
13	M	38	5	2	18	RR	none
14	M	46	6	1	4	RR	none
15	M	47	6.5	3	8	SP	none
16	F	45	7	2	15	SP	none
17	M	60	7	3	14	SP	none
18	F	50	6	2	8	SP	none
19	F	60	6.5	2	20	SP	gabapentin
20	F	53	7	3	18	SP	baclofen
21	F	60	7	1	9	SP	gabapentin
22	M	58	7	1.5	15	SP	none
23	F	67	7.5	2	21	SP	none
24	M	56	6.5	3	26	SP	none
25	M	60	6.5	1	23	SP	none
26	M	57	6	1.5	22	PP	none
27	F	52	6.5	1	8	SP	baclofen
28	F	49	6.5	2	13	SP	baclofen
29	F	49	6.5	2	9	SP	baclofen
30	M	57	6.5	3	20	SP	baclofen

Demographic and disease-related variables of the 30 patients with multiple sclerosis included in the analysis. For clarity purposes, patients' numbering does not reflect their recruitment order. EDSS: Expanded Disability Status Scale; MAS: Modified Ashworth Scale; PP: Primary Progressive; RR: Relapsing Remitting; SP: Secondary Progressive. Disease duration is reported in years.

Table 2

Patient	Side	BPM	TSR slopes	p	SD slopes	p
1	L	120	-0.0276	0.0001		
2	L	120	-0.0111	0.0001		
3	L	60	-0.0103	0.0001		
4	R	60	-0.0094	0.0001		
5	R	60	-0.0081	0.0001		
6	R	120	-0.0080	0.0001		
7	L	90	-0.0070	0.0001		
8	L	120	-0.0058	0.0001		
9	R	60	-0.0049	0.0001		
10	R	40	-0.0048	0.0001		
11	R	40	-0.0040	0.02		
12	R	60	-0.0034	0.81		
13	R	100	-0.0029	0.04		
14	R	120	-0.0019	0.67		
15	L	60	-0.0015	0.23		
16	L	120	-0.0006	0.87		
17	R	90	-0.0005	0.63		
18	R	120	-0.0004	0.84		
19	L	120	-0.0003	0.8		
20	L	120	0.0019	0.24		
21	L	120	0.0024	0.06		
22	R	100	0.0200	0.0001		
23	L	60	-0.0042	0.0005	-0.0020	0.29
24	R	40	-0.0038	0.0001	-0.0060	0.0007
25	R	120	-0.0028	0.09	-0.0059	0.33
26	L	120	-0.0017	0.36	-0.0011	0.65
27	L	120	0.0045	0.07	0.0054	0.11
28	R	40	0.0090	0.0001	0.0018	0.27
29	R	100	0.0164	0.07	0.0065	0.04
30	R	60	0.0182	0.0001	0.0163	0.001

For each of the 30 analyzed patients the table shows: the evaluated body side, selected beats per minute (BPM) for metronome-synchronized passive movements, tonic stretch reflex (TSR) slopes with the p values of corresponding linear regressions, spastic dystonia (SD) slopes with the p values of corresponding linear regressions.

Figure 1

EMG and goniometer time series (movements 1, 10, 20, 30 and 40) in a patient (#3) without spastic dystonia (A) as well as in a patient (#24) with spastic dystonia decreasing across movements (B) and a patient (#30) with spastic dystonia increasing across movements (C).

