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CHAPTER

Ischemic lesion volume correlates with long-term functional outcome and quality of life of middle cerebral artery stroke survivors

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Abstract

Purpose- Previous studies investigating relationships between stroke lesion volume and outcome were restricted to short follow-up periods (3-6 months) and outcome measures of stroke severity and activities only, whereas functional improvement has been found to extend far beyond six months. Therefore, this study investigated relationships between infarct volume and a broad range of outcomes of stroke survivors at a long follow-up period.
Methods- Correlations between lesion volumes (determined by conventional MRI scans in the second week post-stroke) and outcomes after one year of 75 first-ever ischemic stroke survivors were investigated.
Results- Moderate Spearman Rank correlation coefficients were found between lesion volume and motor impairment (Motricity Index (MI): -0.43, p=0.00; Fugl Meyer Motor Assessment Scale (FM): -0.43; p=0.00). Correlation coefficients with activities of daily living were moderate but low associated with Barthel Index (r_s=0.30; p=0.01), modified Rankin Scale (r_s=0.39; p=0.00) and Frenchay Activities Index (r_s= -0.35; p=0.00). Lesion volume had a significant but low association (r_s= 0.27; p=0.02) with patient's health status measured with Sickness Impact Profile 68 (SIP68) and a moderate correlation with well-being assessed with Life Satisfaction Questionnaire (LSQ; r_s=-0.45; p=0.00). Found correlation coefficients were slightly stronger after correction for mixed (cortical/subcortical) and purely subcortical lesion location.
Conclusions- It can be concluded that infarct volume moderately correlates with long-term motor impairment, functional outcome and quality of life patients surviving stroke.

Introduction

Stroke is a frequent and disabling condition[35]. Although it appears obvious that long-term consequences of stroke are related to lesion volume, these relationships have only rarely been studied. Previous studies only used measures of stroke severity[6,29], or activity limitations[37], or rough outcome measures like the Glasgow Outcome Scale or the Rankin Scale [7,18,22,28,29,32,37]. Most research was concentrated on short-term (days or weeks)[6] or mid-term (3-6 months) outcome[7,18,22,28,29,32,37]. In these studies moderate to strong correlations with short-term outcome were found, confirming the importance of lesion volume for functional outcome[6,28,29]. However, these results cannot off hand be extrapolated to longer periods poststroke. Knowledge of the correlation between lesion volume and long-term functional outcome is relevant, since functional improvement occurs even after a period of 6 months[10]. Only two studies are available that investigated the relationship between lesion volume and long-term outcome after stroke[19,23], whereas studies that investigated the impact of lesion volume on quality of life measures are lacking.
Our study was initiated to investigate the strength of relationships between lesion volume and a broad range of functional and quality of life outcomes in stroke survivors one year after ischemic stroke. Subsequently, correlation coefficients between

lesion volume and outcomes in subgroups regarding mixed (cortical/subcortical) and purely subcortical location of lesion were calculated.

Subjects and Methods

Procedure

Patients admitted to the acute stroke units of six regional hospitals (one university and five general hospitals) in the period of 1999-2001 in the Netherlands were asked to participate. After informed consent, an MRI scan was obtained. Data about stroke severity were retrieved from medical files. At one year post-stroke, a trained research assistant interviewed the patients. The Medical Ethics Committees of all participating hospitals approved the research protocol.

Subjects

Included were first-ever ischemic stroke patients, aged between 18 and 85 years, having a premorbid Barthel Index ≥ 18 and a stable neurological condition one week poststroke. All patients had a visible middle cerebral artery (MCA) lesion on the MRI scan obtained in the second week poststroke. Excluded were patients with other lesions, infarctions other than MCA infarctions, borderzone infarctions, multiple infarctions and lacunar infarctions. Lacunar infarctions were defined as infarctions with a diameter ranging from 3-4 mm to a diameter of 15-20 mm located at the site of the basal ganglia, the internal capsule or corona radiata[2,12]. Furthermore, patients with premorbid cognitive limitations or comorbidity influencing functional outcome were excluded. Since the purpose of this study was to examine the relationship between lesion characteristics and long-term outcome, patients who died or had a recurrent stroke during follow-up time were excluded from further analysis.

