ORIGINAL REPORT

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EARLY BRAIN IMAGING PREDICTORS OF POST-STROKE SPASTICITY

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Background: Post-stroke spasticity is a major factor disturbing rehabilitation and functional recovery in stroke survivors. Clinical predictors of post-stroke spasticity have often been discussed, but brain image predictors for spasticity have been insufficiently researched. The aim of this study was to use magnetic resonance imaging data to identify early brain imaging predictors for potential development of spasticity after stroke.

Methods: Consecutive patients admitted to a stroke unit were screened prospectively over 22 months. Patients with first-ever supratentorial ischaemic stroke were included in the study. Standardized clinical assessments for post-stroke spasticity were prospectively performed within 7 days and at 3 months. Brain imaging data (3 Tesla magnetic resonance imaging (3T MRI)) were collected at the baseline and evaluated.

Results: Brain imaging data from 103 stroke patients were collected in the hyperacute phase (< 7 days after stroke onset). A total of 23 patients developed post-stroke spasticity. The volumes of brain lesions involving motor network areas were significantly larger in patients with post-stroke spasticity compared with those without post-stroke spasticity ($p < 0.01$). Supratentorial lesion of < 0.5 cm³ were not associated with risk of post-stroke spasticity, except when the internal capsule and striatum was affected.

Conclusion: Lesions involving motor network areas are considered to be a precondition of post-stroke spasticity. There is, however, a low risk of developing post-stroke spasticity with < 0.5 cm³ volumes of supratentorial brain lesions involving motor network areas. Larger volume brain lesions involving motor network areas, e.g. > 3 cm³, were significantly more common in patients with post-stroke spasticity. Pure cortical lesions has no risk of post-stroke spasticity in stroke survivors.

LAY ABSTRACT

Post-stroke spasticity is a major factor disturbing rehabilitation and functional recovery in stroke survivors. However, few studies have examined brain imaging predictors of post-stroke spasticity. Among patients with first-ever supratentorial ischaemic stroke, association between developing post-stroke spasticity, lesion site and lesion size were analysed in this prospective study. Every patient was clinically evaluated at baseline (7 days) and at 3 months. In magnetic resonance imaging (MRI) of the brain, small brain lesion volumes (< 0.5 cm³) were found to be associated with a low risk of developing post-stroke spasticity in patients with stroke. Larger lesion sizes (> 3 cm³) were significantly more common in patients with post-stroke spasticity and can be a positive predictor of post-stroke spasticity.

of post-stroke spasticity (PSS) is predicted or detected after a stroke, as one of the "plus symptom" following stroke, the more responsive patient management can be to avoid complications and improve prognosis (1, 2). If severe PSS is not managed early it will impair functional activity in affected patients, through complications, e.g. muscle shortening, contractures, pressure sores, additional to the PSS itself (1–5).

Likewise, complications of PSS can lead to severe changes within a short period of time, even within a few weeks or months. If during this period PSS is not appropriately managed or treated, this, together with its complications, may detrimentally impact on patients' physical posture, and positioning of affected joints, and thus their active freedom of movement (1, 6, 7). At a later stage, restriction in passive range of motion (ROM), hardening, or even contractures of the joint capsule may occur, which often prove irreversible in their final stage, so that surgical interventions have to be considered (8).

The definition of spasticity, by Lance in 1980 (9), as a velocity-dependent increase in muscle tone, represents only one "positive" component of the upper motor neuron syndrome (UMNS), but more recent definitions include all positive symptoms (increased tendon reflexes, Babinski group reflexes, clonus, spasm, spastic dystonia and velocity-dependent increase in muscle tone) as spasticity (10), while excluding the "negative" components of the UMNS (e.g. paresis) and the complications of the UMNS (e.g. contractures, loss of muscle fibres).

The pathogenesis of PSS is incompletely understood, thus only symptomatic therapies have been studied and

The earlier the complications of stroke are identified, the greater is the likelihood that patients will avoid secondary and tertiary complications, and the better their prognosis. Therefore the earlier the risk of development

suggested. Therefore the difficulty of management of PSS comes from detecting it at an early stage. It frequently develops gradually, building up with time, and fully manifests itself after weeks and months (11–14).

