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Defining the spectrum of spasticity-associated involuntary movements

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ABSTRACT

Background: Spasticity can be associated with several hyperkinetic involuntary movements generally referred to as "spasms" despite different phenomenology and clinical characteristics.
Objective: To better characterize the phenomenology and clinical characteristics of spasticity-associated involuntary movements.
Methods: We performed a cross-sectional study of a consecutive patient sample from the spasticity clinic. Each patient was interviewed by a movement-disorder neurologist who conducted a standardized movement-disorder survey and a focused exam. Patients with involuntary movements were video-recorded and videos were independently rated by a separate blinded movement-disorder neurologist.
Results: Sixty-one patients were included (54% female, mean age 49.7 ± 13.9 years). Of the entire cohort, 11.5% had spinal, 44.3% had cerebral, and 44.3% had mixed-origin spasticity. Fifty-eight patients (95%) reported one or more involuntary movements: 75% tonic spasms (63% extensor, 58% isometric, 41% flexor/adductor), 52% spontaneous clonus, 34% myoclonus, 33% focal dystonia, and 28% action tremor. One third of the involuntary movements were painful. Only 53% of patients reported that their involuntary movements were much or very-much improved with their current anti-spasticity management. Patients treated with intrathecal baclofen therapy were more likely to report much or very-much improvement compared to patients receiving oral and/or botulinum therapy (P = 0.0061 and 0.0069 respectively).
Conclusion: Most spastic patients experience spasticity-associated involuntary movements of variable phenomenology and impact. However, only half of these patients experience significant improvement with the current management strategies. More research is needed to explore better treatment options for spasticity-associated involuntary movements with focus on phenomenology-specific approaches.

1. Introduction

Spasticity is an abnormal increase in muscle tone secondary to lesions affecting the pyramidal and parapyramidal tracts [1]. Initially the increase in muscle tone is velocity-dependent resulting in the classical clasp-knife quality but in more advanced stages, increased tone becomes persistent throughout the range of motion [23] Spasticity and its associated phenomena can lead to pain, posturing, skin breakdown, impairment of residual neurological function, and eventually contractures [45] Although spasticity along with its associated weakness and spastic co-contraction often lead to hypokinesis, it is commonly associated with several hyperkinetic involuntary movements.[1] Aside from clonus, these hyperkinetic movements are often referred to collectively as "spasms" by both providers and patients despite having different phenomenology, impact, and response to treatment [6] The hypertonia represents the "tonic" component of spasticity while some of the associated involuntary movements represent the "phasic" component [7]. In literature, reports of spastic dystonia, tonic spasms, clonus, myoclonus, and several other involuntary movements have been cited in spastic patients without systematic analysis or detailed expert evaluation.[1] [89] Much is yet to be known about the prevalence and clinical characteristics of these involuntary movements across the wide spectrum of spasticity-associated conditions. The response of these involuntary movements to conventional anti-spasticity measures is

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unknown and so is the impact of the etiology and anatomical generator of spasticity on the phenomenology of the abnormal movements. We sought to study the spectrum of spasticity-associated involuntary movements within a systematic movement disorder-focused and patient-oriented protocol.

2. Methods

We conducted a cross-sectional study on a consecutive sample of adult patients attending a specialized spasticity management clinic over a one-year-period from July-2015 to June-2016. Each patient was given a patient information sheet describing the study with options to opt in or out. All patients with documented spasticity on exam who agreed to participate in the study were included. Eligible patients were interviewed and examined by a movement disorder neurologist and a senior physiatrist to determine the presence of spasticity and evaluate associated involuntary movements present on exam. Each patient was given an in-house movement disorder survey specifically developed for this study based on clinical experience and observations from spastic patients inquiring about the current existence of any of the following abnormal movements in the same body part afflicted by spasticity: tonic spasms (extensor, flexor, or isometric), focal dystonia, myoclonus, clonus, tremor, or other movement disorders. The movement disorder had to have started after the neurological insult that resulted in spasticity. We developed operational definitions to differentiate clinically between these movement disorders based on previous studies of spinal and spasticity-associated movement disorders as shown in table-1.[1, 8, 10, 11]