Instruments

Stroke severity on hospital-admittance was assessed with the National Institutes of Health Stroke Scale (NIHSS)[5] and Glasgow Coma Scale[26] taken from the patient file[14]. Cognitive functioning was assessed with the Mini Mental State Examination[13]. Motor functions were measured with the Motricity Index (MI)[8] and the Fugl-Meyer Motor Assessment Scale (FM)[27]. The MI is a weighted scale derived from the Medical Research Council (MRC) Oxford grades. Scores are calculated by adding together the weighted scores for the three movements of each upper and lower limb (arm motor score total 100, leg motor score total 100, and a total score for normal functioning of 200). The FM measures the motor performance of stroke patients. It adopts a sequential stage model including reflex activity, stereotyped synergy patterns; movements deviated from synergy patterns, and normal movement. There are six

independent subscales: upper extremity, hand, lower extremity, balance, sensation, and pain. The performance of patients is assessed against a three-point scale ranging from 0 (item cannot be performed) to 2 (item can be fully performed).
Activity limitations were assessed with the Barthel Index (BI)[20] and the modified Rankin Scale (mRS)[38]. The modified Rankin Scale measures independence rather than performance of specific tasks. Mental as well as physical adaptations to the neurological deficits are incorporated. This scale consists of 6 grades, from 0 to 5, with 0 corresponding to no symptoms and 5 corresponding to a severe limitation in activities.
Participation restrictions were assessed with the Frenchay Activities Index (FAI)[39]. The FAI measures lifestyle in terms of more complex physical activities and social functioning, looking retrospectively at the past 3 and 6 months. It rates the frequency with which patients perform 15 activities (for example, gardening and washing dishes). The FAI was used as a total score with a scale range of 0-45.
Quality of life was measured using measures of health status and well-being. The Sickness Impact Profile 68 (SIP 68)[1,4,9] measures impact of health problems on physical, mental and social functioning. A higher score means more functional restrictions (scale range 0-68). The Life Satisfaction Questionnaire (LSQ) rates the degree of satisfaction with life as a whole and with eight life domains, like self-care ability, leisure time activities, and relationships[24]. Each item is scored on a 6-point scale. The total LSQ score is the mean of the item scores and has a score range of 1 (low level of well-being) up to 6 (high level of well-being).
If self-reported information on participation restrictions and quality of life could not be obtained from stroke survivors with severe cognitive or communication disorders, proxy ratings from a family member or caregiver were used. If necessary, proxy ratings of the FAI[30,34], the SIP 68[21] and LSQ were used, since the benefits of using proxy ratings outweigh their limitation[31].

Image analysis

In the second week poststroke Magnetic Resonance Imaging was performed. All scans were performed with a standard scanning protocol using 0.5 Tesla, 1.0 Tesla or 1.5 Tesla MRI scans; number of slices, thickness and gap were identical. Scans were digitally stored and further analyzed using a Philips Easy Vision Workstation©. Areas of abnormal hyperintensity typical for recent cerebral infarction were traced on each slice of the T2-weighted and/or FLAIR images. Surfaces of areas of abnormal hyperintensity were summed and multiplied with slice thickness (6 mm) and interslice gap (1.2 mm) to calculate infarct volumes.
Measurement of infarct volume[28,36] was performed while blinded for the patients' clinical status by a research fellow (SKS) in co-operation with an experienced neuroradiologist (ThDW)[36]. For logistic reasons, scans from one hospital were delivered on hard copies. These copies were digitized and analyzed[36]. Since we used both digital analysis and analysis of digitized hard copies, an inter-method analysis was performed for 24 MRI scans that were delivered digitally and on hard copies, giving an intra-class correlation coefficient of 0.97 (95% CI: 0.94-0.99). Because of this high agreement, all scans were used for further statistical analysis. Lesions affecting

cortical grey matter only and lesions affecting cortical grey matter with subcortical structures involved were classified as "mixed" lesions. If cortex was not affected, and only subcortical structures were involved, lesions were defined as purely "subcortical" lesions.