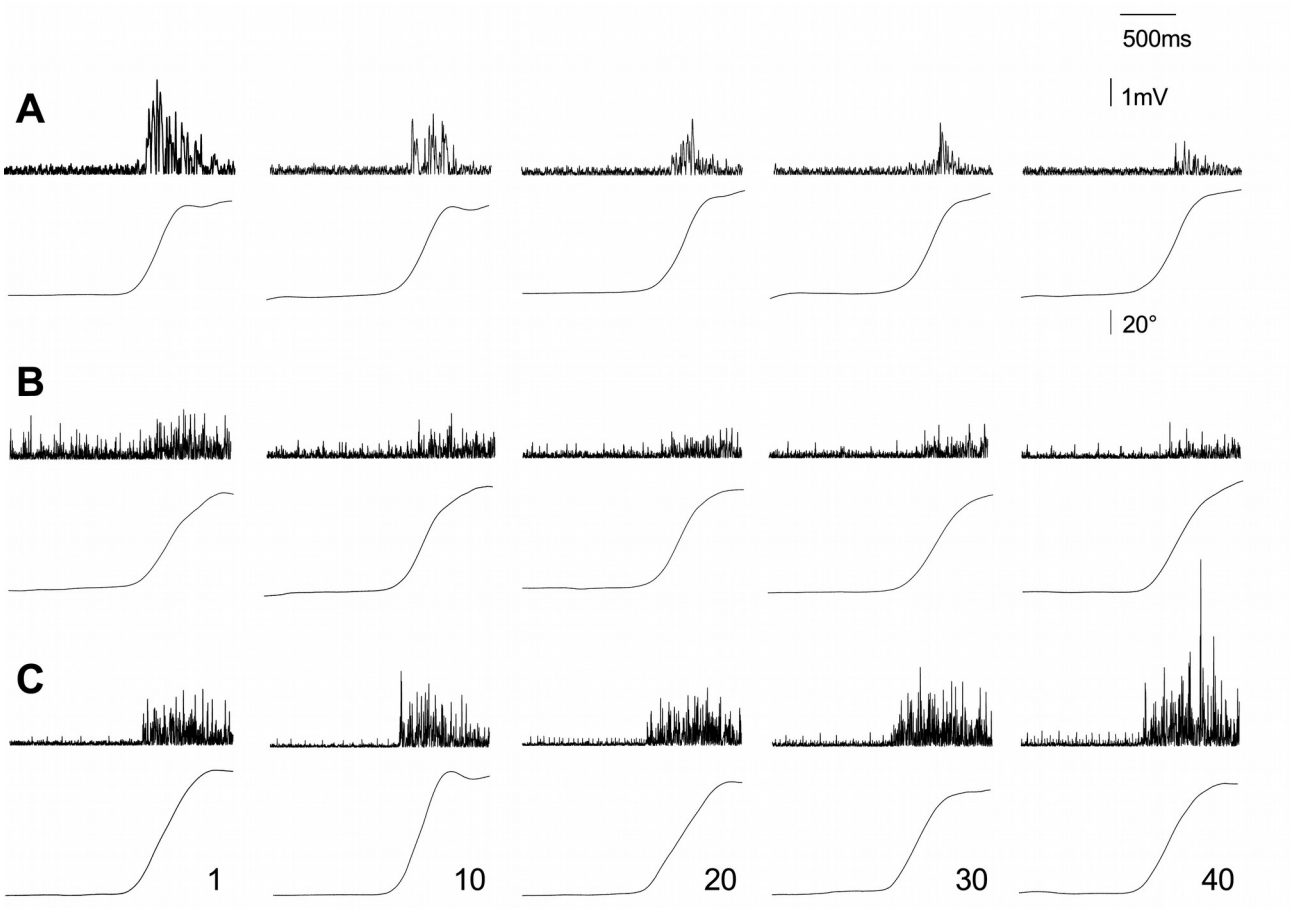

Figure 2

Course of the normalized tonic stretch reflex (TSR) amplitude in patients without spastic dystonia (patients 1-22).

