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Topical distribution of initial paresis of the limbs to predict clinically relevant spasticity after ischemic stroke: a retrospective cohort study

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***Background*. The degree of initial paresis relates to spasticity development in stroke patients. However, the importance of proximal and distal paresis in predicting spasticity after stroke is unclear.**
***Aim*. To investigate the role of topical distribution of initial limb paresis to predict clinically relevant spasticity in adults with stroke.**
***Design*. Retrospective cohort study**
***Methods*. Seventy-two first-ever ischemic stroke patients were examined. At the acute phase of illness, demographics and the European Stroke Scale motor items (maintenance of outstretched arm position, arm raising, wrist extension, grip strength, maintenance of outstretched leg position, leg flexion, foot dorsiflexion) were evaluated. At six months after the stroke onset, spasticity was assessed at the upper and lower limb with the modified Ashworth Scale. Clinically relevant spasticity was defined as modified Ashworth Scale ≥3 (0-5).**
***Results*. The degree of initial paresis of the proximal muscles of the upper limb and the distal muscles of the lower limb showed the strongest association and the best profile of sensitivity-specificity in predicting clinically relevant spasticity at the upper and lower limb, respectively. Younger age showed higher risk for developing clinically relevant spasticity in the upper limb.**
***Conclusions*. Our findings support the hypothesis that the initial degree of proximal paresis of the upper limb and distal paresis of the lower limb as well as age may be considered early predictors of clinically relevant spasticity in adults with ischemic stroke.**
***Clinical rehabilitation impact*. Our findings further improve the role of initial paresis as predictor of spasticity after stroke.**

KEY WORDS: Prognosis - Muscle hypertonia - Muscle weakness - Rehabilitation.

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Stroke is a leading cause of acquired adult disability in developed Countries.[1] Lesions in the pyramidal and parapyramidal tracts may raise positive and negative symptoms.[2] Negative features of the upper motor neuron syndrome are a consequence of deficient voluntary muscle activity and include muscle weakness, loss of finger dexterity and the inability to selectively control limb movements.[2, 3] Positive signs of upper motor neuron lesions are characterized by a number of different types of muscle overactivity comprising exaggerated stretch reflexes, muscle spasms, co-contraction, synkinesias, spastic dystonia and increased muscle stiffness.[2, 3]

Motor impairment occurs frequently in patients with stroke and greatly contributes to dependency in activities of daily living.[4, 5] Prognostic accuracy of motor outcome after stroke is important to take into consideration when programming an efficient treatment plan (including type and duration of rehabilitation) and allocating resources.[4] Despite their prognostic reliability, neuroimaging and neurophysiological assessments are not yet used routinely, and there is a need for simple, accurate and inexpensive methods to predict motor outcome after stroke.[4] In line with these considerations, the degree of motor impairment has been described as the simplest predictor of functional recovery in patients with stroke.[4, 6, 7] In particular, topical distribution of initial paresis showed predictive value for the recovery of motor function after stroke onset,[4, 8-11] according to the different corticomotoneuronal representation of proximal and distal movements of the upper and lower limbs.[12, 13]

Spasticity is a well-recognized consequence of stroke that mainly occurs within the first few months after the onset.[2, 3] It is defined as a state of increased muscle tone with exaggerated reflexes that is characterized by a velocity-dependent increase in the resistance to passive movement.[2, 3, 14] The degree of initial paresis has been showed to relate with the risk of developing spasticity after stroke.[3, 15-18] However, the role of topical distribution of initial limb paresis for predicting clinically relevant spasticity after stroke has never been examined.

The aim of this is study was to investigate the prognostic value of topical distribution (proximal versus distal) of initial paresis of the upper and lower limbs as a simple bedside test for predicting clinically relevant spasticity in patients with ischemic stroke.