The survey included a 7-point patient global impression (PGI) questionnaire inquiring about the impact of the current anti-spasticity treatment (oral, injectable, intrathecal, or combined) on each of the involuntary movements listed on the survey. The PGI scale ranged from 1 (very-much-improved) to 7 (very-much-worse). The survey was written in layperson terms and when needed, the involuntary movement in question was explained and demonstrated by the examiner. The examiner performed a movement disorder-focused exam on each participant then rated and video-recorded abnormal movements evident on exam. The videos were independently rated again for phenomenology by a separate movement disorder neurologist blinded to the patients' clinical data. The blinded rater was asked to give one primary and two alternative phenomenology ratings for each video. This was done to accommodate potential differences in the subjective interpretation of the phenomenology of each involuntary movement. Movement disorders raters may have a primary phenomenology rating for a particular involuntary movement and several other possible ratings of the same movement especially if blinded to the rest of the clinical data of the patient (e.g. when rating an isolated video showing involuntary movement of the fingers without any additional clinical data, the rater might rate the movement as athetosis, pseudoathetosis, or postural tremor). Allowing one primary rating and two additional alternative ratings could reduce artificial inter-rater disagreement that might stem from blinded video-rating. In case of inter-rater disagreement, the second and third phenomenology ratings by the blinded rater were taken into account and compared to the rating of the primary investigator. This method has already been used and published by the authors in previous work [11].

2.1. Statistical analysis

Fisher's exact test was used to compare the frequency of the different movement disorders among the three types of spasticity (cerebral, spinal, and mixed-origin) and the three major etiological categories (demyelination, stroke, and miscellaneous). Chi-square test was used to compare prevalence of the involuntary movements in the upper extremity (UE) versus the lower extremity (LE) and to compare anti-spasticity treatment in patients with much or very-much improved rating on the PGI versus those with all other ratings. This study was approved by the institutional review board of the Cleveland Clinic. Written informed consent was obtained from each patient before video-recording.

3. Results

Sixty-one patients were included (54% female, mean age 49.7 ± 13.9 years). Of the entire cohort, 7 (11.5%) patients had spinal, 27 (44.3%) cerebral, and 27 (44.3%) mixed-origin spasticity. The most common causes of spasticity were multiple sclerosis (MS) (n = 26,42%), stroke (n = 15,24.5%), cerebral palsy (n = 4,6.5%), spinal cord injury (SCI) (n = 4,6.5%), mitochondrial disease (n = 2,3.2%), epilepsy surgery (n = 2,3.2%), and one (1.6%) each of the following: traumatic brain injury (TBI), brain meningioma, spinal cord tumor, neuromyelitis Optica, autoimmune encephalitis, lupus cerebritis, sarcoid myelitis, and hereditary spastic paraplegia. Mean disease duration at the time of the study was 16.4 ± 10.9 years.

Fifty-eight patients (95%) reported one or more involuntary movements on the survey. Thirty-three patients (54%) manifested the

Table 1
Proposed definitions and classification of spasticity-associated movement disorders.

Movement disorder	Definition
Flexor tonic spasm	Paroxysmal sustained increase in muscle tone resulting in visible tonic posturing of the affected body part (often the whole limb or part of the limb) in flexion associated with spasticity.
Extensor tonic spasm	Paroxysmal sustained increase in muscle tone resulting in visible tonic posturing of the affected body part (often the whole limb or part of the limb) in extension associated with spasticity.
Adductor/Inversion tonic spasm	Paroxysmal sustained increase in muscle tone resulting in visible tonic posturing of the affected body part (often the whole limb or part of the limb) in adduction or inversion associated with spasticity.
Isometric tonic spasm	Paroxysmal sustained increase in muscle tone that can be felt by the patient and palpated by the examiner but does not result in visible change in posture (e.g. abdominal wall muscles) associated with spasticity.
Complex tonic spasm	Paroxysmal sustained increase in muscle tone resulting in visible tonic posturing of one or more body parts in more than one position (extension, flexion, adduction or inversion) with or without other involuntary movements associated with spasticity.
Paroxysmal focal dystonia	Paroxysmal sustained muscle contraction of antagonistic muscle groups resulting in a complex abnormal posture (other than simple flexion, extension, or adduction) associated with spasticity.
Non-paroxysmal (fixed) focal dystonia	Persistent (non-paroxysmal) sustained muscle contraction resulting in a fixed abnormal posture associated with spasticity with complete or partial preservation of passive range of motion (may be referred to as spastic posturing).
Spasticity-associated myoclonus	Sudden, brief (non-sustained), shock-like muscle contraction associated with spasticity. It may be focal, segmental, or generalized.
Spontaneous clonus	Spontaneous Involuntary, rhythmic muscle contractions and relaxations of the upper or lower extremity (e.g. ankle) associated with spasticity.
Spasticity associated tremor	Constant or intermittent rhythmic to and fro movement of the same body part afflicted by spasticity accentuated by action or in certain postures in the absence of alternative explanation for tremor and in the presence of robust response to anti-spasticity treatment.

Table 2
Clinical characteristics and location of spasticity-related involuntary movements.

