Severity of leukoaraiosis determines clinical phenotype after brain infarction

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ABSTRACT

Objective: To determine whether the extent of leukoaraiosis, a composite marker of baseline brain integrity, differed between patients with TIA with diffusion-weighted imaging (DWI) evidence of infarction (transient symptoms with infarction [TSI]) and patients with ischemic stroke.

Methods: Leukoaraiosis volume on MRI was quantified in a consecutive series of 153 TSI and 354 ischemic stroke patients with comparable infarct volumes on DWI. We explored the relationship between leukoaraiosis volume and clinical phenotype (TIA or ischemic stroke) using a logistic regression model.

Results: Patients with TSI tended to be younger (median age 66 vs 69 years, $p = 0.062$) and had smaller median normalized leukoaraiosis volume (1.2 mL, interquartile range [IQR] 0.2–4.7 mL vs 3.5 mL, IQR 1.2–8.6 mL, $p < 0.001$). In multivariable analysis controlling for age, stroke risk factors, etiologic stroke mechanism, infarct volume, and infarct location, increasing leukoaraiosis volume remained associated with ischemic stroke (odds ratio 1.05 per mL, 95% confidence interval 1.02–1.09, $p = 0.004$), along with infarct volume and infarct location.

Conclusion: The probability of ischemic stroke rather than TSI increases with increasing leukoaraiosis volume, independent of infarct size and location. Our findings support the concept that the integrity of white matter tracts connecting different parts of the brain could contribute to whether or not patients develop TSI or ischemic stroke in an event of brain infarction. *Neurology*® 2011;77:55–61

GLOSSARY

CCS = Causative Classification of Stroke; **CI** = confidence interval; **DWI** = diffusion-weighted imaging; **FLAIR** = fluid-attenuated inversion recovery; **IQR** = interquartile range; **OR** = odds ratio; **TSI** = transient symptoms with infarction.

Approximately one-third of traditionally defined TIAs present with imaging evidence consistent with acute infarction (now termed transient symptoms with infarction [TSI]).¹ Rapid and complete clinical recovery in TSI suggests that the brain has the ability to quickly compensate for the neurologic dysfunction caused by underlying infarcts. One of the most characteristic features of TSI-related infarcts is that they are invariably very small²; 96% of all infarcts in TSI are smaller than 1 mL. While small infarcts are frequent in TSI, they are not specific; such small infarcts also occur in patients with clinical deficits lasting for more than 24 hours (traditionally defined ischemic stroke).² Furthermore, small infarcts in TSI do not occur solely in so-called silent brain regions but can also involve the same brain structures that are often infarcted in ischemic stroke.² Hence, it is not known how neurologic symptoms rapidly recover in some patients, but do not in others, despite the evidence of cerebral infarction of similar size and in similar location.

Functional recovery after brain injury is a complex process which involves recruitment and reorganization of structures that are functionally similar but anatomically distinct from those that are infarcted.^{3–5} Prior observations suggest that the integrity of the white matter as quanti-

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fied by the volume of leukoaraiosis contributes to variability in poststroke functional outcome.^{6–9} We hypothesized that the extent of leukoaraiosis would be smaller in TSI compared to ischemic stroke and partially explain why some individuals develop TSI and others develop ischemic stroke after brain infarction.

METHODS Patient population. We retrospectively analyzed consecutive patients presenting to a single tertiary care center with symptoms of TIA or stroke and acute brain infarction on diffusion-weighted imaging (DWI) obtained within 24 hours of symptom onset, over a 3-year period. Patients were identified from a prospectively maintained database that included all consecutive admissions with imaging evidence of acute brain infarction. We excluded patients in whom the quality of MRI was not sufficient to reliably assess the presence of acute infarction or volume of leukoaraiosis. Because large infarcts are invariably associated with ischemic stroke rather than TSI,² we restricted our study to the population of ischemic stroke patients with infarcts that were comparable in size to those in TSI. Hence, the study population was composed of TSI and ischemic stroke patients with similar infarct volumes (figure 1). We use the term TSI to designate patients with focal symptoms lasting less than 24 hours who had DWI evidence of acute infarction.² Patients with clinical symptoms lasting more than 24 hours were classified as ischemic stroke.¹⁰ Symptom duration was estimated from

neurologists' notes based on neurologic examination findings and interviews with patients and their reliable observers.