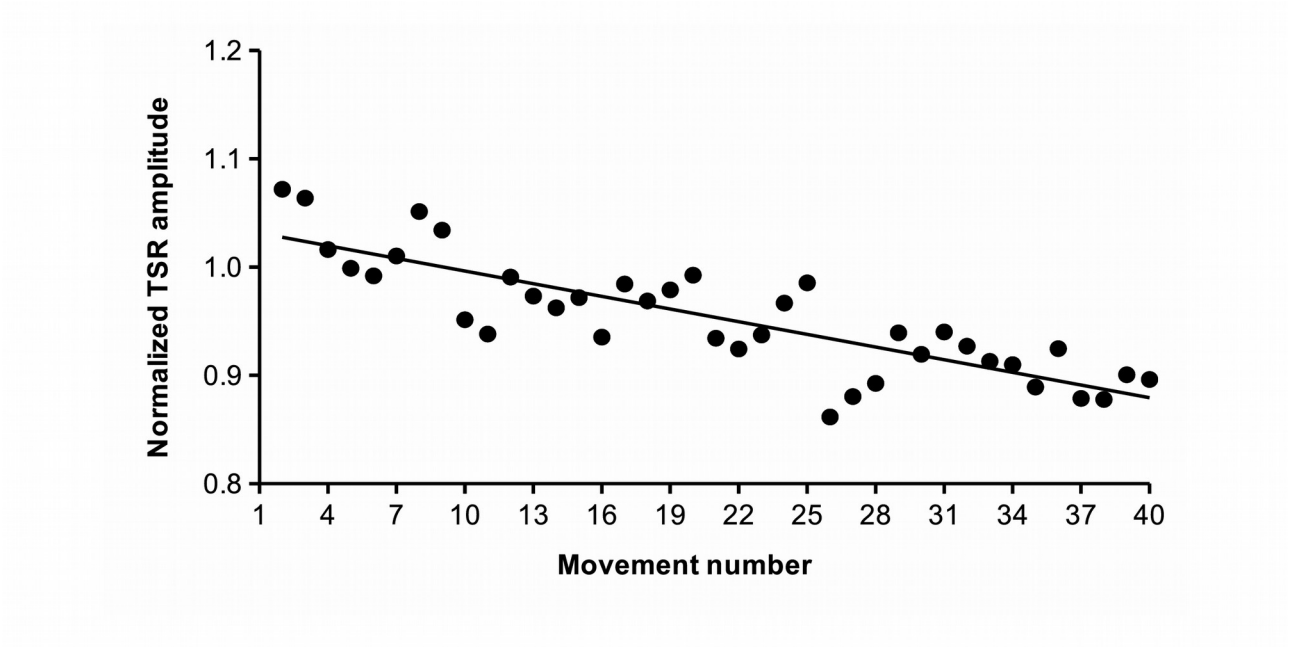

Figure 3

Course of the normalized tonic stretch reflex (TSR) amplitude (upper panel) and the course of the normalized spastic dystonia (SD) amplitude (lower panel) in the 4 patients (23-26) with negative spastic dystonia slopes (see Table 2).

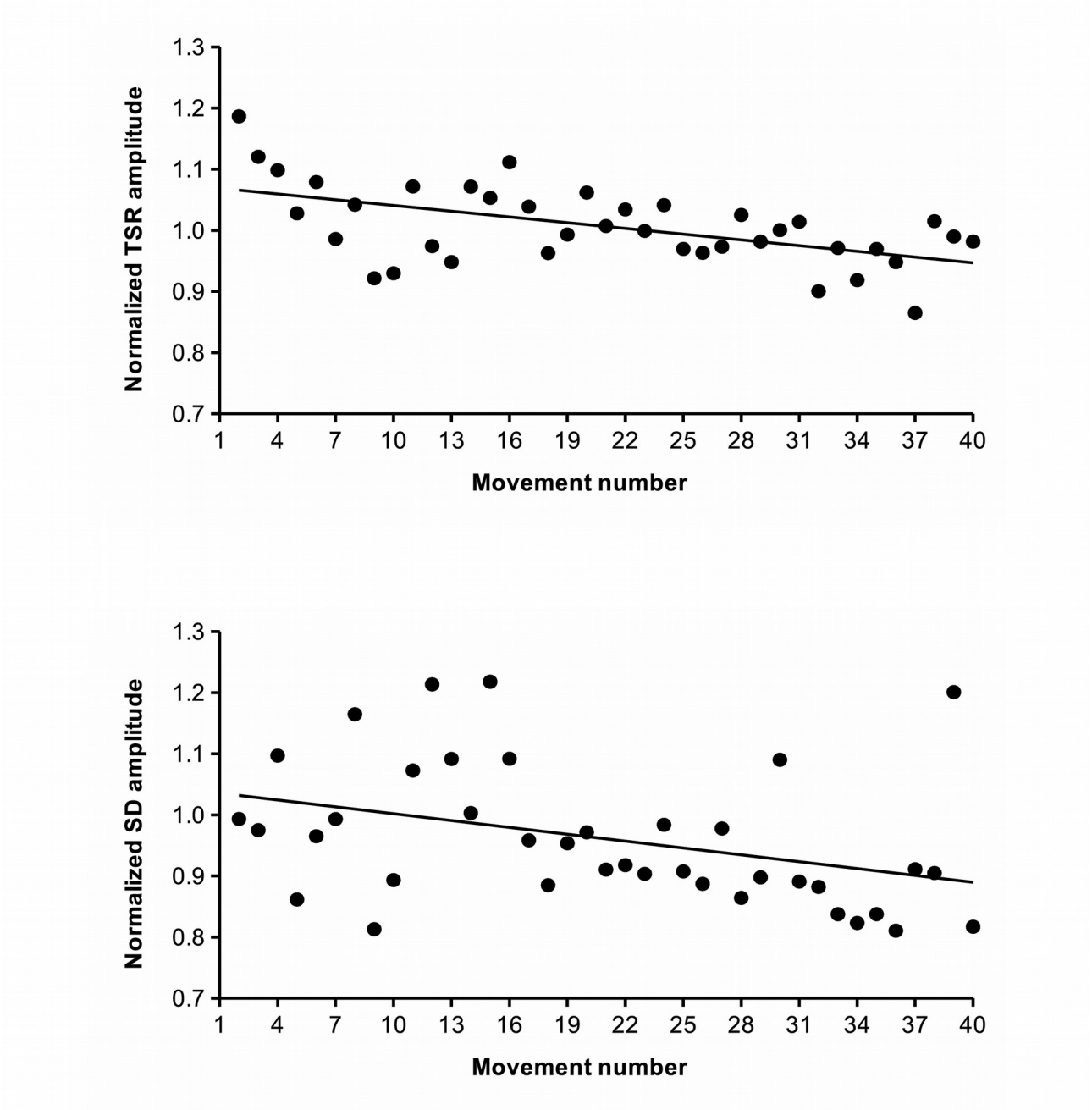

Figure 4

Course of the normalized tonic stretch reflex (TSR) amplitude (upper panel) and the course of the normalized spastic dystonia (SD) amplitude (lower panel) in the 4 patients (27-30) with positive spastic dystonia slopes (see Table 2).