Clinical feature	Extensor spasm n = 29	Flexor spasm n = 19	Isometric spasm n = 27	Focal dystonia n = 20	Myoclonus n = 21	Spontaneous clonus n = 32
Painful	7 (24%)	**7 (37%)**	9 (33%)	2 (10%)	0 (0%)	1 (3%)
Kinesogenic (triggered by action)	14 (48%)	**12 (63%)**	4 (15%)	1 (5%)	1 (4.7%)	17 (53%)
Stimulus-sensitive (e.g. triggered by touch or change in temperature)	**12 (42%)**	7 (37%)	3 (11)%	3 (15%)	5 (24%)	12 (37.5%)
Upper extremity	1 (3.4%)	3 (16%)	5 (18.5%)	**14 (70%)**	5 (24%)	3 (9%)
Lower extremity	**29 (100%)**	18 (95%)	21 (78%)	5 (25%)	10 (48%)	30 (94%)
Trunk	4 (14%)	0 (0%)	4 (15%)	0 (0%)	**6 (28.5%)**	0 (0%)

The highest percentage of each category is highlighted in bold while the lowest percentage is underlined.

involuntary movements on exam. The inter-rater agreement was 80% for first phenomenology rating and 100% when other ratings taken into account. Of the entire cohort, 46 patients (75%) had one or more type of tonic spasms (63% extensor, 58% isometric, 41% flexor/adductor), 32 (52%) had spontaneous ankle or wrist clonus, 21 (34%) had focal or truncal myoclonus, 20 (33%) had focal dystonia (10 paroxysmal and 10 fixed), and 17 (28%) had action tremor. Table-2 summarizes the clinical features and locations of these involuntary movements.

Some patients had complex involuntary movements (e.g. flexor spasm in one LE with simultaneous extensor spasm and clonus of the other LE). Two patients reported subjective fasciculations, one reported hyperkeplexia, and one had episodes resembling paroxysmal kinesogenic dyskinesia thought to be functional based on clinical judgement, phenomenology rating, and relation to stress. See Supplemental Videos 1–9 for phenomenology examples from the study cohort.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.05.007.

There was no statistically-significant difference in the prevalence and subtypes of involuntary movements between the different types and etiological categories of spasticity (table-3).

The LE was involved by spasticity-associated involuntary movements in 52 patients (85.2%), the UE in 30 (49.2%), and the trunk in 6 (9.8%). Extensor spasms (p-value ≤ 0.00001), flexor spasms (p-value = 0.013), isometric spasms (p-value = 0.026), and clonus (p-value = 0.00002) were all significantly more represented in the LE than the UE while focal dystonia, both fixed and paroxysmal, was significantly more represented in the UE (p-value = 0.00012). There was no statistical difference in myoclonus frequency between the UE and LE. All six patients with truncal involvement manifested truncal myoclonus, 4 patients also manifested truncal extensor spasms, and 4 also manifested truncal isometric spasms.

Table 3
Prevalence of movement disorders per cause and type of spasticity.

Symptom	Cause of Spasticity			P-value
	CVA (n = 15)	DD (n = 27)	Misc (n = 19)	
Movement disorder	14 (93.3%)	27 (100%)	17 (89.5%)	0.166
Tonic spasm	11 (73.3%)	21 (77.8%)	14 (73.7%)	1.000
Extensor TS	6 (40%)	14 (51.9%)	9 (47.4%)	0.761
Flexor TS	4 (26.7%)	7 (25.9%)	8 (42.1%)	0.495
Isometric TS	5 (33.3%)	14 (51.9%)	8 (42.1%)	0.482
Paroxysmal dystonia	2 (13.3%)	3 (11.1%)	5 (26.3%)	0.370
Fixed Dystonia	3 (20%)	5 (18.5%)	2 (10.5%)	0.744
Myoclonus	4 (26.7%)	10 (37%)	7 (36.8%)	0.833
S clonus	5 (33.3%)	15 (55.6%)	12 (63.2%)	0.213
Tremor	3 (20%)	11 (40.7%)	3 (15.8%)	0.163
Symptom	Type of Spasticity			P-value
	Cerebral (n = 27)	Spinal (n = 7)	Mixed (n = 27)	
Movement disorder	24 (88.9%)	7 (100%)	27 (100%)	0.332
Tonic spasm	19 (70.4%)	6 (85.7%)	21 (77.8%)	0.765
Extensor TS	12 (44.4%)	3 (42.9%)	14 (51.9%)	0.935
Flexor TS	7 (25.9%)	5 (71.4%)	7 (25.9%)	0.072
Isometric TS	9 (33.3%)	4 (57.1%)	14 (51.9%)	0.382
Paroxysmal dystonia	6 (22.2%)	1 (14.3%)	3 (11.1%)	0.636
Fixed Dystonia	4 (14.8%)	1 (14.3%)	5 (18.5%)	1.000
Myoclonus	8 (29.6%)	3 (42.9%)	10 (37%)	0.800
S clonus	11 (40.7%)	6 (85.7%)	15 (55.6%)	0.122
Tremor	5 (18.5%)	1 (14.3%)	11 (40.7%)	0.159

CVA: cerebrovascular accident, DD: demyelinating disease, Misc: miscellaneous.