Statistical analysis

Spearman rank correlation coefficients were used to analyze bivariate relationships because outcome measures were of ordinal level and lesion volumes were not normally distributed. These correlation coefficients were computed separately for persons with different lesion locations (mixed lesions versus purely subcortical lesions) to adjust for the influence of lesion location and corresponding partial correlation coefficients (corrected for mixed and subcortical location) were computed.
All analyses were performed using SPSS package (version 12.0.1 for Windows)

Results

From a total of 115 included patients, 21 patients were excluded because of MRI findings: other lesions (4 patients); infratentorial lesions (10 patients); multiple infarctions (left and right hemisphere) (5 patients); borderzone infarction (1 patient); from one patient the MRI scan could not be evaluated because of movement artifacts.
At one year poststroke, 19 of these 94 patients were excluded from further analysis: 9 patients died; 4 patients had recurrent stroke; 2 patients developed co-morbidity that seriously affected their functional outcome and four patients refused further examination. The 13 patients who died or had another stroke incident were analyzed and compared with the other 75 patients. These groups did not significantly differ considering age (p=0.19); sex (p=0.63); stroke severity (NIHSS; p=0.71); lesion location (mixed/subcortical, p=0.89; hemisphere, p=0.83) and mean lesion volume (p=0.87).
Stroke survivors were investigated at one year post-stroke (mean 377 days post-stroke; SD 22). Measurements at one year post-stroke were available for 75 stroke survivors. The study population consisted of 35 men and 40 women. Patient's mean age one year poststroke was 63 years (SD 15). Eighty-four percent of the patients were admitted to the hospital at the day of stroke onset. MRI scans were obtained at a mean of 11 days post-stroke (Standard Deviation, SD 3.5). Median Glasgow Coma Scale at admission was 15 (Interquartile Range, IQR, 15-15) and median stroke severity at admission was 11 (NIHSS; IQR 7-15), indicating that most patients had moderate neurological deficits. Median Barthel Index 6 days post-stroke was 8/20 (IQR 4-17).
Discharge status of patients after hospital stay: 35 % home; 37% rehabilitation center; 4% geriatric home; 23% nursing home; 1% otherwise. Stroke survivors were investigated at one year post-stroke (mean 377 days post-stroke; SD 22).
Table 1 shows score distributions of lesion volume and outcome measures. Mean lesion volume was 61 ml (SD 76) with a median of 32 ml (IQR 6.3-91.2). Lesion volume

was not normally distributed. Mixed lesions were substantially bigger (p<0.00) than (purely) subcortical lesions (Table 1).

Table 1. Lesion volume and functional outcome one year post-stroke

		All patients			Mixed lesion			Subcortical lesion		
	Scale Range	N	Median	IQR	N	Median	IQR	N	Median	IQR
Lesion volume (ml)		75	31.89	6.34-91.20	48	58.95	23.65-140.93	27	6.34	1.99-21.10
MMSE, total	0-30	68	28.00	25.00-29.00	41	28.00	25.50-29.00	27	27.00	23.00-29.00
MI (total)	0-200	75	163.00	81.00-200.00	48	170.50	71.00-200.00	27	147.00	81.00-200.00
FM (total)	0-114	75	99.00	34.00-112.00	48	100.00	31.25-113.00	27	83.00	35.00-111.00
Barthel Index	0-20	75	18.00	15.00-20.00	48	18.00	12.00-20.00	27	18.00	16.00-20.00
Mod. Rankin	0-5	75	3.00	2.00-4.00	48	3.00	2.00-4.00	27	2.00	2.00-4.00
FAI, total	0-45	75	17.00	6.00-27.00	48	16.50	4.50-27.50	27	17.00	7.00-27.00
SIP 68, total	0-68	72	19.00	8.00-30.00	46	18.00	8.00-30.00	26	21.00	7.75-31.00
LSQ	1-6	75	4.38	3.43-4.88	48	4.19	3.33-4.80	27	4.50	4.00-5.00

There were no significant age and sex differences, nor significant differences on any outcome assessment instrument between patients with mixed or subcortical lesions. Table 2 shows that motor functioning and lesion volume correlated moderately both with MI and FM (R=-0.43) for all patients. No significant correlation coefficient was found between lesion volume and cognitive functioning (MMSE) (Table 2). Patient's activities of daily living assessed with BI and modified Rankin scale showed significant correlations with lesion volume (respectively r_s=-0.30; p=0.01 and r_s=0.39; p=0.00). A moderate correlation between lesion volume and participation (FAI; r_s=-0.35; p=0.00) was found. Lesion volume and quality of life showed varying correlations: a weak but significant correlation with functional health status (SIP68; r_s=0.27; p=0.02), and a moderate correlation with life satisfaction (LSQ; r_s=-0.45;p=0.00).