Data collection. We collected data on baseline patient characteristics and published predictors of short-term stroke outcome through chart review. These predictors included age,¹¹ gender,¹² stroke risk factors,^{13,14} admission NIH Stroke Scale score,¹⁵ thrombolytic treatment,¹⁶ and etiologic stroke subtype.¹⁷ Stroke etiology was classified using the Causative Classification of Stroke (CCS) system.¹⁸ We also recorded the time from symptom onset to MRI, the number of acute infarcts, the location of acute infarcts, and whether there were chronic infarcts on MRI or arterial occlusion on admission CT or magnetic resonance angiography in major branches of the circle of Willis. We classified infarct location based on visual assessment of images into 6 categories: brainstem, cerebellum, the basal region supplied by deep penetrating arteries, subcortical white matter region, cortex, and multiple regions.

Image acquisition and analysis. MRI was performed by 1.5 T GE Signa (GE Medical Systems, Milwaukee, WI) or Siemens Sonata (Siemens Medical Solutions, Erlangen, Germany) scanners using the image acquisition and processing protocols that have been summarized in detail previously.¹⁹ Acute ischemic lesion volume on DWI and leukoaraiosis volume on fluid-attenuated inversion recovery (FLAIR) images acquired within 24 hours of symptom onset were determined using semiautomated region of interest outlining and volume calculation tools on the MRIcro software (www.mricro.com, University of Nottingham, UK).⁹ DWI and leukoaraiosis volume measurements were performed by investigators blinded to the clinical status (TSI or ischemic stroke). We measured leukoaraiosis volume separately in each hemisphere and calculated the sum for use in further analyses. We defined leukoaraiosis as hyperintense white matter regions on FLAIR images excluding the convolutional white matter, U-fibers, corpus callosum, internal capsule, anterior commissure, and infratentorial regions.²⁰ We also excluded chronic white matter infarcts that clearly conformed to a vascular territory. All volume calculations were normalized according to the intracranial area using the following formula²¹: normalized lesion volume = lesion volume $\times$ mean intracranial area of the population/intracranial area of an individual patient. Intracranial area was measured by outlining the inner table on the mid-sagittal T1 images. The methods used for calculation of infarct volume, leukoaraiosis volume, and intracranial area were previously shown to have high interrater reliability (intraclass correlation coefficient: 0.99 for infarct volume, 0.98 for leukoaraiosis volume, and 0.97 for intracranial area).^{21–23}

Statistical analysis. All numerical variables are expressed as median (interquartile range [IQR]). The differences between ischemic stroke and TSI cohorts were assessed by χ^2 test for categorical variables and Mann-Whitney *U* test for continuous variables. A logistic regression model was used for multivariable analysis. The model included ischemic stroke vs TSI as the dependent variable. All variables with a *p* value of <0.05 in bivariate analyses (history of hypertension, history of atrial fibrillation, CCS stroke subtype, IV tissue plasminogen activator treatment, DWI lesion location, arterial cutoff in proximal branches of the circle of Willis, normalized DWI lesion volume, and normalized leukoaraiosis volume) were introduced into the model as independent variables. All categorical variables were entered as dummy variables into the model. Data were examined for collinearity. Associations were presented as odds ratios (OR) with corresponding 95% confidence intervals (95% CI). A 2-tailed *p*

Figure 1 Probability of transient symptoms with infarction (TSI) decreases as diffusion-weighted imaging (DWI) volume increases

Circles represent individual data points. Lines represent the probability curve and 95% confidence interval. The area left to the vertical dotted line (DWI volume = 13.7 mL) represents the region of overlapping infarct volumes in subjects with TSI and ischemic stroke.

value of <0.05 was considered significant. Statistical analyses were performed using SPSS 16.0.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local Human Studies Committee.

RESULTS A total of 1,085 consecutive patients with DWI evidence of acute infarction within the first 24 hours of symptom onset were admitted during the study period. We excluded 57 patients with either missing FLAIR images or FLAIR images with motion artifacts or extensive chronic ischemic lesions that prevented reliable assessment of the boundaries of leukoaraiosis. The remaining population comprised 153 patients with TSI and 875 patients with

ischemic stroke. Infarct volume ranged between 0.1 mL and 13.7 mL in TSI and 0.1 mL and 367.1 mL in ischemic stroke. In 354 of the 875 patients with ischemic stroke, the infarct volume was within the TSI range (smaller than 13.7 mL, figure 1). Thus, the final study population was composed of 153 patients with TSI and 354 patients with ischemic stroke.

In the TSI subjects, the median symptom duration was 1 hour (IQR 10 minutes–4 hours). Symptoms lasted less than 1 hour in 71 (46.4%), 1 hour to 2 hours in 40 (26.1%), and longer than 2 hours in 42 (27.4%) patients. There were only 6 patients with symptoms lasting more than 12 but less than 24 hours. Leukoaraiosis volume correlated with symptom duration in patients with TSI ($r = 0.20$, $p = 0.015$).