One third of the involuntary movements were painful, 57.4% were kinesogenic (brought on or worsened by action), and 52.4% were stimulus-sensitive. The most frequently-cited triggers to the involuntary movements were: temperature changes especially cold exposure (6 patients), resting or lying down (6), transfers and weight bearing (5), tactile stimulation (4), stretching or yawning (2), and physical overexertion (2). Single reports of the following triggers were noted: urinary tract infections (UTIs), emotional stress, coughing, speaking, removing LE braces, and fork holding (triggering paroxysmal hand dystonia).

Thirty-two (52.2%) patients were receiving oral anti-spasticity agents alone (n = 9) or combined with botulinum-toxin injections (BTX) and/or intrathecal baclofen (ITB) pump (n = 23), 31 (51%) were getting 3-monthly BTX alone (n = 9) or combined with oral agents and/or ITB (n = 22), and 18 (29.5%) had ITB alone (n = 10) or combined with oral agents and/or BTX (n = 8).

Fifty-three (87%) patients answered the PGI survey (Supplemental figure- 1). Only 53% reported much or very-much improvement in their involuntary movements with their current anti-spasticity management which was started to address spasticity and associated “spasms” as generally described by patients. Patients treated with ITB were more likely to report much or very-much improvement in their overall involuntary movements compared to patients receiving oral agents (p-value = 0.0061) and/or BTX only (p-value = 0.0069).

All patients with extensor spasms reported response to their anti-spasticity treatment regardless of treatment type except one patient who was resistant to BTX. One patient reported resistance to oral medications but improvement after BTX addition. Of the 19 patients with flexor spasms, 4 (21%) reported treatment resistance and were all treated with oral medications and/or BTX. All patients with flexor spasms treated with ITB (n = 7) reported much or very-much improvement. Isometric spasms were the most difficult to treat with one-third of patients reporting treatment resistance including 6 patients treated with ITB.

Spontaneous clonus was generally responsive to anti-spasticity management with only 19% reporting resistance to oral medications and/or BTX. All patients with spontaneous clonus reported marked improvement after ITB with one patient reporting additional benefit after adding BTX to ITB. Forty percent of focal dystonia patients did not respond to anti-spasticity management including three patients treated with ITB, three with BTX, and two with oral medications only. One patient reported resistance of LE focal dystonia to ITB followed by response when BTX was added. Forty-eight percent of myoclonus patients did not respond to spasticity management including ITB. One patient

with bilateral LE myoclonus reported improvement only after addition of pramipexole.

Of the 17 patients with coexisting tremor in the spastic limb, 13 had a separate etiology to explain the tremor such as demyelination or infarction in a tremor-generating structure (e.g. cerebellum, thalamus, or brainstem) and therefore the tremor was not considered spasticity-related in those patients. In the remaining four patients, tremor was thought to be possibly spasticity-related. These included an SCI patient and postural toe tremor, a patient with corona radiate infarct and postural LE tremor, a TBI patient and finger tremor, and a patient with mitochondrial encephalopathy and LE tremor. All four patients lacked visible lesions in typical tremor-generating structures and all reported significant tremor improvement in response to anti-spasticity measures (ITB in one patient and BTX in three).

4. Discussion

We performed a cross-sectional study of spasticity-associated involuntary movements in a consecutive sample of adult patients attending a specialized spasticity-management clinic over a one-year period. All but 3 patients reported 1 or more involuntary movements most commonly tonic spasms, spontaneous clonus, myoclonus, and focal dystonia. Our proposed classification of spasticity-associated involuntary movements (table-1) differentiated among several types of spastic hyperkinetic movements, each with distinct phenomenology, impact, triggers, and treatment responsiveness. Although the most widely-used spasm scale – the Penn Spasm Frequency Scale (PSFS) – has been useful in quantifying spasticity-associated hyperkinetic movements, it does not provide a qualitative evaluation of these abnormal movements nor does it provide information regarding potential triggers or anatomical location [6]. This information is detrimental for the treating physician as it can affect the treatment choice and rehabilitation plan. Our results also show that typical spasticity-associated involuntary movements like extensor spasms and clonus are often responsive to anti-spasticity treatment while less common movements like focal dystonia, myoclonus, and isometric spasms are less responsive and may require combination therapy or addition of phenomenology-specific medications. Therefore, identifying the correct phenomenology as well as the anatomical location is key for successful treatment. For example, a patient with stereotypic extensor spasms of both knees may be a good candidate for ITB while a patient with unilateral elbow flexor spasms may be better treated with BTX to the involved biceps. Likewise, identifying common triggers can guide required adjustments of living conditions and development of effective rehabilitation program; for example, by adjusting household temperature, bed inclination, and/or transfer mechanisms. Lastly, it is important to critically evaluate the impact of each movement. Our results show that the general concept of “painful spasms” is inaccurate since about two thirds of the involuntary movements were painless. However, pain is not the only impact of these involuntary movements; they can also cause discomfort or interfere with residual function and predispose to falls.[4 5] Inquiring about the impact of each involuntary movement is therefore extremely important when implementing a spasticity management plan. In light of these concepts and our study results, we propose an improved scale for evaluating spasticity-associated hyperkinetic movements as shown in table-4.