Table 2. Spearman rank correlation coefficients between the volume of ischemic lesion and long-term functional outcome.

	All patients (n=75)	Mixed/subcortical lesion		
		Mixed (n=48)	Subcortical (n=27)	Partial correlation
MMSE	-0.18	-0.19	-0.29	-0.31**
MI (total)	-0.43**	-0.60**	-0.44*	-0.50**
FM (total)	-0.43**	-0.59**	-0.42*	-0.50**
Barthel Index	-0.30**	-0.36*	-0.27	-0.42**
Mod. Rankin	0.39**	0.41**	0.46*	0.40**
FAI	-0.35**	-0.43**	-0.29	-0.37**
SIP 68	0.27*	0.35*	0.35	0.34**
LSQ	-0.45**	-0.42**	-0.30	-0.30**

*significant at P<0.05

**significant at P<0.01

In comparison to patients with purely subcortical lesions, patients with mixed lesions had stronger correlation coefficients between lesion volume and outcomes (Table 2). But partial correlation coefficients corrected for mixed/subcortical lesions did not differ much from correlation coefficients of the total (uncorrected) patient group. Nevertheless, the partial correlation coefficient between lesion volume and MMSE was significant (-0.31;p=0.01), whereas in the whole patient group a non-significant correlation coefficient (-0.18; p=0.15) was found. Partial correlation coefficient between lesion volume and Barthel Index was higher than the correlation coefficient in all patients, but only small differences were seen for the other outcome measures. Partial correlation coefficients between lesion volume and all outcome instruments were calculated, corrected for age, sex and educational level. Since these partial correlation coefficients did not differ significantly from the correlation coefficients shown in Table 2, they are not shown.

Discussion

Our study shows that lesion volume of MCA infarcts correlates moderately with functional outcome and quality of life in stroke survivors. When corrected for influence of lesion localization (mixed/purely subcortical), partial correlation coefficients between lesion volume and functional outcome were slightly stronger.
This study adds to the literature by using a long follow up period, focussing on a broad range of outcomes, studying a large homogenous group of stroke survivors with MCA infarcts, and by using precise lesion volume measurements on MR-images obtained in the second week poststroke. Assessing the measurement of lesion volume of MCA infarction with MRI is known to be accurate and reproducible[29].
The study population consisted of stroke survivors of whom prediction of long-term functional outcome is relevant.
Results of our study were in part comparable to those of earlier studies. Correlation coefficients between lesion volume and BI (r_s=-0.30) and mRS (r_s=0.39) in our study were slightly lower than those found by Maddox and colleagues[19] who found coefficients between lesion volume (using CT scans) and BI of r=0.37 and Rankin Score of r=0.46 in a more heterogeneous population of 60 patients with ischemic and hemorrhagic stroke one year poststroke. Pineiro and colleagues[23] assessed lesion volume on T2-weighted MRI scans in a smaller study population (18 patients). They found the same correlation coefficient between lesion volume and BI (r_s=0.30). However, the correlation coefficient between lesion volume and a combined motor deficit score that included the MI (next to grip strength, 9-hole peg test time and leg extensor power, compared with the unaffected limbs), was higher in their study (r_s=0.76). This combination of more tests might have increased the sensitivity of assessment of the paresis and therefore strengthened the correlation between volume and motor impairment. Furthermore, their use of a “corticospinal mask” made it possible to evaluate the influence of lesion location on the correlation between lesion volume and motor impairment. The corticospinal mask was based on neuroanatomic landmarks from a subset of MRI data and determined the maximum proportion of the cross-sectional area of this mask occupied by stroke. They

showed that the maximum proportion of the mask cross-sectional area occupied by stroke was a more discriminatory measure for associated motor deficit and axonal injury in the descending motor pathways than is the total stroke volume and that this is particularly the case for small strokes.

