Leukoaraiosis Predicts Poor 90-Day Outcome after Acute Large Cerebral Artery Occlusion

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Key Words

Acute stroke • CT • Leukoaraiosis • Outcome • Tissue plasminogen activator • Thrombolysis

Abstract

Background: To date limited information regarding outcome-modifying factors in patients with acute intracranial large artery occlusion (ILAO) in the anterior circulation is available. Leukoaraiosis (LA) is a common finding among patients with ischemic stroke and has been associated with poor post-stroke outcomes but its association with ILAO remains poorly characterized. This study sought to clarify the contribution of baseline LA and other common risk factors to 90-day outcome (modified Rankin Scale, mRS) after stroke due to acute anterior circulation ILAO. **Methods:** We retrospectively analyzed 1,153 consecutive patients with imaging-confirmed ischemic stroke during a 4-year period (2007–2010) at a single academic institution. The final study cohort included 87 patients with acute ILAO subjected to multimodal CT imaging within 24 h of symptom onset. LA severity was assessed using the van Swieten scale on non-contrast CT. Leptomeningeal collaterals were graded using CT angiogram source images. Hemorrhagic transformation (HT) was determined on follow-up CT. Multivariate logistic regression

controlling for HT, treatment modality, demographic, as well as baseline clinical and imaging characteristics was used to identify independent predictors of a poor outcome (90-day mRS >2). **Results:** The median National Institutes of Health Stroke Scale (NIHSS) at baseline was 15 (interquartile range 9–21). Twenty-four percent of the studied patients had severe LA. They were more likely to have hypertension ($p = 0.028$), coronary artery disease ($p = 0.015$), poor collaterals ($p < 0.001$), higher baseline NIHSS ($p = 0.003$), higher mRS at 90 days ($p < 0.001$), and were older ($p = 0.002$). Patients with severe LA had a uniformly poor outcome ($p < 0.001$) irrespective of treatment modality. Poor outcome was independently associated with higher baseline NIHSS ($p < 0.001$), worse LA (graded and dichotomized, $p < 0.001$), reduced leptomeningeal collaterals (graded and dichotomized, $p < 0.001$), presence of HT ($p < 0.001$), presence of parenchymal hemorrhages ($p = 0.01$), baseline mRS ($p = 0.002$), and older age ($p = 0.043$). The association between severe LA ($p = 0.0056$; OR 13.86; 95% CI 1.94– ∞) and baseline NIHSS ($p = 0.0001$; OR 5.11; 95% CI 2.07–14.49 for each 10-point increase) with poor outcome maintained after adjustment for confounders in the final regression model. In this model, there was no significant association between presence of HT and poor outcome ($p = 0.0572$). **Conclusion:** Coexisting LA may predict poor functional outcome in patients with acute anterior cir-

culation ILAO independent of other known important outcome predictors such as comorbid state, admission functional deficit, collateral status, hemorrhagic conversion, and treatment modality.

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Introduction

Intracranial large artery occlusion (ILAO) in the anterior circulation accounts for a significant number of ischemic strokes and predicts a poor outcome [1–3]. However, factors modifying the outcome following acute ILAO remain incompletely characterized. Knowledge of such aspects appears paramount to aid in the clinical decision making and to help identifying those patients at high risk or unlikely benefit from advanced treatment strategies, such as thrombolysis or endovascular approaches to therapy. Originally noted as diffuse, non-specific subcortical white matter lesions on CT, leukoaraiosis (LA) is a common finding among patients with ischemic stroke and has been associated with poor post-stroke outcomes as well as increased risk for recombinant tissue plasminogen activator (rtPA)-associated intracranial hemorrhage [4–7]. LA has been associated with reduced brain perfusion and cerebrovascular reactivity and may therefore considerably decrease penumbral survival and negatively affect outcome [8, 9]. Yet, contribution of LA to outcome in stroke patients with ILAO remains to be clarified. To further elucidate this issue, we sought to determine the association between LA severity as assessed by non-contrast CT (NCCT) and 90-day outcomes in patients following acute anterior circulation ILAO.