The scale can be useful clinically for better evaluation of hyperkinetic movements associated with spasticity and to support treatment decisions. Integrating the PSFS frequency scoring system with additional scoring of the type, triggers, impact, and treatment-responsiveness of each involuntary movement can also provide a more meaningful outcome for both clinical monitoring and future research. The wide scoring range allows more sensitivity to clinical change in response to treatment or spasticity progression and resembles other movement disorder scales such as the unified-Parkinson's-disease-rating-scale or the dystonia-rating-scale. A real-life example is presented in supplemental table 1.

Our study provides clinically-meaningful information regarding each spasticity-associated involuntary movement. As expected, tonic spasms were the most common involuntary movement, but the different spasm subtypes had different clinical characteristics. Contrary to prior reports (especially the ones focused on spinal spasticity),[1] [12] we found that extensor spasms are more common than flexor spasms. They were also the most responsive to treatment and had the least association with pain and highest sensitivity to external stimuli. Flexor spasms were the most painful and were commonly kinesogenic and more responsive to ITB than oral or injectable therapy. Although we expected flexor spasms to be more common in the UEin keeping with the central distribution of hypertonia [13] our results did not support this, as all spasm subtypes were more common in the LE. Isometric spasms were the second commonest spasm subtype and were commonly –but not predominantly-painful. In addition to the LE, they were also common in truncal muscles and tended to be mostly spontaneous and less sensitive to movement or other triggers. They were more ITB-responsive compared to oral and injectable medications.

Although spontaneous clonus was very common, it was often painless and readily responsive to anti-spasticity treatment. Focal dystonia was more common in the UE and was less responsive to anti-spasticity treatment regardless of type including BTX. This was somewhat unexpected since dystonia is typically BTX-responsive [14]. This could reflect the pathophysiological difference between extrapyramidal and spastic dystonia or simply the small number of focal dystonia cases in our cohort may have precluded sufficient comparison between the different treatment modalities. Although the term paroxysmal dystonia is commonly used interchangeably with tonic spasms [15], our current and previous research[10 11] demonstrate a clear difference between these two entities in terms of movement complexity, association with pain, sensitivity to action and other stimuli, and most importantly, treatment responsiveness (table-2). Spasticity-associated myoclonus was predominantly non-kinesogenic and often resistant to anti-spasticity treatment, however, it was often painless, of low frequency, and of limited impact. Lastly, although tremor was largely not directly related to spasticity in this cohort, a few cases seemed potentially spasticity-related and responsive to spasticity treatment.

Prior attempts have been made to classify spasticity-associated involuntary movements according to movement disorder terminology but were either based on consensus or limited electrophysiological data.[8 9] Our study is the first to involve protocoled evaluations by both movement disorder and physical medicine experts including video-recording and blinded phenomenology rating. To our knowledge, it is also the first study to focus on patient perception of spasticity-associated hyperkinetic movements and their selective response to treatment. In the recent consensus paper by Dressler and colleagues, two hyperkinetic phenomena were included in their proposed updated spasticity definition: action dystonia and spasms [8]. Their new definition did not include spontaneous clonus, myoclonus, or tremor, nor did it specify or differentiate between the different spasm subtypes. Although fixed dystonia was not included in the definition, the authors proposed a documentation sheet that includes a section dedicated for spastic postures; those are concordant to our fixed dystonia designation. The authors included movement disorder experts and aimed to utilize movement disorder terminology to approach spasticity from a new perspective similar to the goal of our study. However, our study had the advantage of capturing a broader range of involuntary movements. One of the main goals of our study was to explore under-reported and under-recognized involuntary movements associated with spasticity. Given the brief and occasionally non-impactful nature of some of these movements, they are often overlooked by the clinician and under-reported by the patient unless they were specifically sought after. This may explain why the rates of these involuntary movements are higher in our study compared to prior reports.