Therefore, it is essential to find predictors, or their "red flags", which indicate the potential development of spasticity with a high probability at early stages following stroke. Using such predictors, patients could be identified early following stroke and managed or treated with an appropriate approach (1, 2, 8, 11).

To date, a number of studies have discussed clinical predictors for subsequent stroke-associated spasticity. Those studies include clinical predictors, such as poor functional status in the acute phase (low Barthel Index, higher modified Rankin scale, severe affected functions of the limbs), severe paresis, sensitivity loss to sensory stimuli, and young patient age (3, 12, 13, 15–17). These clinical predictors, which are associated with severe paresis and functional disorders, imply that certain locations and the size of brain lesions may be good predictors of developing PSS.

Clinical predictors are considered to be an important and effective approach for the prediction of PSS (11–13); however, the performance of clinical assessments, which are needed in order to predict more accurately, can often be limited in the hyperacute or acute phases following stroke, due to individual and clinical limitation. Therefore, analysis of brain imaging, which is a routine procedure in stroke evaluation, will be a good additional option for predicting early risk of development of PSS.

There are a few studies that have investigated early brain imaging predictors of spasticity following stroke, and have suggested large volume and multiple lesion locations as possible brain imaging predictors of PSS in stroke survivors (18–23). However, these studies have suggested larger or extensive lesions as possible predictors with no mention of cut-off values for lesion size, and have suggested various possible lesion sites in the brain.

The current study analysed 3 Tesla magnetic resonance imaging (3T MRI) data in order to identify early brain imaging predictors for potential development of spasticity after stroke, such as the sites and "red flags" values (sizes) of brain lesions. Patients admitted to a stroke unit were prospectively clinically examined in the acute stage (within 7 days of stroke onset) and at 3 months, for the occurrence of PSS, and MRI findings were analysed to correlate with clinical data.

METHODS

Subjects and method

Consecutive patients admitted to an inter-regional stroke unit in Germany were screened over a period of 22 months. Inclusion criteria for this prospective study were: patients with a first-ever supratentorial ischaemic stroke; 3T MRI data within the first 7 days following stroke; consent to study information; and age over 18 years. Patients with aphasia, recurrent ischaemic stroke, brainstem/cerebellum infarct, brain trauma or haemorrhagic stroke were excluded. Patients were clinically examined in the hyperacute phase (within 7 days of onset, T0) and at 3 months after stroke (T1). Standardized clinical examination included the summary rating scale for resistance to passive movement (REPAS) for assessment of increased muscle tone (Ashworth Scale ≥1: increased muscle tone) in every joint of assessed limbs, which is based on the Ashworth scale (24). Other extensive clinical examinations for spastic movement disorder were also performed, but the current study focused on PSS and early brain imaging predictors.

Brain imaging data

All brain imaging data came from 3T MRI (3 Tesla MRT Magnetom Trio, Siemens Healthcare, Erlangen, Germany) at the Charité University Hospital Berlin, Campus Benjamin Franklin. Stroke lesions were analysed on diffusion-weighted imaging (DWI) sequences, fluid-attenuated inversion recovery (FLAIR), T1-weighted anatomical sequences and T2-weighted sequences. The aetiological TOAST classification (25) of ischaemic stroke was assessed as TOAST I–V. Microangiopathy was assessed regarding the severity using the Wahlund score (26), with a graduation ranging from 0 to 3.

Lesion volume measurement

MRIcro is a program for neuroimaging visualization, developed by Chris Rorden (2011) (https://people.cas.sc.edu/rorden/mricro/mricro.html). MRIcro was used to measure the volume of affected brain lesions or the volumes of brain lesions involving motor network structures (including pyramidal tracts, motor cortex, parapyramidal structures, directly adjacent neighbours). The preparation of regions of interest (ROIs), represented in colour, and the calculation of the size of ischaemic lesions were computed semi-automatically. The intra-individual size and shape of the lesions were defined manually, layer by layer, according to an atlas of cross-section anatomy (27). The manually labelled ROI were calculated automatically by the MRIcro program 3-dimensionally and computed as total volume data.