Table 1 summarizes demographic, clinical, and imaging characteristics of TSI and ischemic stroke populations. There was no difference in baseline features between the study population and the population excluded due to insufficient quality of images. Patients with ischemic stroke more frequently had a history of hypertension, atrial fibrillation, small artery occlusion as the etiologic stroke mechanism, isolated deep or brainstem infarct, arterial cutoff on angiography, and more often received IV tissue plasminogen activator treatment. Patients with TSI were more likely to have isolated cortical infarcts and infarcts restricted to the subcortical white matter.

The normalized median infarct volume on DWI was 0.82 mL (IQR 0.32–2.93 mL) in ischemic stroke and 0.31 mL (IQR 0.11–0.95 mL) in TSI ($p < 0.001$). Patients with ischemic stroke showed more extensive leukoaraiosis as compared to patients with TSI (figure 2); the normalized median leukoaraiosis volume was 3.5 mL (IQR 1.2–8.6 mL) in ischemic stroke and 1.2 mL (IQR 0.2–4.7 mL) in TSI ($p < 0.001$). In multivariable logistic regression, leukoaraiosis volume, infarct volume, and infarct location were independently associated with TSI vs ischemic stroke status (table 2). The probability of ischemic stroke increased substantially with increasing leukoaraiosis volume. Ischemic stroke was at least 10 times more likely to develop than TSI when leukoaraiosis volume exceeded 30 mL (figure 2). In contrast, in patients with no leukoaraiosis, the probability of TSI and ischemic stroke were almost identical.

The relationship between leukoaraiosis volume and clinical status persisted in a separate model where the TSI population was restricted to only those with symptoms that lasted less than 1 hour (OR 1.06 [95% CI 1.00–1.12], $p = 0.034$). Likewise, the regression model repeated after excluding

Table 1 Demographic, clinical, and imaging characteristics of subjects with TSI and ischemic stroke

	Ischemic stroke (n = 354)	TSI (n = 153)	p
Age, y, median (IQR)	69 (59–78)	66 (52–77)	0.062
Female gender, n (%)	151 (43)	61 (40)	0.559
Risk factors, n (%)			
Hypertension	258 (73)	96 (63)	0.022
Diabetes mellitus	76 (22)	23 (15)	0.093
Congestive heart failure	36 (10)	11 (7)	0.288
Atrial fibrillation	74 (21)	17 (11)	0.008
Coronary heart disease	83 (23)	33 (22)	0.644
Time to MRI, h, median (IQR)	9.8 (4.9–17.0)	9.8 (5.7–16.9)	0.458
CCS subtype, n (%)			0.002
Large artery atherosclerosis	73 (21)	38 (25)	0.292
Cardioaortic embolism	135 (38)	50 (33)	0.241
Small artery occlusion	72 (20)	14 (9)	0.002
Other uncommon causes	19 (5)	17 (11)	0.021
Undetermined	55 (15)	34 (22)	0.069
IV rtPA treatment, n (%)	16 (5)	1 (1)	0.029
Lesion location, n (%)			<0.001
Brainstem	34 (10)	2 (1)	<0.001
Cerebellum	23 (7)	8 (5)	0.584
Basal ganglia	64 (18)	19 (12)	0.114
Subcortical white matter	44 (12)	32 (21)	0.014
Cortex	58 (16)	54 (35)	<0.001
Multiple regions	131 (37)	38 (25)	0.008
Multiple acute infarcts, n (%)	133 (38)	68 (44)	0.146
Arterial cutoff in proximal branches of the circle of Willis, n (%)	48 (14)	8 (5)	0.006
Chronic infarcts, n (%)	98 (28)	38 (25)	0.507
Normalized DWI lesion volume, mL, median (IQR)	0.82 (0.32–2.93)	0.31 (0.11–0.95)	<0.001
Normalized leukoaraiosis volume, mL, median (IQR)	3.5 (1.2–8.6)	1.2 (0.2–4.7)	<0.001

Abbreviations: CCS = Causative Classification of Stroke; DWI = diffusion-weighted imaging; IQR = interquartile range; rtPA = recombinant tissue plasminogen activator; TSI = transient symptoms with infarction.