Thomas and colleagues studied involuntary movements of the LE in four patients with SCI using continuous EMG [9]. They identified five

Table 4
Spasticity-associated hyperkinetic movements scale.

Spasticity-related involuntary movement	Presence	Frequency (specify)	Location	Triggers	Impact	Current treatment and response	Row Score
Extensor spasm	0 No _ 1 Yes _ **Score** _	(1) Rare _ (2) < 1/hour _ (3) 1–9/hour _ (4) ≥ 10/hour _ **Score** _	(1) 1 limb _ (2) 2 limbs _ (3) 3 limbs _ (4) 4 limbs _ + add 1 point if trunk involved **Score** _	(1) Action _ (2) Other (specify) _ (3) Spontaneous _ **Score** _	(0) None _ (1) Pain _ (2) Function _ **Score** _	Oral (specify) _ BTX _ ITB _ (0) Responsive _ (1) Partial response _ (2) Resistant _ **Score** _	
Flexor spasm	0 No _ 1 Yes _ **Score** _	(1) Rare _ (2) < 1/hour _ (3) 1–9/hour _ (4) ≥ 10/hour _ **Score** _	(1) 1 limb _ (2) 2 limbs _ (3) 3 limbs _ (4) 4 limbs _ + add 1 point if trunk involved **Score** _	(1) Action _ (2) Other (specify) _ (3) Spontaneous _ **Score** _	(0) None _ (1) Pain _ (2) Function _ **Score** _	Oral (specify) _ BTX _ ITB _ (0) Responsive _ (1) Partial response _ (2) Resistant _ **Score** _	
Isometric spasm	0 No _ 1 Yes _ **Score** _ _	(1) Rare _ (2) < 1/hour _ (3) 1–9/hour _ (4) ≥ 10/hour _ **Score** _	(1) 1 limb _ (2) 2 limbs _ (3) 3 limbs _ (4) 4 limbs _ + add 1 point if trunk involved **Score** _	(1) Action _ (2) Other (specify) _ (3) Spontaneous _ **Score** _	(0) None _ (1) Pain _ (2) Function _ **Score** _	Oral (specify) _ BTX _ ITB _ (0) Responsive _ (1) Partial response _ (2) Resistant _ **Score** _	
Complex spasm	0 No _ 1 Yes _ **Score** _	(1) Rare _ (2) < 1/hour _ (3) 1–9/hour _ (4) ≥ 10/hour _ **Score** _	(1) 1 limb _ (2) 2 limbs _ (3) 3 limbs _ (4) 4 limbs _ + add 1 point if trunk involved **Score** _	(1) Action _ (2) Other (specify) _ (3) Spontaneous _ **Score** _	(0) None _ (1) Pain _ (2) Function _ **Score** _	Oral (specify) _ BTX _ ITB _ (0) Responsive _ (1) Partial response _ (2) Resistant _ **Score** _	
Clonus	0 No _ 1 Yes _ **Score** _	(1) Rare _ (2) < 1/hour _ (3) 1–9/hour _ (4) ≥ 10/hour _ **Score** _	(1) 1 limb _ (2) 2 limbs _ (3) 3 limbs _ (4) 4 limbs _ + add 1 point if trunk involved **Score** _	(1) Action _ (2) Other (specify) _ (3) Spontaneous _ **Score** _	(0) None _ (1) Pain _ (2) Function _ **Score** _	Oral (specify) _ BTX _ ITB _ (0) Responsive _ (1) Partial response _ (2) Resistant _ **Score** _	
Paroxysmal dystonia	0 No _ 1 Yes _ **Score** _	(1) Rare _ (2) < 1/hour _ (3) 1–9/hour _ (4) ≥ 10/hour _ **Score** _	(1) 1 limb _ (2) 2 limbs _ (3) 3 limbs _ (4) 4 limbs _ + add 1 point if trunk involved **Score** _	(1) Action _ (2) Other (specify) _ (3) Spontaneous _ **Score** _	(0) None _ (1) Pain _ (2) Function _ **Score** _	Oral (specify) _ BTX _ ITB _ (0) Responsive _ (1) Partial response _ (2) Resistant _ **Score** _	
Fixed dystonia	0 No _ 1 Yes _ **Score** _	NA	(1) 1 limb _ (2) 2 limbs _ (3) 3 limbs _ (4) 4 limbs _ + add 1 point if trunk involved **Score** _	NA	(0) None _ (1) Pain _ (2) Function or hygiene or cosmetic _ **Score** _	Oral (specify) _ BTX _ ITB _ (0) Responsive _ (1) Partial response _ (2) Resistant _ **Score** _	
Myoclonus	0 No _ 1 Yes _ **Score** _	(1) Rare _ (2) < 1/hour _ (3) 1–9/hour _ (4) ≥ 10/hour _ **Score** _	(1) 1 limb _ (2) 2 limbs _ (3) 3 limbs _ (4) 4 limbs _ + add 1 point if trunk involved **Score** _	(1) Action _ (2) Other (specify) _ (3) Spontaneous _ **Score** _	(0) None _ (1) Pain _ (2) Function _ **Score** _	Oral (specify) _ BTX _ ITB _ (0) Responsive _ (1) Partial response _ (2) Resistant _ **Score** _	
Spasticity-related tremor	0 No _ 1 Yes _ **Score** _	(1) Intermittent _ (2) Constant _ **Score** _	(1) 1 limb _ (2) 2 limbs _ (3) 3 limbs _ (4) 4 limbs _ + add 1 point if trunk involved **Score** _	(1) Action _ (2) Other (specify) _ (3) Spontaneous _ **Score** _	(0) None _ (1) Function or cosmetic _ **Score** _	Oral (specify) _ BTX _ ITB _ (0) Responsive _ (1) Partial response _ (2) Resistant _ **Score** _	
Total score (sum of all row scores)							