Methods

Patient Selection and Clinical Data

This study was Institutional Review Board approved and Health Insurance Portability and Accountability Act compliant. We analyzed data from 1,153 consecutive adult patients with imaging-confirmed diagnosis of ischemic stroke evaluated at a single academic institution between January 2007 and October 2010 (fig. 1). Patients were included if they had admission NCCT, followed by CT angiogram (CTA) and perfusion CT (CTP) performed within 24 h after time of symptom onset. Time of onset was defined as either witnessed symptom onset or time of last known well for unwitnessed events. Patients were excluded if there was no evidence of intracranial arterial occlusion on CTA in the anterior circulation [internal carotid artery (ICA) to the M2 segment of the middle cerebral artery (MCA)]. Three patients with angiographically proven proximal M3 occlusion were included as CT imaging was consistent with M2 occlusion suggest-

Fig. 1. Flow chart for the study. Patient exclusion as well as distribution according to outcome. * Note that this number includes patients transferred from referring hospitals to our facility, which serves as the regional tertiary care referral center.

ing clot migration during neurointervention. Further, only patients with documented perfusion deficit on their CTP images were included to avoid confounding by stroke mimics in the setting chronic ILAO. Time-to-CTP was defined as the time (min) between symptom onset and completion of the CTP imaging protocol. National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) score were assessed at the time of initial presentation as part of the admission workup. Patients were allocated to endovascular therapy according to our institutional protocol. Patient demographics, admission vital signs, laboratory data, comorbidities, preadmission medications, stroke risk factors, and stroke etiology [using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification] [10] were collected on all patients by review of the medical chart. Follow-up mRS was

obtained at 90 days during follow-up in our stroke prevention clinic by a stroke-trained physician, certified in mRS [11]. When the mRS was unavailable, the same observers reconstructed the score from the case description, according to the mRS criteria [12].

Neuroimaging Protocol

All CT sequences were performed on a 64-row detector Philips scanner. NCCT was performed in a non-helical mode at 120 KvP and 200 mA with data reconstruction at 5 mm axial slices. CTA was performed using 64 × 0.625 mm detector configuration with a pitch of 0.673 from the arch of aorta to the vertex using 120 KvP, 300 mA, and 0.5 s rotation time. Patients received 60–80 ml of Isovue 370 (Bracco Diagnostics, Princeton, N.J., USA) at a rate of 4 mm/s through a power injector followed by 40 ml saline. 3D orthogonal maximum intensity projection images were created in 3 planes. CTP was performed with detector configuration of 64 × 0.625 mm at 80 KvP and 100 mAs creating 4 slices of 10 mm thickness (total coverage 40 mm). The plane of imaging was parallel to the floor of the anterior cranial fossa starting just above the orbits. Thirty cycles were obtained at 2 s (total duration of 60 s). CTP data were analyzed utilizing a stand-alone version of CTP software developed by Philips Medical Systems (Cleveland, Ohio, USA), which automatically calculated mean transit time and cerebral blood volume defects as previously described in detail [13]. The anterior cerebral artery was used for arterial input function [14].

Image Review and Analysis

Admission NCCT, CTA, and CTP were reviewed independently and blindly to both clinical data and follow-up scans by two experienced readers. Disagreements were resolved by consensus. Variable window width and center level settings were used for optimal ischemic hypoattenuation detection with NCCT and CTA images [15, 16]. Presence and extent of LA was assessed utilizing the van Swieten Scale (VSS) grading the white matter lesions for the regions anterior and posterior to the central sulcus on a 3-point scale from 0 (no LA) to 2 (confluent white matter involvement from the ventricles to the grey matter). Summing the score from the anterior and posterior region provided a total score ranging from 0–4 [17]. In the present study, LA was separately assessed in both hemispheres. After un-blinding, only the score from the non-ischemic hemisphere was considered. Location of occlusions within arterial segments was noted on CTA. CTA source images were used to assess for the presence of collateral vessels as previously described [15]. Briefly, leptomeningeal collaterals were graded on a 5-point scale (from 1 denoting absence to 5 denoting exuberant collaterals) compared to the contralateral unaffected side. Hemorrhagic transformation (HT) on follow-up imaging was determined according to the ECASS (European Cooperative Acute Stroke Study) definition [18]. To avoid confounding we also dichotomized the degree of LA [VSS 0–2 (absent to moderate) vs. 3–4 (severe)], collateral status [1–2 (poor) vs. 3–5 (good)], HT (absent vs. present), site of intracranial occlusion proximal (ICA–M1) versus distal (M2–M3), and treatment modality [no therapy vs. intravenous (i.v.) rtPA and/or endovascular treatment]. Lastly, since i.v. rtPA represents the approved therapy for patients without contraindications, treatment modality was also included as a trichotomized variable (no therapy vs. i.v. rtPA vs. endovascular treatment).