Materials and methods

In a retrospective cohort study, all stroke patients admitted to the Neurological Rehabilitation Unit of the Azienda Ospedaliera-Universitaria Integrata of Verona, Italy, were consecutively recruited during a 20-month period. Included were all adults (age >18 years) with hemiparesis due to a first-ever ischemic stroke (documented by a computerized tomography scan or magnetic resonance imaging) who showed spasticity (defined as 1 point or higher on the modified Ashworth scale),[19] in at least one limb at six months after the onset of stroke. Exclusion criteria were: transient ischemic attack, previous brain lesions independent of their etiology, neglect, limb apraxia, aphasia, impaired somatic sensation, assumption of oral antispastic drugs, treatment of spasticity with botulinum toxin and other orthopedic or neurologic conditions that may have interfered with motor assessment. The study was carried out according to the Declaration of Helsinki and was approved by the local Ethics Committee. We received written informed consent to perform this study.

Evaluation procedures

Data about initial paresis were obtained through participant records stored in the Neurology Unit database of the Azienda Ospedaliera-Universitaria Integrata of Verona, Italy. Motor impairment evaluated in the acute phase of illness (within 7 days after the onset of stroke) was quantified by means of the European Stroke Scale (ESS) motor items: maintenance of outstretched arm position (range 0-4), arm raising (range 0-4), wrist extension (ESS wrist: range 0-8), grip strength (ESS grip: range 0-8), maintenance of outstretched leg position (range 0-4), leg flexion (range 0-4), foot dorsiflexion (ESS foot: range 0-8).[20] For statistical purposes we combined the scores of maintenance of outstretched arm position and arm raising (ESS arm: range 0-8), as well as the scores of maintenance of outstretched leg position and leg flexion (ESS leg: range 0-8). Data about age, sex, education, smoking, handedness, side of stroke and co-morbidity (cardiovascular and metabolic diseases) were also obtained.

At six months after stroke onset, spasticity was assessed on the Modified Ashworth Scale (MAS).[19] The MAS is a 6-point scale grading the resistance of a relaxed limb to rapid passive stretch (0: no increase in muscle tone; 1: slight increase in muscle tone at the end of the range of motion; 1+: slight increase in muscle tone through less than half of the range of motion; 2: more marked increase in muscle tone through most of the range of motion; 3: considerable increase in muscle tone; 4: joint is rigid).[19] For statistical purposes, a score of 1 was considered a 1 while a score of 1+ was considered a 2 and so on, until 5.[21] Evaluation of spasticity included several muscle groups of the upper and lower limbs. In the present study we tested shoulder abductors, elbow flexors and extensors, wrist flexors and extensors as well as fingers flexors with the patient in sitting position (if possible).[15] Moreover we tested hip adductors, knee flexors and extensors as well as ankle plantar flexors and dorsiflexors with the patient in prone position. Patients were classified according to the presence/absence of clinically relevant spasticity that was defined as a MAS score ≥3 for any of the movement performed.[15] The same examiner (F.D.) evaluated all patients.

Statistical analysis

Pre-study power calculation estimated that a total of 70 patients would provide 80% power (significance level of 5%) to detect a change in Prob (Y=1) from the baseline value of 0.500 to 0.187 considering an odds ratio of 0.23,[15] in a logistic regression of a binary response variable (paresis, Y) on a binary independent variable (spasticity, X) of which 50% of the patients are in the clinically relevant spasticity group (X=0) and 50% are in the not clinically relevant spasticity group (X=1).

Age, sex, education, smoking, handedness, side of stroke, co-morbidity and ESS scores were tested between groups (clinically relevant spasticity: yes/no) and separately for the upper and lower limbs with the paired Student's t (continuous data) or the Pearson's χ^2 (categorical data) test. Multivariate logistic regression analysis, adjusted for age, sex, smoking, education and comorbidity, was performed to determine the ESS prognostic value for clinically relevant spasticity. Odds ratios were calculated for each factor.

Sensitivity, specificity, percentage of correctly classified observations and Youden Index (sensitivity +; specificity – 1) were calculated for ESS scores. The corresponding Receiver Operating Characteristics (ROC) curves were plotted and Area Under the Curve (AUC) calculated. The alpha level for significance was set at P<0.05 (two-tailed). Data were analyzed with STATA 11.0 software.

Results

Seventy-two subjects (48 men, 24 women; mean age±SD: 70.6±10.4 years) with first unilateral ischemic stroke were recruited from among 115 patients consecutively admitted to Neurological Rehabilitation Unit of the Azienda Ospedaliera-Universitaria Integrata of Verona, Italy, from December 2009 to July 2011. All patients involved in the study underwent a neuromotor rehabilitation treatment program for three months (mean duration: 88.3±5.7 days) according to the Italian guidelines, which are in agreement with current international rehabilitation guidelines.[22, 23] The total number of sessions was defined according to each patient's neurological severity.