Patients receive one point for each type of involuntary movement. The frequency of each involuntary movement is described in the second column (e.g. four spasms per day) and scored similar to the Penn Spasm Frequency Scale. One point is added for each limb involved by the involuntary movement plus one additional point if truncal muscles are also involved. One point is added if the involuntary movement is triggered by action (kinesogenic), two additional points in case of sensitivity to other triggers (e.g. touch or cold weather), and 3 additional points if the involuntary movement occurs spontaneously. One point is added if the involuntary movement is painful and/or two points if impacting function (e.g. ambulation or balance). Additional point is added if the involuntary movement is partially responsive to current treatment or two points if treatment-resistant. The total score is calculated by adding the scores from each row. Note that frequency and triggers do not apply to fixed dystonia and that it can have additional cosmetic or hygienic impact. Tremor frequency is rated as intermittent or constant and pain is excluded from the impact column for tremor. This proposed scale can be used as a documentation sheet to identify potential areas for intervention and support future therapeutic decisions. The total score can be used for longitudinal monitoring in clinic and as an outcome for spasticity research. See example in supplemental table 1.

EMG patterns of involuntary movements: unit, tonic, myoclonic, clonus, and mixed. Although corresponding clinical data were not collected, it is possible to imply that tonic EMG pattern corresponds clinically to tonic spasms, the clonus pattern to spontaneous clonus, the myoclonic pattern to myoclonus, and the mixed pattern to either complex spasms or paroxysmal dystonia. The total 48-h spasm frequency was much higher than the expected frequency of clinically-detectable involuntary movements suggesting that many of these abnormal movements remain subclinical until a certain threshold is crossed allowing them to clinically-manifest.

In their description of the hyperkinetic types of motor overactivity in the upper motor neuron syndrome, Sheean and McGuire included tonic spasms (flexor, extensor, adductor), clonus, action dystonia (corresponding to our paroxysmal dystonia), and mass movement (likely corresponding to our complex spasms) [1]. Their hypokinetic designation included tonic spasticity, spastic co-contraction, and static-spastic dystonia (the latter corresponds to our fixed dystonia). In agreement with our study and in contrast to Dressler's, the authors considered spastic posture a form of static dystonia as originally described by Denny-Brown [16].

Many of the involuntary movements described in this study resemble our previously-reported demyelination-related movement disorders. These can occur independent of and before the development of tonic spasticity secondary to demyelination of the pyramidal tracts in the brain or the spinal cord.[10 11] Since a large number of patients in our current cohort had MS, a question rises whether the observed involuntary movements were truly spasticity-related or simply the direct effect of demyelination. Since the prevalence and types of the involuntary movements were the same regardless of the etiology of spasticity (e.g. demyelinating versus cerebrovascular), the abnormal movements described were likely spasticity-related rather than demyelination-related even in MS patients. Patients with demyelinating diseases in this cohort had long-standing disease with established tonic spasticity; they were fundamentally different from our previously-reported cohort with early MS in whom movement disorders were thought to be directly related to demyelination in absence of tonic spasticity.[11] The similarity between spasticity and demyelination-related involuntary movements especially those originating in the spinal cord suggests that these movements (e.g. tonic spasms, paroxysmal dystonia) could represent a unique category of “pyramidal” movement disorders as opposed to the classical extrapyramidal prototypes. However, we do acknowledge that the absence of statistically-significant difference in the prevalence and subtypes of involuntary movements between the different etiological and anatomical categories of spasticity is only suggestive of these movements being spasticity-related but would not confirm this association in the absence of a comparison group with the same neurological disorders but without spasticity. However, such a comparison group, with the same disease duration, would be hard to assemble since spasticity is nearly universal in most of these neurological disorders beyond the early phase of the disease. Another important question is whether some of the observed involuntary movements could be the direct anatomical effect of the causative lesion rather than a spasticity-associated phenomenon. Based on MRI results, we excluded tremor in 13 patients from the spasticity-associated category due to the presence of lesions in common tremor-generating locations. As for dystonia, we found two patients with paroxysmal focal dystonia who had lesions in the contralateral basal ganglia which may suggest that their dystonia could be the direct extrapyramidal effect of the ganglionic lesion, however, the dystonia in these two patients developed simultaneously with significant spasticity of the same limb and had a phenomenology that was more suggestive of spastic dystonia rather than the typical extrapyramidal phenotype.

