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Importance of Leukoaraiosis on CT for Tissue Plasminogen Activator Decision Making: Evaluation of the NINDS rt-PA Stroke Study

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Key Words
Thrombolysis · Thrombolytic therapy · Leukoaraiosis

Abstract
Background: Leukoaraiosis is associated with microhemorrhages on T_2*-weighted magnetic resonance imaging of the brain. Such hemorrhages have been postulated to be responsible for symptomatic intracerebral hemorrhage (ICH) after thrombolytic treatment. We examined the relationship between small-vessel ischemic disease and symptomatic ICH within the NINDS rt-PA Stroke Study. ***Methods:*** Baseline CT scans from the NINDS rt-PA Stroke Study were re-evaluated retrospectively by blinded expert CT readers using the van Swieten Score (vSS) for leukoaraiosis. The scale examined the severity of white-matter changes on 3 serial CT slices and graded separately for the 2 distinct regions anterior and posterior to the central sulcus: 0 = no lesion, 1 = partly involving the white matter, and 2 = extending up to the cortex. ***Results:*** 603 CT scans were interpreted. The risk of symptomatic ICH increased with higher vSS in both the placebo and treatment groups. The absolute risk of symptomatic hemorrhage was 7.9% in the rt-PA-treated cohort among patients with severe white-matter disease (vSS = 3–4) versus 2.9% receiving placebo. Among severe leukoaraiosis patients (vSS = 3–4), no differential treatment effect was seen with rt-PA patients achieving better outcomes than placebo, modified Rankin score 0–1 in 31.6% of rt-PA-treated versus 14.7% of placebo-treated patients. ***Conclusion:*** The results from the present study do not support the concept that leukoaraiosis present on baseline noncontrast CT scanning is critical to thrombolysis decision making in the first 3 h from symptom onset. No clear leukoaraiosis threshold was identified below which no benefit or harm could be seen from intravenous rt-PA therapy.

Background

Hachinski et al. [1] introduced the term 'leukoaraiosis' (Greek word 'white rarefaction') to describe white-matter changes observed on cross-sectional computed tomographic (CT) images of the brain. A high burden of leukoaraiosis is associated with increased complications when anticoagulation is used [2, 3]. Major hemorrhage into an old microbleed is described following intra-arterial [4] and intravenous thrombolytic therapy [5]. In a mouse model of cerebral amyloid angiopathy, cerebral hemorrhages were frequent after intravenous thromboly-

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sis [6]. This has raised concern regarding the safety of thrombolysis in such patients. If one extrapolates the link between microbleeding and leukoaraiosis [7], a high risk for hemorrhagic complications after thrombolysis might exist in such patients.

In the NINDS rt-PA Stroke Study which determined the efficacy of recombinant tissue plasminogen activator (rt-PA) [8] all patient subgroups benefited from treatment [9] with no CT variables influencing the response to therapy. A recent re-evaluation of the NINDS rt-PA Stroke Study CT scans affirmed that signs of ischemic change did not modify the treatment effect based on the European Cooperative Acute Stroke Study (ECASS) early ischemic change CT criteria of one-third involvement of the middle cerebral artery territory [10]. Unfortunately leukoaraiosis was not examined by the NINDS rt-PA trialists, and so no information is available for predicting the outcome in the setting of leukoaraiosis. Recently the ECASS stroke study group assessed whether the degree of leukoaraiosis determined the risk of hemorrhage after thrombolysis in acute stroke. Using the van Swieten Score (vSS) [11], the ECASS group could not find an increased risk of parenchymal hematoma among ischemic stroke patients enrolled in ECASS-1 or ECASS-2 [12]. Our primary objective was to determine if leukoaraiosis is a treatment modifier within 3 h of treatment with intravenous rt-PA in the NINDS rt-PA Stroke Study trial assessed blinded to treatment assignment and clinical outcomes.

Methods

The NINDS rt-PA Stroke Study was a multicenter, prospective, double-blind, placebo-controlled, randomized trial of intravenous rt-PA for acute ischemic stroke, performed from January 1991 to October 1994. It was conducted in 2 parts. The first 291 patients tested the effect of rt-PA 24 h after stroke and then tested 333 patients for favorable outcome at 3 months measured by 4 clinical outcome scales (NIH Stroke Scale [13], Barthel Index [14], modified Rankin Scale [15] and the Glasgow Outcome Scale [16]). Treatment included either placebo or rt-PA (0.9 mg/kg body weight, maximum 90 mg), 10 mg as initial bolus over 1 min followed by 1 h infusion of the remainder of the dose. Treatment was initiated within 3 h (n = 302 within 90 min and n = 322 within 91–180 min from symptom onset). Eight clinical centers were involved which consisted of 43 hospital sites. A CT scan of the brain was mandatory prior to enrolment in the study to rule out intracranial hemorrhage. All CT scans were performed on third- or fourth-generation CT scanners. All the baseline CT scans were obtained with 10 mm slice thickness and consisted of the following technical factors: 120 kV, 170 mA, matrix size 512 × 512, 3 s scanning time for posterior fossa and 2 s scanning time for supratentorial compartment. Window levels and window widths were optimized for gray/white matter distinction.