Figure 2 Probability of transient symptoms with infarction (TSI) decreases as leukoaraiosis volume increases

The circles represent individual data points. Lines represent the probability curve and 95% confidence interval. DWI = diffusion-weighted imaging.

patients with chronic white matter infarcts demonstrated that leukoaraiosis volume was still an independent predictor of clinical status (OR 1.04 [95% CI 1.00–1.09], $p = 0.040$).

DISCUSSION We have shown that among patients presenting with acute infarction on DWI, those with stroke symptoms that resolve within 24 hours have smaller leukoaraiosis volume compared to patients with persistent symptoms indicating an ischemic stroke. The median normalized leukoaraiosis volume

was approximately 3 times higher in patients with ischemic stroke as compared to TSI. In addition to leukoaraiosis volume, infarct size and infarct location also differed between TSI and ischemic stroke; the probability of ischemic stroke increased with rising infarct volume. Infarcts that included critical structures with compact anatomic organization such as the brainstem or in locations where typical lacunar infarcts occurred were also more likely to be associated with ischemic stroke.

While infarct size and location are important, they together explain only half of the variability in functional outcome in patients with ischemic stroke.²⁴ Our data suggest that the brain's intrinsic capacity to recover from ischemic brain injury may be in part determined by the extent of leukoaraiosis, which is also known to contribute to the variability in outcome.^{6–9} Pathology findings in leukoaraiosis include, among other things, axonal changes ranging from mild demyelination to severe axonal disruption.²⁵ The severity of these pathologic changes correlates with the extent of leukoaraiosis on MRI.²⁶ Published evidence from studies using transcranial magnetic stimulation, fMRI, and diffusion tensor imaging suggests that recruitment and reorganization of ipsilesional and contralesional brain regions during poststroke recovery requires the presence of intact connections between different parts of the brain.^{27–29} An in silico model of activity-dependent plasticity has supported this view, showing that axonal dysfunction caused by blocking of the propagation of action potentials between neurons results in deficits in pruning and recovery of functional synapses and this in turn produces a negative impact on adaptive plasticity that is much greater than the impact of gray matter injury.³⁰

The view that leukoaraiosis impairs the brain's ability to compensate for the lost function is supported by multiple recent studies indicating that the extent of leukoaraiosis correlates with poor functional outcome and low quality of life after ischemic stroke.^{6–8} We have previously shown that leukoaraiosis volume is a predictor of modified Rankin Scale score at 6 months following ischemic stroke after controlling for age, infarct volume, etiologic stroke mechanism, initial stroke severity, and preventive stroke treatment; the highest quartile of leukoaraiosis volume is associated with a 1.5-fold higher modified Rankin Scale score as compared with the lowest quartile.⁹ The current data offer additional evidence that leukoaraiosis volume is a marker for the brain's capacity for rapid and complete recovery of the lost function.

It is notable that clinical recovery in TSI is a strikingly rapid process. In the present dataset, 46% of

Table 2 Independent predictors of ischemic stroke status

	Odds ratio (95% confidence interval)	p
Lesion location		
Cerebellum	1.00	0.001
Brainstem	6.67 (1.16–38.51)	
Basal ganglia	0.58 (0.14–2.34)	
Subcortical white matter	0.34 (0.12–0.98)	
Cortex	0.28 (0.10–0.79)	
Multiple regions	0.51 (0.18–1.42)	
Normalized DWI lesion volume (per 1 mL)	1.31 (1.16–1.49)	<0.001
Normalized leukoaraiosis volume (per 1 mL)	1.05 (1.02–1.09)	0.004

Abbreviation: DWI = diffusion-weighted imaging.

TSIs lasted less than 1 hour and another 26% lasted between 1 and 2 hours. The majority of TSI events lasting less than 1 hour lasted often only 1 to 10 minutes (66%). It is thus plausible to presume that most small infarcts (i.e., those within the region of overlap in figure 1) either recover completely and very rapidly often within minutes or recover gradually and often only partially in longer than 24 hours. This tendency toward bimodal distribution of symptom duration in small infarcts suggests that there is a threshold in the brain's capacity to regain the lost function, which, when exceeded, symptoms that would otherwise last only for a few minutes could persist for more than 24 hours. The association between ischemic stroke and increasing leukoaraiosis volume may suggest that leukoaraiosis impairs the brain's reserve capacity so that small infarcts could easily overcome the threshold to result in lasting ischemic stroke symptomatology.