Statistics

Continuous variables are reported as mean ± SD or as median ± interquartile range (IQR). Categorical variables are reported as proportions. Univariate analysis was used to test the association between baseline characteristics and dichotomized variables with the 90-day mRS using the χ^2 test, Fisher's exact test, Student's t test, and Mann-Whitney U test as appropriate for dichotomous or continuous variables (table 1). Multivariate logistic regression with forward elimination (probability value for elimination of 0.1) was used to identify independent predictors for good outcome (90-day mRS ≤ 2). Variables significantly associated with a good outcome in the univariate analysis ($p < 0.1$) were included in the multivariate logistic model (PASW Statistics 18, Chicago, Ill., USA). Given their reported association with clinical outcomes, we repeated this analysis forcing the following additional variables into the model: time-to-CTP, acute intervention, pre-stroke mRS, site of intracranial occlusion, and atrial fibrillation. The final model was fitted using exact logistic regression (Log Xact, Cytel Inc., Version 8.0, Cambridge, Mass., USA).

Results

Of the 1,153 patients included in the database, 115 subjects were identified as having acute isolated anterior circulation ILAO involving a single hemisphere. Nineteen subjects were excluded due to poor image quality. Nine patients had no perfusion deficit (all had a low NIHSS of ≤ 4 and incomplete vascular occlusion). Baseline characteristics are summarized in table 1.

Univariate analysis showed that poor 3-month outcome (mRS > 2) was associated with higher baseline NIHSS ($p < 0.001$), worse LA (graded and dichotomized, $p < 0.001$; fig. 2a), reduced leptomeningeal collaterals (graded and dichotomized, $p < 0.001$), presence of HT ($p < 0.001$), presence of parenchymal hemorrhages [18] (PH1 and PH2, $p = 0.01$), baseline mRS ($p = 0.002$), and older age ($p = 0.043$). There was a significant association between LA and collateral status ($p < 0.001$).

After adjustment (table 2), it appeared that poor outcome was associated with severe LA (OR 13.86, 95% CI 1.94–∞, $p = 0.0056$) and baseline NIHSS (for each 10-point increase OR 5.11, 95% CI 2.07–14.49, $p = 0.0001$). There was a trend for an association between presence of HT and poor outcome ($p = 0.0572$). These results did not change after forcing additional variables into the statistical model.

There was no significant association between LA grade and good recanalization (TIMI ≥ 2, $p = 0.388$). Good recanalization was achieved in 74% of patients subjected to endovascular therapy with no significant difference in the recanalization rates between patients with good versus poor outcome ($p = 0.194$) in this subgroup.

Table 1. Baseline characteristics (unadjusted) of the studied patient population as stratified by LA severity