For this study all baseline CT scans were re-evaluated retrospectively by one of two groups of three expert CT readers [17] using the vSS for leukoaraiosis. The scale examines the severity of white-matter changes on 3 serial CT slices (figures provided in the original article) [11] and is graded separately for the regions anterior and posterior to the central sulcus: 0 = no lesion, 1 = partly involving the white matter and 2 = extending up to the cortex. The scores for the 2 regions have to be added together.

The review was done over a 2-day period with all scans randomized between both groups. One member from each group switched teams the second day to ensure uniform rating between groups. Three raters in each team agreed on a consensus leukoaraiosis vSS after discussing each scan. If disagreement existed, the majority rule applied. All members of the CT reading review had undergone a detailed tutorial prior to initiating reading. The reviewers were blind to all clinical information except the symptom side.

Statistical Analysis

The primary outcomes were excellent functional outcome defined as a 90-day modified Rankin Scale score less than 2, occurrence of symptomatic intracerebral hemorrhage (ICH) and death. Symptomatic ICH was defined based on the classification used in the original NINDS rt-PA Stroke Study [8], and so any neurological deterioration within 24 h of treatment associated with intracranial hemorrhage was considered significant. Secondary outcomes were excellent neurological outcome defined as a 90-day NIH Stroke Scale score less than 2 and good functional activity recovery defined as a 90-day Barthel Index score of 95 or greater. The vSS was analyzed as an ordinal variable with integer values from 0 to 4. The data are described with standard descriptive statistics (Fisher's exact test) and stratified analysis. Logistic regression was used to assess whether a vSS by treatment interaction was present for the primary outcomes using a likelihood ratio test.

Results

Of the 624 patients enrolled in the trial, 620 CT scans were available for interpretation and 603 CT scans were of sufficient quality to allow for reasonable interpretation. A study was excluded for insufficient quality, if the interpretation of leukoaraiosis was not deemed possible. There were 304 patients treated with placebo and 299 patients treated with rt-PA. No differences in baseline characteristics or outcome were detected between 21 patients excluded and 603 included in this study. However, exclusion of these 21 patients excluded 2 patients who suffered symptomatic ICH.

vSS in the two imaging interpretation teams were median 0 and 0. There was no difference in the scores between the two groups (p = 0.489). A logistic regression analysis using leukoaraiosis as an ordinal variable vSS of

Table 1. Relationship of leukoaraiosis severity and risk of symptomatic ICH

vSS	Symptomatic ICH, %		RR
	rt-PA	placebo	
0	5.5 (11/200)	0.0 (0/203)	●●
1	0.0 (0/29)	0.0 (0/38)	–
2	6.3 (2/32)	3.5 (1/29)	1.8 [0.2–19.0]
3	0.0 (0/17)	0.0 (0/11)	–
4	14.3 (3/21)	4.4 (1/23)	3.3 [0.4–29.2]

RR = Relative risk. Figures in parentheses are numbers out of total, those in square brackets are 95% confidence intervals.

Table 2. Relationship of leukoaraiosis severity to 3-month functional outcome

vSS	3-month mRS 0–1, %		RR
	rt-PA	placebo	
0	49.0 (98/200)	27.6 (56/203)	1.8 [1.4–2.3]
1	37.9 (11/29)	26.3 (10/38)	1.4 [0.7–2.9]
2	28.1 (9/32)	31.0 (9/29)	0.9 [0.4–2.0]
3	35.3 (6/17)	0.0 (0/11)	●●
4	28.6 (6/21)	21.7 (5/23)	1.3 [0.5–3.7]

mRS = Modified Rankin Scale; RR = relative risk. Figures in parentheses are numbers out of total, those in square brackets are 95% confidence intervals. Note that while the 95% confidence intervals exclude 1, the overall test of heterogeneity was neutral, indicating no interaction between rt-PA treatment and vSS (p = 0.395).