Leukoaraiosis is not only a predictor of functional outcome but also has been reported to predict future episodes of stroke in individuals with or without previous stroke.^{31–33} It has been suggested that leukoaraiosis reflects an increased burden of stroke risk factors and therefore identifies individuals at high risk of stroke.³¹ Data from the Atherosclerosis Risk in Communities study, on the other hand, challenges this view by showing that the association between leukoaraiosis and stroke risk is independent of conventional stroke risk factors such as hypertension, diabetes, and cigarette smoking.³³ Our findings may shed light into the mechanism of increased stroke risk in individuals with leukoaraiosis by suggesting that leukoaraiosis-mediated impaired capacity to compensate for injury results in occurrence of symptomatic stroke in an event of acute infarction. This view is further supported by evidence indicating that leukoaraiosis confers an increased perioperative symptomatic stroke risk after procedures that are known to be associated with high rate of brain embolism such as carotid artery stenting,³⁴ carotid endarterectomy,³⁴ intraoperative shunt placement during carotid endarterectomy,³⁵ and total aortic arch replacement.³⁶ Future research examining leukoaraiosis load-by-treatment efficacy interaction in conditions associated with small brain infarcts such as those occurring following carotid endarterectomy and stenting might demonstrate practical utility of the current findings. Leukoaraiosis information could also be used to generate predictive algorithms (along with other independent predictors of clinical outcome) to optimize benefit and minimize risk from thrombolytic therapy. Such models might identify individuals with high likelihood of early spontaneous recovery in whom withholding thrombolytic therapy could be

justified. In contrast, in patients with extensive leukoaraiosis, the high risk of intracranial hemorrhage might outweigh the benefit by thrombolysis that accrues from reduced risk of developing disabling permanent deficit.³⁷

Our findings are subject to a number of limitations. First, time-based categorization of clinical status (TSI vs ischemic stroke) might have introduced ascertainment bias in subjects with small infarcts who had symptoms lasting for around 24 hours. Nevertheless, the observed association between leukoaraiosis and clinical phenotype was strong and persisted in sensitivity analyses in subsets with symptoms that lasted for <1 hour vs >24 hours. Second, although we stratified infarct location into anatomically distinct and clinically important categories, our approach did not take into account the regional differences within each category. A more detailed segmentation of the brain employing a voxel-by-voxel approach might provide more accurate estimation of the impact of location on clinical phenotype, and highlight specific regions of the brain where the impact of leukoaraiosis on persistence of symptoms might be highest. Such methods demand large datasets for adequate sampling of each brain compartment. Finally, patients who had MRI with motion artifacts were excluded from the study. This, however, did not appear to have caused a significant selection bias as none of the baseline clinical features listed in table 1 were significantly different between the study population and the excluded patients.

These data show that rapid functional recovery after small infarcts appears to be associated with integrity of white matter tracts as manifested by the amount of leukoaraiosis detected by MRI. The finding that individuals with increasing leukoaraiosis are at higher risk of developing ischemic stroke (rather than TSI) supports further studies to uncover the added value of baseline leukoaraiosis burden information in patient selection for clinical stroke trials.

AUTHOR CONTRIBUTIONS

E.M.A. and H.A. conceived and designed the research. E.M.A., A.B., and H.A. acquired and interpreted the data. E.M.A. and M.V. performed statistical analysis. E.M.A., A.B., and H.A. drafted the manuscript. N.S.R., J.R., K.L.F., and A.G.S. made critical revision of the manuscript for important intellectual content. H.A. and A.G.S. handled funding and supervision.

DISCLOSURE

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SEIZURE RECURRENCE AFTER A 1ST UNPROVOKED SEIZURE: AN EXTENDED FOLLOW-UP

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Neurology 1990;40:1163–1170

We followed 208 patients identified on the day of their 1st unprovoked seizure for a mean duration of 4 years. Seizures recurred in 64. Recurrence risks were estimated to be 14%, 29%, and 34% at 1, 3, and 5 years following the 1st episode. A history of previous neurologic insult (remote symptomatic) was associated with a 2.5-fold increased risk of recurrence. Among idiopathic cases, a sibling with epilepsy, a generalized spike and wave EEG, or a history of acute symptomatic seizure increased risk for recurrence. Among remote symptomatic cases, status epilepticus, a prior acute symptomatic seizure, or Todd's paresis increased risk. Depending upon clinical features, recurrence risk at 5 years following a 1st seizure ranged from 23% to 80%. Treatment with anticonvulsant medication was not associated with a decrease in recurrence risks.

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Comment from Gregory D. Cascino, MD, FAAN, Associate Editor: A pivotal study that demonstrated risk of seizure recurrence in patients with a single, unprovoked seizure. The significant predictive factors, e.g., presence of remote symptomatic neurological disease, were identified. The investigators also showed that long-term antiepileptic drug therapy did not affect seizure recurrence.