Our study has several limitations. First, the study was purely clinical without supportive electrophysiological data or analysis of pathophysiology. We did not collect the Modified Ashworth Spasticity Scale (MASS) but the study focus was mainly on phasic rather than tonic spasticity as measured by the MASS. Selection bias may have occurred since patients with mild spasticity, and potentially less involuntary movements, are commonly treated outside of specialized spasticity clinics. We did not account for recall bias or shifting expectations on the part of the patients. Lack of randomization and non-blinding of both patients and investigators to treatment modality likely confounded the treatment-response results. However, these were real-life results and were based on patient-reported outcomes which are more relevant to clinical practice. Many of the spasticity-associated involuntary movements were paroxysmal in nature so some of the involuntary movements reported on the survey could not be verified objectively during the brief exam period. This of course raises the possibility that some degree of misclassification might have occurred. However, every effort was made to explain the movement in question to the patient during the survey and when necessary the involuntary movement was demonstrated to the patient by the examiner as detailed in the Methods section. We did not collect data on medications other than anti-spasticity agents and medications directly used to address involuntary movements. Although we acknowledge this as a limitation to the study, we would like to point out that only focal involuntary movements restricted anatomically and chronologically to the same limb or body part inflicted by spasticity were considered spasticity-associated. These restrictions make it less likely that any of the analyzed involuntary movements were drug-induced since these tend to be more generalized in distribution and chronologically related to drug administration rather than to the neurological insult the resulted in spasticity. Another limitation is the fact that the two raters did not have a 100% phenomenology agreement for first rating and that alternative ratings had to be taken into account to reach a 100% agreement. Our proposed hyperkinetic spasticity scale will need validation in different cohorts in order to be useable in clinical practice and research. Lastly, the cross-sectional design did not allow for longitudinal patient monitoring. Future prospective studies including randomized controlled trials are needed for better evaluation of the long-term prognosis and treatment response in patients with spasticity-associated hyperkinetic movements.

Authors’ roles

HA: Study concept and design, patient evaluation, phenomenology rating, video-recording, data collection, interpretation of data, statistical analysis, writing the first draft, final approval of the manuscript.

GM: Data collection, interpretation of data, review and critique.

XY: Blinded video rating, review and critique.

KK: Statistical analysis, co-writing results, review and critique.

HF: Overseeing movement disorder content, interpretation of data, review and critique.

FB: Study concept and design, patient evaluation, interpretation of data, overseeing physical medicine content, final approval of the manuscript.

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speaker in CME events), Biogen GE Healthcare, Lundbeck, Merz, Pfizer, and Zambon Pharmaceuticals (as a consultant); serves as Editor-in-Chief of Parkinsonism and Related Disorders; has received personal compensation for serving as Co-Medical Editor of the Movement Disorders Society website; is a patent co-owner of COMPRESS, a neurosurgical candidate selection tool; has received publishing royalties from Demos Publishing, Manson Publishing, and Springer Publishing; and has received research support from AbbVie, Acadia, Auspex/Teva, Biotie Therapeutics, Civitas, EMD Serono, Merck, Novartis, Kyowa/Prostrakan, Rhythm, Synosia, Abbott, Merz Pharmaceuticals, Xeomin Registry Study, Ipsen Pharmaceuticals, National Institute of Neurological Disorders and Stroke, Huntington Study Group, Parkinson Study Group, Michael J. Fox Foundation, Movement Disorders Society, National Parkinson Foundation, and Society of Progressive Supranuclear Palsy. Dr. Bethoux receives fees as a paid consultant, speaker or member of an advisory committee for the following companies: IPSEN. He receives or has the right to receive royalty payments for inventions or discoveries commercialized through Biogen Idec, Inc. and Demos Medical Publishing.

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Appendix A. Supplementary data

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