Clinically relevant spasticity was present in the upper limb in 55.6% and in the lower limb in 51.4% of patients. As reported in Table I, among all variables considered only age and ESS scores were significantly lower in patients with clinically relevant spasticity.

As reported in Table II, multivariate logistic analysis showed that patients with lower ESS arm and foot scores had a greater probability of developing

TABLE I.—*Descriptive statistics.*

Upper limb	MAS<3 (N.=32)	MAS≥3 (N.=40)
Age	73.8 (10.2)	68.1 (10.0)*
Sex (male) (n,%)	20 (62.3)	28 (70.0)
Education (high school) (N., %)	7 (21.9)	11 (27.5)
Smoking (>5 cigarettes/day) (N., %)	14 (43.8)	23 (57.5)
Handedness (right) (N., %)	27 (84.4)	36 (90.0)
Side of stroke (right) (N., %)	12 (37.5)	20 (50.0)
Comorbidity	1.3 (0.7)	1.0 (0.7)
ESS arm	4.8 (2.1)	1.3 (2.0)*
ESS wrist	4.3 (2.7)	1.3 (2.1)*
ESS grip	3.3 (2.6)	1.0 (1.6)*
Lower limb	**MAS<3 (N.=35)**	**MAS≥3 (N.=37)**
Age	73.1 (10.5)	68.3 (10.0)*
Sex (male) (N., %)	22 (62.8)	26 (70.3)
Education (high school) (N., %)	9 (25.7)	9 (24.3)
Smoking (>5 cigarettes/day) (N., %)	18 (51.4)	19 (51.4)
Handedness (right) (N., %)	30 (85.7)	33 (89.2)
Side of stroke (right) (N., %)	13 (37.1)	19 (51.4)
Comorbidity	1.1 (0.8)	1.1 (0.7)
ESS leg	4.9 (2.4)	1.9 (2.0)*
ESS foot	5.1 (2.8)	1.0 (1.6)*

Data expressed as a mean (SD) or count number (%). *P<0.05.
MAS: Modified Ashworth Scale; ESS: European Stroke Scale.

TABLE II.—*Logistic regression analysis of the independent predictors of clinically relevant spasticity.*

Upper limb	Odds ratio [95% CI]	P value
Age	0.90 [0.83-0.99]	0.040*
Sex (male)	1.19 [0.26-5.53]	0.823
Education (high school)	0.20 [0.02-1.82]	0.156
Smoking (N., %)	4.53 [0.85-23.9]	0.075
ESS arm	0.45 [0.31-0.65]	<0.001*
Lower limb	**Odds ratio [95% CI]**	***P* value**
Age	0.93 [0.85– 1.01]	0.116
Sex (male)	0.99 [0.22-4.38]	0.986
Education (high school)	0.34 [0.51-2.26]	0.264
Smoking (N., %)	0.96 [0.24-3.91]	0.953
ESS foot	0.54 [0.41-0.71]	<0.001*

*P<0.05. ESS: European Stroke Scale.

clinically relevant spasticity at the upper and lower limbs, respectively.

A one-point increase of the ESS arm and foot scores corresponded to a risk reduction of developing clinically relevant spasticity at the upper and lower limbs of 55% and 46%, respectively. Age was a predictor of clinically relevant spasticity development only for the upper limb. As reported in Table III, arm and foot scores showed the best profile of sensitivity, specificity, percentage of correctly classified observations and Youden index for predicting development of upper and lower limbs clinically relevant spasticity, respectively (Figure 1). Incorporating all items into a composite score did not enhance the predictive value for clinically relevant spasticity.