Characteristics	All patients (n = 87)	None to moderate LA (VSS ≤2) (n = 66)	Severe LA (VSS ≥3) (n = 21)	p value
Age, years	67 (± 16)	64 (± 16)	76 (± 12)	0.002
Male sex	48 (55%)	36 (55%)	12 (57%)	1.000
Baseline NIHSS, median (IQR)	15 (9–21)	12 (7–20)	18 (15–23)	0.003
Baseline mRS, median (IQR)	0 (0–0)	0 (0–0)	0 (0–1)	0.151
Systolic blood pressure, mm Hg	149 (± 31)	146 (± 27)	156 (± 42)	0.487
Mean arterial blood pressure, mm Hg	102 (± 22)	101 (± 19)	107 (± 28)	0.416
Admission glucose, mg/dl	126 (± 35)	125 (± 36)	129 (± 32)	0.585
Admission creatinine, mg/dl	1.10 (± 0.86)	1.12 (± 0.95)	1.02 (± 0.48)	0.988
Admission white blood cell count, × 10 ⁹ /l	9.5 (± 4.1)	9.3 (± 4.0)	10.4 (± 4.4)	0.233
LDL-C within 24 h of admission, mg/dl	82 (± 35)	85 (± 36)	74 (± 29)	0.157
Preadmission medications				
Antiplatelets	31 (36%)	20 (30%)	11 (52%)	0.074
Warfarin	6 (7%)	4 (6%)	2 (10%)	0.628
Statin	34 (39%)	24 (36%)	10 (48%)	0.443
Antiglycemic	10 (11%)	7 (11%)	3 (14%)	0.699
ACEi/ARB	26 (30%)	20 (30%)	6 (29%)	1.000
Preexisting risk factors				
Hypertension	62 (71%)	43 (65%)	19 (90%)	0.028
Atrial fibrillation	27 (31%)	17 (26%)	10 (48%)	0.102
Dyslipidemia	44 (51%)	33 (50%)	11 (52%)	1.000
Diabetes	13 (15%)	9 (14%)	4 (19%)	0.505
Prior stroke or transient ischemic attack	14 (16%)	10 (15%)	4 (19%)	0.736
Coronary artery disease	29 (33%)	17 (26%)	12 (57%)	0.015
Congestive heart failure	17 (20%)	12 (18%)	5 (24%)	0.544
Peripheral vascular disease	5 (6%)	2 (3%)	3 (14%)	0.088
Dementia	4 (5%)	3 (5%)	1 (5%)	1.000
Smoking	25 (29%)	20 (30%)	5 (24%)	0.783
Alcohol abuse	9 (10%)	7 (12%)	1 (5%)	0.446
Time-to-CTP, min	339 (± 269)	345 (± 273)	320 (± 263)	0.648
Acute intervention				0.755
Conservative management	30 (34%)	43 (65%)	14 (67%)	
i.v. rtPA	15 (17%)	12 (18%)	3 (14%)	
Endovascular intervention without i.v. rtPA	27 (31%)	20 (24%)	7 (35%)	
Endovascular intervention with i.v. rtPA	15 (17%)	11 (17%)	4 (19%)	
Final TOAST stroke mechanism				0.105
1 (large-artery atherosclerosis)	20 (23%)	17 (26%)	3 (14%)	
2 (cardioembolic)	38 (44%)	24 (36%)	14 (67%)	
3 (small-artery occlusion)	0 (0%)	0 (0%)	0 (0%)	
4 (stroke of other determined cause)	11 (13%)	9 (14%)	2 (10%)	
5 (stroke of undetermined cause)	18 (21%)	16 (24%)	2 (10%)	
Site of intracranial occlusion				0.335
ICA	6 (7%)	6 (9%)	0 (0%)	
ICA-MCA tandem	22 (25%)	19 (29%)	3 (14%)	
MCA M1	40 (46%)	28 (42%)	12 (57%)	
MCA M2	16 (18%)	11 (17%)	5 (24%)	
MCA M3	3 (3%)	2 (3%)	1 (5%)	
Leukoaraiosis grade (VSS)				<0.001
0	30 (34%)	30 (46%)	0 (0%)	
1	17 (20%)	17 (26%)	0 (0%)	
2	19 (22%)	19 (29%)	0 (0%)	
3	10 (11%)	0 (0%)	10 (48%)	
4	11 (13%)	0 (0%)	11 (52%)	
Pattern of leptomeningeal collaterals				<0.001
Absent	24 (28%)	11 (17%)	13 (62%)	
Less than contralateral hemisphere	44 (51%)	38 (58%)	6 (29%)	
Equal to contralateral hemisphere	15 (17%)	13 (20%)	2 (10%)	
Greater than contralateral hemisphere	4 (5%)	4 (6%)	0 (0%)	
Exuberant	0 (0%)	0 (0%)	0 (0%)	

Data are n (%) or mean (±SD) unless otherwise indicated. ACEi = Angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Fig. 2. **a** Functional outcome at 90 days (mRS) stratified by severity of LA grades (VSS 0–2 vs. 3–4, $p < 0.001$). **b** Relative frequency of parenchymal type hemorrhages (PH1 and PH2) and poor outcome (mRS 3–6) stratified according to LA severity.

Finally, there was no significant association between LA grade and parenchymal hemorrhages ($p = 0.077$) and there appeared to be a dissociation between outcome and the relative frequency of parenchymal hemorrhages as indicated by the similar incidence in patients with a VSS of 4 (who had a uniformly poor outcome) and a VSS of 0 or 1 (fig. 2b).