The pyramidal tract including precentral gyrus, parapyramidal tract, internal capsule, and basal ganglions were defined in this study as supratentorial brain lesions involving motor network areas (MNA). The volume of lesions affecting MNA (VMNA) was calculated separately after total lesion volume and analysed.

Analysis and marking of the lesions on MRI were performed separately by 1 neurologist and 1 neuroradiologist and were discussed for each patient. The volumes of lesions marked by these researchers were calculated as the number of voxels (ROI) and the size of a voxel unit, using the MRIcro program.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) program, version 21.0 (IBM, California, USA), was applied. To compare the 2 patient groups, with and without PSS, in the 3 months following stroke, Student's t-test or Mann–Whitney U test, and χ^2 test were used. The odds ratio (OR) with 95% confidence interval (95% CI) regarding the appearance of the condition (with lesion size as a "red flag" value) was evaluated between both groups with/without spasticity, and predictive values were calculated for the "red flag" values of lesion size for prediction of PSS.

RESULTS

A total of 764 patients were consecutively screened and 103 patients with first-ever supratentorial ischaemic stroke were finally included in this prospective study (Fig. 1). The patients were examined within 7 days (T0) and after 3 months (T1). Twenty-three (22.3%) patients showed spasticity (AS ≥ 1) following stroke, and 80 (77.7%) showed no increased muscle tone. The general characteristics data, distribution of affected sides, aetiology of ischaemic stroke, and subcortical microangiopathic changes were not significantly different between the 2 groups ($p > 0.05$, Table I).

Size of stroke lesions

Mean lesion size was significantly larger in patients with PSS compared with patients without PSS (median (interquartile range; IQR); 7.3 cm^3 (2.1–37.3 cm^3) vs 0.8 cm^3 (0.2–4.7 cm^3), $p < 0.01$. However, 18 (22.5%) patients without PSS also showed large total volumes (>5 cm^3). The lesion volume involving motor network structures was also significantly larger in patients with PSS compared with patients without PSS (median (IQR); 3.6 cm^3 (0.7–36.3 cm^3) vs 0.2 cm^3 (0–0.6 cm^3), $p < 0.01$ (Table II).

Is there a lesion volume that acts as a "red flag" for spasticity?

Both total lesion sizes and lesion sizes involving motor network structures were graded discretely regarding lesion size, in the following categories: 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 20, 30, 40, 50 cm^3, and larger than 50 cm^3