Table 3. Relationship of leukoaraiosis severity to 3-month secondary outcome parameters

vSS	BI 95–100, %			NIHSS 0–1, %			GOS 1, %		
	rt-PA	placebo	RR	rt-PA	placebo	RR	rt-PA	placebo	RR
0	58.0 (116/200)	42.4 (86/203)	1.9 [1.3–2.8]	38.5 (77/200)	21.7 (44/203)	2.3 [1.5–3.5]	51.0 (102/200)	32.5 (66/203)	2.2 [1.4–3.2]
1	44.8 (13/29)	31.6 (12/38)	1.8 [0.6–4.8]	24.1 (7/29)	15.8 (6/38)	1.7 [0.5–5.7]	41.4 (12/29)	28.9 (11/38)	1.7 [0.6–4.8]
2	40.6 (13/32)	31.0 (9/29)	0.9 [0.3–2.5]	31.2 (10/32)	27.6 (8/29)	1.2 [0.4–3.6]	31.2 (10/32)	34.5 (10/29)	0.9 [0.3–2.5]
3	35.3 (6/17)	18.2 (2/11)	2.5 [0.4–15.3]	29.4 (5/17)	9.1 (1/11)	4.2 [0.4–41.8]	35.3 (6/17)	9.1 (1/11)	5.5 [0.6–53.5]
4	38.1 (8/21)	21.7 (5/23)	2.2 [0.6–8.3]	19.0 (4/21)	13.0 (3/23)	1.6 [0.3–8.0]	33.3 (7/21)	26.1 (6/23)	1.4 [0.4–5.2]

BI = Barthel Index; GOS = Glasgow Outcome Score; NIHSS = National Institute of Health Stroke Score; RR = relative risk. Figures in parentheses are numbers out of total, those in square brackets are 95% confidence intervals. Note that good outcome is defined as BI 95–100, NIHSS 0–1 and GOS 1.

0–4 showed that age, systemic hypertension and diabetes were independent predictors of leukoaraiosis ($p < 0.05$).

There were 18 symptomatic hemorrhages observed, 16 in the rt-PA group and 2 in the placebo group. The absolute risk of symptomatic hemorrhage among patients with extensive white-matter disease (vSS = 4) was 14.3% in the rt-PA-treated cohort. However, this risk was not statistically different among treated and placebo patients (table 1). The risk of symptomatic hemorrhage was not significantly different between rt-PA and placebo groups, even if the leukoaraiosis severity is graded as no leukoaraiosis (vSS = 0; 5.5 vs. 0%), mild to moderate leukoaraiosis (vSS = 1–2; 3.3 vs. 1.5%) or severe leukoaraiosis (vSS = 3–4; 7.9 vs. 2.9%) grades. Even dichotomization into no leukoaraiosis (vSS = 0; 5.5 vs. 0%) and any leukoaraiosis (vSS = 1–4; 5.1 vs. 2%) did not show any significant higher risk in the rt-PA-treated group. Multiple logistic regression, adjusting for known predictors of ICH (age, baseline NIH Stroke Scale score, serum glucose, diabetes mellitus, hypertension) did not substantially alter the unadjusted estimates of risk.

Neurological outcome as assessed by the 3-month modified Rankin Scale was worse and the risk of death higher among patients with severer white-matter disease, but no differential effect of treatment was evident (table 2). There was no significant interaction between rt-PA treatment and vSS in the multivariate logistic regression analysis using the likelihood ratio test (p = 0.528). Generally, a higher trend to good outcome was seen in the rt-PA-treated patients compared to placebo, even in the presence of severe leukoaraiosis (vSS = 3–4, relative risk = 1.9 with 95% confidence interval = 0.8–4.7). Analysis of the other secondary clinical outcome measures revealed similar trends in favor of rt-PA treatment, despite severe leukoaraiosis (table 3).

Discussion

The results from the present study do not support the concept that leukoaraiosis present on baseline noncontrast CT scanning is critical to thrombolysis decision making in the first 3 h from symptom onset. No clear leukoaraiosis threshold was identified below which no benefit or harm could be seen from intravenous rt-PA therapy. Our study is consistent with the recently presented preliminary data from the ECASS thrombolysis trials [16].

Leukoaraiosis is most frequently seen in elderly people and has been associated with hypertension [18] and with an increased stroke risk [19] and vascular death [20]. Blood-pressure-lowering treatment appears to lessen the progression of these white-matter changes [21]. Magnetic resonance imaging (MRI) demonstrates the white-matter changes more clearly than CT scanning by detection of fluid-attenuated inversion recovery and T_2-weighted hyperintensities. White-matter lesions have been considered most likely due to small-vessel ischemic disease from hypertension; however, other hypotheses have been suggested which include blood-brain barrier alterations [22], chronic brain edema [23] and genetic factors. Genetic factors for leukoaraiosis include apolipoprotein E [24], homozygous methylene tetrahydrofolate reductase 677TT and angiotensin-converting enzyme D/D genotypes [25] and NOTCH-3 [26].