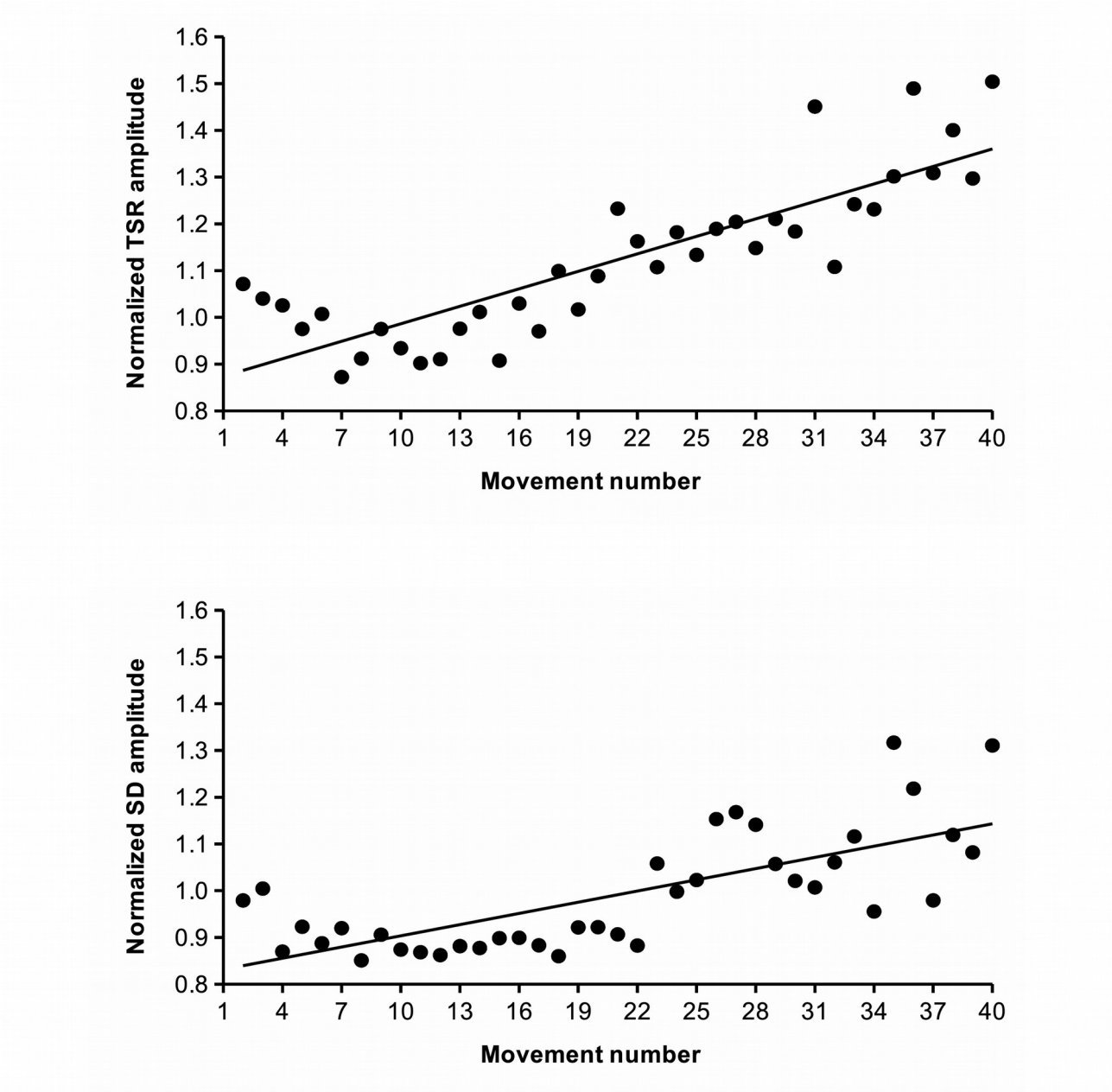

Figure 5

Linear regression between normalized tonic stretch reflex (TSR) slopes and spastic dystonia (SD) slopes (patients 23-30). There was a positive correlation between the 2 variables (R=0.90; p=0.0026).