Table I. Patient characteristics and brain imaging findings

	All $n=103$	No spasticity $n=80$	Spasticity $n=23$	*p*-value
Sex, female, *n* (%)	44 (42.7)	34 (42.5)	10 (43,5)	>0.05[a]
Age, years, mean (SD)	71 (11.3)	70 (11.7)	74 (9.2)	>0.05[b]
Left affected, *n* (%)	42 (40.8)	33 (41.3)	9 (39.1)	>0.05[a]
Right affected, *n* (%)	45 (43.7)	34 (42.5)	11 (47.8)	
Both sides affected, *n* (%)	16 (15.5)	13 (16.3)	3 (13)	
Microangiopathy, *n* (%)	95 (92.2)	73 (91.2)	22 (95.7)	>0.05
Wahlund score, mean (SD)	7.3 (5.6)	7.3 (5.5)	7.4 (6.1)	>0.05[a]
TOAST classification, *n* (%)				
TOAST-I	18 (17.5)	15 (18.8)	3 (13.0)	
TOAST-II	16 (15.5)	10 (12.5)	6 (26.1)	
TOAST-III	22 (21.4)	17 (21.3)	5 (21.7)	
TOAST-IV	0 (0)	0 (0)	0 (0)	>0.05[a]
TOAST-Va	4 (3.9)	2 (2.5)	2 (8.7)	
TOAST-Vb	30 (29.1)	25 (31.3)	5 (21.7)	
TOAST-Vc	7 (6.8)	6 (7.5)	1 (4.3)	
Not evaluated	6 (5.8)	5 (6.3)	1 (4.3)	
ACA, *n* (%)	9 (8.7)	6 (7.5)	3 (13.0)	
MCA, *n* (%)	72 (69.9)	54 (67.5)	18 (78.3)	
PCA, *n* (%)	24 (23.3)	21 (26.3)	3 (13.0)	
ACA/MCA, *n* (%)	10 (9.7)	6 (7.5)	4 (17.4)	
MCA/PCA, *n* (%)	10 (9.7)	5 (6.3)	5 (21.7)	>0.05
Striatum, *n* (%)	19 (13.4)	11 (10.0)	8 (25.0)	
Thalamus, *n* (%)	15 (10.6)	11 (10.0)	4 (12.5)	
AchA, *n* (%)	2 (1.9)	2 (2.5)	0 (0)	
Cortical, *n* (%)	10 (9.7)	10 (12.5)	0 (0)	
Subcortical, *n* (%)	59 (57.3)	50 (62.5)	9 (39.1)	<0.05
Cortical/subcortical, *n* (%)	34 (33.0)	20 (25.0)	14 (60.9)	

[a]χ^2 test; [b]Student's *t*-test; SD: standard deviation; ACA: anterior cerebral artery territory; MCA: middle cerebral artery territory; PCA: posterior cerebral artery territory; ACA/MCA: border area between ACA and MCA; MCA/PCA: border area between MCA and PCA; AchA: anterior choroidal artery territory.

(Fig. 2). Lesion sizes of 0.5 and 3 cm^3 were chosen as suitable cut-off values: 14 (60.9%) patients with PSS, but only 6 (7.5%) patients without PSS, showed lesion volumes (involving motor network structures) larger than 3 cm^3 (odds ratio: 19.19, 95% CI 5.89–62.46;
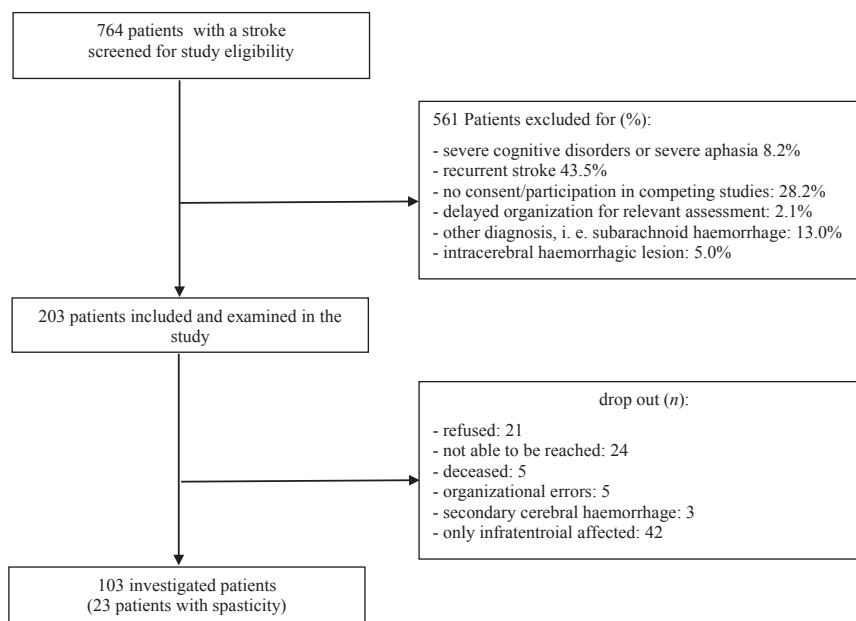

Fig. 1. Study flow chart.