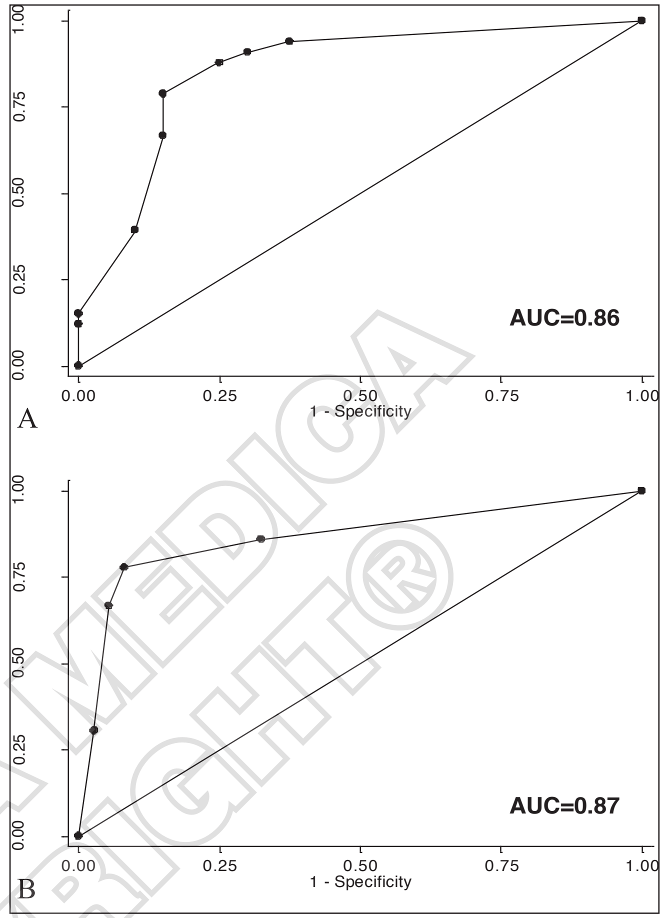

Figure 1.—ROC curves and AUC for ESS arm (A) and foot (B) scores. ROC: Receiver Operating Characteristics; AUC: Area Under the Curve; ESS: European Stroke Scale.

Discussion

Our results support the hypothesis that the degree of initial paresis relates to the risk of developing clinically relevant spasticity in adult patients with ischemic stroke. The most interesting finding of this retrospective cohort study is that the degree of proximal upper limb and distal lower limb initial paresis showed the best profile of sensitivity and specificity for predicting the development of clinically relevant spasticity at six months after stroke onset.

To date, the specific relationship between spasticity and disability is still object of debate.[2] However, it has been known that spasticity may affect motor function negatively or cause pain contributing to the level of independency in activities of daily living and leading to secondary complications in patients with stroke.[2-4] On this basis, spasticity with an impact that intervention (*i.e.* intensive physiotherapy, orthoses or pharmacologic treatment) should be offered has been described as disabling.[3] Thus, it is plausible that clinically relevant spasticity (MAS score ≥3) can be a key contributory to disability in patients with chronic stroke. In consequence, it is important, from a rehabilitative point of view, to find predictors of clinically relevant spasticity after stroke.[4]

TABLE III.—*Sensitivity, specificity, percentage of correctly classified observations and Youden index for ESS scores.*

	Cut-off score*	Sensitivity (%)	Specificity (%)	Correctly classified (%)	Youden Index
Upper limb					
ESS arm	3	85.0	78.8	82.2	0.64
ESS wrist	4	80.0	66.7	74.0	0.40
ESS grip	4	85.0	66.7	76.7	0.52
All ESS scores†	N.A.	85.0	78.8	82.2	0.64
Lower limb					
ESS leg	4	75.6	80.5	78.0	0.56
ESS foot	2	91.9	77.8	84.9	0.70
All ESS scores†	N.A.	91.9	77.8	84.9	0.70

*Cut-off score that resulted in the larger % of correctly classified patients. †Results using a composite score that included all ESS items.