Studies with a shorter follow-up time[7,28,29,33,37] also showed stronger correlation coefficients with activities assessed with BI and mRS than in our study. This might indicate, that the influence of personal or environmental factors increases in time, leading to lower correlation coefficients in our study. Lower coefficients could also have resulted from a more evident ceiling effect of the BI and mRS at one year post-stroke.

Also, reorganization of functional circuits are known to continue far into the chronic phase poststroke[15]. This might have resulted in moderate correlations between lesion volume and long-term outcome as well. A large amount of unexplained variance might be due to non-lesion related functional changes of the brain.

Our quality of life results could not be compared to previous studies since in those studies outcome was assessed with stroke severity scales, neurological outcome scales or disability variables only.

Correlation coefficients between lesion volume and outcome were higher in patients with mixed lesions, compared to (purely) subcortical lesions. This corroborates the study by Lovblad and colleagues[17] in which the correlation coefficient between T2-weighted infarct volume and NIHSS at a median of 8 weeks post-stroke increased from 0.4 to 0.8 when only cortical infarcts were evaluated. Lovblad and colleagues[17] suggested that lesion location must be an important factor determining outcome particularly from small strokes, which might be the reason for our lower correlation coefficients. For motor impairment, lesion location is known to be of great influence[23]. Partial correlation coefficients between lesion volume and outcomes after correction for mixed/subcortical localization were comparable with correlation coefficients between lesion volume of all patients and outcome (Table 2).

Our study had some limitations. First, patients were included within the first week after admittance to the neurology ward. Patients with a severe stroke might have died before inclusion, and very mild stroke patients might have been discharged home before inclusion into our study was possible. This time point of inclusion in the first week poststroke might have affected our study population leading to a selection bias. Although patient characteristics of analyzed patients were comparable to previous study in the Netherlands[16], patients in our study were younger in comparison with global stroke studies and had an overall more favorable prognosis and milder strokes in comparison to the known stroke epidemiology and prognosis. As confirmed by data from other studies, it is known that although large strokes do badly, moderate-size strokes have a more variable outcome[28,29,37]. Therefore, knowledge of the strength of relationships between lesion volume and long-term outcome is especially important in this group of (mild) stroke survivors.

Second, lesion volume was assessed on conventional MRI scans (T2-weighted and FLAIR images) at a mean of 11 days poststroke, just after the time point of a maximum increment of lesion volume known at 7 days poststroke as assessed before on Diffusion-Weighted imaging[3]. This time point of scanning might have lead to an overestimation of lesion volume in our study population in particular for those

patients with larger ischemic infarcts due to vasogenic edema. Nevertheless, at the time of our project, the knowledge of lesion evolvement was not so far developed as it is now using DW-MRI scanning techniques. Furthermore, scans were obtained in the second week poststroke for pragmatic reasons, since otherwise patients would have been transferred (to other hospitals, rehabilitation centres or home) resulting in an unwanted loss of MRI scans or increment of travel costs of patients. In future studies the volume of ischemic lesion (and location) in acute stroke can more validly be obtained by using DW-MRI scans[3,25].

Third, the T2-weighted MRI slices used for lesion segmentation were relatively thick (6 mm). This could have resulted in an underestimation of lesion volume, particularly when lesions were small. However, a study in patients with multiple sclerosis showed that computed lesion volume did not increase much if lesion slice-thickness of 6 mm was further minimized[11] and it appears unlikely that minimization of lesion slice-thickness would have lead to different results in our study.

Fourth, the primary objective of our study was to examine the correlation between lesion volume and functional outcome. The influence of lesion location within the hemisphere and within cortex/subcortex fell outside the scope of this paper and was not studied. This might have weakened the correlation between volume and outcome on the level of impairment[23].

Conclusion

The volume of cerebral infarction moderately correlates with long-term motor impairment and with long-term functional outcome and quality of life of stroke survivors. Future studies defining the influence of neuro-anatomic lesion location on a broad range of long-term functional outcome is necessary.

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