Table II. Lesion volumes (cm³)

	All 103	Patients with no PSS 80	Patients with PSS 23	p-value
n				
Volume of total lesions in a patient, cm³, mean, median (IQR)	10.3, 1.5 (0.3–6.2)	6.6, 0.8 (0.2–4.7)	22.9, 7.3 (2.1–37.3)	<0.01[a]
volume of lesions only involving motor network structures in a patient, cm³, mean, median (IQR)	5.1, 0.2 (0–1.3)	1.3, 0.2 (0–0.6)	18.5, 3.6 (0.7–36.3)	<0.01[a]

[a]Mann–Whitney U test, median (IQR): median (interquartile range). PSS: post-stroke spasticity.

sensitivity 70%, specificity 89.1%). Only 5 (21.7%) patients with PSS showed lesion volumes involving motor network structures smaller than 0.5 cm³, but 71.3% of patients without PSS showed lesion volumes involving motor network structures smaller than 0.5 cm³ (odds ratio: 8.92, 95% CI 2.96–26.88; sensitivity 43.9%, specificity 91.9%). Out of a total of 5 patients with PSS and VMNA of <0.5 cm³, 3 had lesions of the basal ganglions, and the other 2 had multi-lesions, e. g. thalamus and subcortical lesions.

Localization of stroke lesions

The affected sides of the brain were not significantly different between the groups with and without PSS. The distribution of brain lesion locations according to artery territory were also not significantly different between the patients with and without PSS (respectively, $p > 0.05$). However, middle cerebral artery (MCA) territory and striatum were more frequent in spastic patients, however many patients without PSS also showed lesions in these areas (Table I).

No patients with PSS had small cortical lesions, but 10 (9.7%) of the non-spastic patients did. In 14 (60.9%) patients with PSS, simultaneous cortical and subcortical lesions were found, compared with the patients with no PSS ($p < 0.01$). Nine patients with PSS showed only subcortical lesions, which involved the striatum and thalamus (Table I).

Fig. 2. Lesion volume involving motor network affection in patients with post-stroke spasticity (PSS) ($n = 23$) and without PSS ($n = 80$).

<div style="text-align:center">DISCUSSION</div>

In this study, 22.3% of patients showed PSS within 3 months. This prevalence is not low compared with previous studies, which showed PSS prevalences ranging from 19% to 26.7% (11). Brain imaging data (3T MRI) were collected at baseline (<7 days) and the characteristics of brain lesions evaluated to find possible predictors of PSS within 3 months following stroke.

The most significant criteria for a high probability of development of PSS was the volume of the ischaemic lesions involving motor network structures. In addition, pure cortical lesions were not associated with the development of PSS in this study.

The size of brain lesions has been suggested as a risk factor for development of PSS in previous studies; however, lesion size alone was not found to be very highly correlated with PSS (18, 20, 28). In the current study, more than 20% of patients without PSS also had large lesion volumes greater than 5 cm³. Lesion volume alone is not a reliable predictor of PSS. It has been suggested that the development of PSS is mostly associated with persistent paresis or persistent motor dysfunction, and its severity is highly correlated with the severity of paresis of limbs (3, 8, 11, 12, 14–16). Several studies have reported that lesions affecting motor network areas were associated with the development of spasticity after stroke (18, 19, 21), and the larger the sizes of brain lesions in stroke survivors, the higher the risk of spasticity (18)