The prediction of spasticity after stroke has been reported to relate with the degree of initial paresis.[3, 15-18] In particular, patients with severe paresis in the acute phase of stroke have been described to develop higher degrees of spasticity than those with a slight initial paresis.[15, 17, 24]

In this study we further investigate the role of initial paresis as a clinical predictor of spasticity after stroke, finding that not only its severity, but also its topical distribution relates with the development of clinically relevant spasticity in patients with ischemic stroke. A challenging question is to understand why proximal upper limb and distal lower limb initial paresis showed to relate with the risk of developing clinically relevant spasticity after stroke. Previous studies about the prediction of recovery of motor function after stroke explained the predictive value of the topical distribution of initial paresis according to the different cortico-motoneuronal representation of proximal and distal movements of the limbs.[4, 8-11] As to the lateralization of brain activity during upper limb movements, an exclusive contralateral activation has been reported in the primary sensori-motor cortex during hand tasks.[12] Conversely, proximal shoulder tasks have been observed to activate also the ipsilateral primary sensori-motor cortex (about 30% of activation).[12] With regards to the lower limb, an increase of the lateralization of brain activity has been reported from proximal to distal movements.[13] Interestingly, during ankle movement has been observed an activation of the ipsilateral primary sensori-motor cortex similar to the proximal shoulder tasks (about 30%).[13] On this basis, our findings may be explained by considering the comparable cortico-motoneuronal representation of the proximal upper limb and distal lower limb movements. At variance, we might speculate that the distal upper limb paresis was found less specific for predicting clinically relevant spasticity after ischemic stroke as it is frequent even after small brain lesions, because of nearly-complete contralateral representation of the distal upper limb movements.[12] For the same reason, proximal lower limb paresis might be found less sensitive because of the large bilateral representation of the proximal lower limb movements.[13] Further studies including neuroimaging and neurophysiological assessments are needed in order to further investigate our hypotheses.

As to the relation between clinically relevant spasticity and other variables, we observed that younger age might represent a clinical predictor of upper limb clinically relevant spasticity in patients with ischemic stroke. This finding is in keeping with previous studies, which reported that younger patients develop spasticity more often than older ones as well as patients with disabling spasticity are younger than those without disabling spasticity.[3, 24] In order to explain these relationships has been hypothesized that pathologic reflexes (as the tonic stretch reflex) would be lower in older patients in line with the normal decline of reflex activities with age.[3] However, the role of age for predicting spasticity after stroke remains object of debate, also considering that no previous study identified a direct influence of age on the occurrence of spasticity after stroke.[15, 24, 25]

About 20-25% of all patients with first-ever stroke suffer from spasticity.[3] In particular, post-stroke spasticity (defined as 1 point or more on the MAS) has been reported to have a prevalence of 23-43% at six months after onset.[3, 15] Moreover, about 14-15% of patients become severely spastic (MAS≥3) at six months after a first-ever stroke.[3, 15] As observed in this retrospective cohort study, more than 50% of patients suffered from clinically relevant spasticity. This was probably because we included only patients with a MAS score ≥1 in at least one limb according to our main aim that was to evaluate only potential predictors of clinically relevant spasticity and not to quantify the prevalence of spasticity after stroke.

This study has several limitations. First, we examined a small number of potential predictors. In particular a previous study reported that patients with hemihypesthesia have higher risk for developing spasticity of the upper and lower limbs after ischemic stroke.[15] However the role of hypesthesia in predicting spasticity is still controversial according to the close topographical arrangement of pyramidal tract fibers and sensory pathways.[15] Thus, we decided to exclude patients with impaired somatic sensation from this study. Second, we included only patients with spasticity (MAS≥1) in at least one limb at six months after the onset. This was in line with the retrospective design of the present study, which was mainly aimed at evaluating the role of initial paresis and its topical distribution in the prediction of clinically relevant poststroke spasticity (MAS≥3). Third, even if our patients received a similar type and amount of rehabilitation treatment, they were treated individually and according to each one's neurological severity. Thus, we cannot exclude that rehabilitation treatment influenced the present findings. Finally, we did not perform neuroimaging or neurophysiological assessments to support our hypotheses.

Conclusions

Accurate prediction of clinically relevant spasticity after stroke may be useful for planning adequate rehabilitation procedures also considering that the healthcare cost of spastic patients is four times the cost of medical care for those patients with no increase of muscle tone after stroke.[2, 3] This study showed that the initial degree of proximal paresis of the upper limb and distal paresis of the lower limb might be considered early reliable predictors of clinically relevant spasticity in adults with ischemic stroke. In addition, age was found to relate with the risk of developing clinically relevant spasticity at the upper limb in stroke patients.

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