Discussion

In our study, approximately one fourth of patients with acute anterior circulation ILAO had severe LA on baseline CT. After accounting for relevant confounders, presence of severe LA was independently associated with the risk for a poor outcome after ILAO. In fact, ~70% of patients in this subgroup were either severely disabled or dead at 90 days. These findings add to the notion that LA is an important risk factor for poor outcome after ischemic stroke [5, 7, 19–23]. Interestingly, other common contributors to a poor outcome, such as the site of arterial occlusion, presence of HT, or treatment modality [1–3, 24–26], did not appear to modify the outcome in the studied patient group.

Common risk factors associated with LA include aging, arterial hypertension, diabetes mellitus, and cardiac disease [27, 28]. Indeed, we have found that patients with severe LA were more likely to have hypertension and coronary artery disease, and they were older. Age, which is

Table 2. Factors independently associated with poor outcome at 90 days

Independent variable	OR (95% CI)	p value
Baseline NIHSS*	5.11 (2.07–14.49)	0.0001
LA grade (VSS 3–4)	13.86 (1.94–●●)	0.0056
Hemorrhage (present)	4.82 (0.96–32.65)	0.0572

* For each 10-point increase in the NIHSS, there is an OR of 5.11 for poor outcome (mRS >3).

an important non-modifiable risk factor for ischemic stroke and poor post-stroke outcome [29], was associated with outcome in our study. However, this association was no longer present following multivariate analysis. Similar observations have been reported and may suggest that the degree of LA, rather than biological age alone, is an important modifier of outcome in the elderly [5]. This notion is further substantiated by a recent report demonstrating that moderate to severe LA is associated with increased risk for poor outcome in young ischemic stroke patients [22].

The mechanisms underlying the influence of LA on functional outcome are not entirely clear. LA has been associated with spontaneous and thrombolysis-related intracranial hemorrhage as well as hematoma expansion [30–32]. While there was an increasing incidence of parenchy-

mal hemorrhages with worsening LA in our study, this observation did not reach statistical significance. Further, among patients with the most severe LA grade (VSS 4), only 1 patient developed a parenchymal hemorrhage (PH1) indicating that mechanisms different from HT determined outcome in these patients [6]. Impaired brain recovery mechanisms and a reduced brain reserve capacity for injury have been suggested [33]. In addition, reduced penumbral survival following acute ischemic stroke, possibly due to chronically impaired tissue perfusion and cerebrovascular reactivity, has been described in patients with severe LA [8, 9, 34]. Our study provides new insight by showing a significant inverse correlation between LA severity and robustness of leptomeningeal collaterals, indicating a collective role in the reduction of autoregulatory mechanisms with subsequently aggravated tissue damage.

Major strengths of this study are the large sample size of a hospitalized, homogenous patient population undergoing multimodal CT imaging and the collection of extensive clinical information. Our study and this analysis are unique and add novel information compared with prior reports [5, 23, 35]. The approach is contemporary and important as it uses CT technology that is now frequently applied in most centers worldwide as the first-line imaging method in acute stroke prior to patient selection for different acute therapies due to its ease of access, rapidness, and reliability. We investigated various variables that have been associated with a poor outcome in the setting of large arterial stroke as well as LA. We included patients that received various treatment modalities allowing utilization of data on LA as a potential additional clinical marker for the assessment of risk and prognosis in acute ILAO.

Our study has several limitations. First, our study was retrospective in nature and the number of observations per

subgroup was limited. The findings of this study require testing in a prospective study with a much larger sample size. Second, while our data shows a strong association between LA and outcome, a causal relationship remains to be established. Third, misclassification of LA is possible given the CT-based visual grading system. However, in contrast to MRI, CT scans are broadly available, routinely used in the early evaluation of stroke patients, and our approach has been found to be a reliable method in prior studies without requiring time consuming post-processing [5, 17, 20, 30]. Lastly, our results are exclusive to a highly selected patient population. However, these patients are unique in that they often respond poorly to systemic thrombolysis and are therefore frequently considered for aggressive treatment strategies involving endovascular techniques [24, 25]. Identifying markers associated with a poor outcome in this population is an important goal that may ultimately help improve future patient selection for therapy to maximize their risk-to-benefit ratio.

In conclusion, we describe a significant association of LA with poor functional outcome in a large cohort of patients with anterior circulation ILAO independent of other known important outcome predictors such as comorbid state, admission functional deficit, collateral status, hemorrhagic conversion, and treatment modality.

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Disclosure Statement

N.H., E.L., S.P.B., D.T., A.K.W. and M.M. report no conflicts of interest.

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