In the current study the larger lesions affecting motor network areas including premotor cortex, as well as pyramidal and parapyramidal tracts, internal capsule, and basal ganglions, were also more strongly associated with the development of PSS. In 1994, Brown stated that the extent of the lesion alone does not cause spasticity (29). The risk of developing PSS pertains rather to the alterations within the relevant motor pathways (30, 31). Recent studies with small sizes have suggested several locations that may be associated with the development of PSS, including thalamus, basal ganglia, corona radiate, insula, internal (posterior limb) and external capsule, and premotor cortex (19–22). Lesions affecting the pyramidal tract were also suggested as a risk factor for developing PSS (23). In a recent short report we discussed the volume and location of lesions associated with the
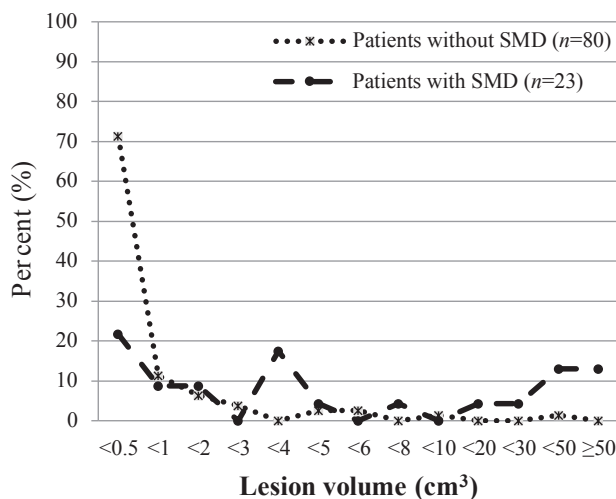
development of PSS, and suggested that larger volumes brain lesions, especially those affecting motor network areas, were more strongly associated with development of PSS (18). However, patients with brainstem lesions were not separately evaluated in that study, and further analysis of brain lesion size as a predictor of PSS is necessary.

The distribution of lesion volumes in supratentorial infarcts was analysed in the current study, and it was found that volumes of 0.5 and 3 cm^3 were high peaks of distribution. With these 2 sizes of lesions as cut-off values, the current study evaluated the sensitivity and specificity of lesion volumes involving motor network structures to predict PSS. Most of the patients with lesions volumes <0.5 cm^3 showed no PSS, but lesion volumes >0.5 cm^3 were not sensitive enough to predict it (sensitivity 43.9%, specificity 91.9%). However, of the 5 spastic patients with lesions smaller than 0.5 cm^3 of motor-network areas, 3 patients had lesions of basal ganglions and other 2 had multi-infarcts with thalamus lesions plus other subcortical lesions. On the other hand, more patients with PSS (60.8%) had lesion volumes larger than 3 cm^3 involving motor network structures, and most patients (92.5%) without PSS had smaller lesion volumes involving motor network structures of <3 cm^3 (sensitivity 70%, specificity 89.1%). Therefore, lesion volumes <0.5 cm^3, involving motor network structures, except for the brainstem, internal capsule, and basal ganglions, can be very effective to differentiate the risk of development of PSS, and ≥3 cm^3 lesion volumes involving motor network structures are a positive predictor of PSS.

In addition, this study found that pure cortical lesions were less strongly associated with the development of PSS. Conversely, simultaneous cortical and subcortical lesions indicated a higher risk. Even though no significant differences were found in the distribution of lesions according to artery territories in patients with or without PSS, the association between development of PSS and several brain lesion locations, including the striatum and thalamus infarct, is in agreement with the results of other studies, and requires further research (18–22)

These results suggest that larger lesions, especially those affecting motor-network areas, are a risk factor for developing PSS. The results also confirm the clinical predictors of PSS, such as severe paresis and functional disorders, following stroke. Clinically, larger lesions and those more strongly affecting the motor-network area are associated with more severe paresis and lower functional status. Even with small lesion volumes (<0.5 cm^3) , 2 patients with multiple infarcts, including thalamus lesions, showed PSS, which are associated with sensory disorder following stroke. Sensory disorder or hypaesthesia after stroke has also been found to be a risk factor for PSS in some studies (13).

Study limitations

A limitation of the current study was the number of patients with PSS; however, its prevalence in this prospective study was not low. Secondly, clinical observation ended at 3 months after stroke, and data on patients with no initial paresis were collected if all inclusion criterion were fulfilled. Further studies with a larger size are necessary.

Conclusion

Patients with PSS often showed larger lesions, especially involving cortical and subcortical motor network structures. However, the size of lesions (≥3 cm^3) is in itself a sensitive positive predictor of PSS, but also a specific indicator to differentiate the risk of PSS (>0.5 cm^3). Large infarct volumes associated with persistent motor deficits are more likely to lead to PSS, while purely cortical lesions rarely result in PSS.

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