One important recent observation with respect to leukoaraiosis is the correlation with microhemorrhages in the brain of elderly patients as visualized by MRI using T_2*-weighted gradient echo sequences and other susceptibility-weighted-imaging techniques [7]. The association of microbleeding with diabetes, chronic hypertension and severe white-matter change supports a small-vessel disease mechanism [27, 28]. Although major hemorrhaging into an old microbleed is described following intraarterial [29] and intravenous thrombolytic therapy [30] and appears logical, a large phase 4 MRI study suggests no significant relationship between microhemorrhage and symptomatic ICH after intravenous rt-PA [31]. Since CT scan is the commonest imaging modality used in rt-PA decision making of acute ischemic stroke and microhemorrhages are correlated with leukoaraiosis, delineation of the hemorrhage risk associated with leukoaraiosis in CT of the brain is practically important. Reanalysis of large CT-based thrombolytic trials is helpful in this regard. The ECASS group has already published their results, and they appear comparable to ours [12]. Classifying the vSS into 0, 1 or 2 and 3 or 4, parenchymal hemorrhage rates were 12.7, 15.7 and 17.9% in the rt-PA-treated group as against 2.1, 5.6 and 2.0% in the placebo group (p = 0.21). Compared with absence of leukoaraiosis (vSS = 0), neither mild disease (vSS = 1 or 2) nor severe disease (vSS = 3 or 4) were associated with an increased risk of parenchymal hemorrhage in a multivariate analysis (odds ratio = 0.78 and 2.32 in the placebo group, 0.9 and 1.02 in the rt-PA group). These results are comparable to ours except the fact that the overall hemorrhage rates are lower in our study. Fiorelli et al. [12] looked into parenchymal hemorrhages (both symptomatic and asymptomatic), whereas we focused on symptomatic ICH, thus explaining the discrepancy. Further, we looked into the functional outcome and demonstrated a better outcome in the rt-PA-treated group, even at higher vSS grades, thus proving the effectiveness of thrombolysis irrespective of the severity of leukoaraiosis.

Two recent publications, of Palumbo et al. [32] and Neumann-Haefelin et al. [33], have both demonstrated a slight increase in ICH rates with leukoaraiosis. Palumbo et al. [32], analyzing the data from the Canadian national registry of thrombolyzed patients with ischemic stroke, showed a higher rate of symptomatic ICH in those with severe (vSS >4 in an 8-point scale, combining white-matter changes on both sides) leukoaraiosis compared to those with no or moderate leukoaraiosis (8.4 vs. 3%, relative risk = 2.7, 95% confidence interval = 1.1–6.5). Similarly, Neumann-Haefelin et al. [33] demonstrated a higher rate of symptomatic ICH in those with moderate to severe (Fazekas score 2–3) leukoaraiosis as against absent or mild (Fazekas score 0–1) disease (10.5 vs. 3.8%, odds ratio = 2.9, 95% confidence interval = 1.29–6.59). They analyzed multicentric MRI-based, 6-hour window thrombolysis data to draw the conclusions. Leukoaraiosis

did not affect the 3-month clinical outcome in the study of Palumbo et al. [32], whereas this aspect was not studied by Neumann-Haefelin et al. [33]. Both studies are limited by the lack of placebo versus rt-PA data on whether leukoaraiosis has a treatment interaction with rt-PA efficacy. Our study clearly shows that this does appear to be the case and that despite a slight increase in symptomatic ICH, the efficacy is still significant with rt-PA in the presence of significant leukoaraiosis (vSS = 3 or 4).

One limitation of the study was the use of a simple CT-based scale to estimate the degree of leukoaraiosis vSS. This was chosen because it is simple and practical to use for clinicians, has been previously validated [32] and was used in the combined ECASS-1 and ECASS-2 trial analysis of leukoaraiosis [12]. A more sophisticated evaluation of white matter with MRI may have provided more discriminate information, and so the precision of our estimates could be altered with MRI. MRI was the method of leukoaraiosis detection in the study of Neumann-Haefelin et al. [33], wherein a higher symptomatic ICH rate was shown with severe leukoaraiosis. However, another MRI-based study, looking into the ICH risk associated with cerebral microbleeds, a different imaging correlate of cerebral small-vessel disease, did not duplicate this finding [31]. Nevertheless, CT remains the current community standard for emergent brain imaging, and so these data may be useful to clinicians seeking to counsel individual patients with leukoaraiosis and their families about the empirical risks of thrombolysis in the setting of the acute ischemic stroke. Another limitation is that we did not separately determine whether the white-matter lesions were anterior or posterior to the central sulcus. We do not know if the risk associated with rt-PA for symptomatic ICH is dependent on anterior or posterior location of white-matter changes. Previous studies have not suggested an association as such [32, 33]. Another concern is the dilution effect of the 5-point scale on the overall low ICH rate. However, dichotomizing or trichotomizing the leukoaraiosis score did not significantly change the statistical analysis and hence the conclusions of the study. Lastly the study was not sufficiently powered to determine the potential interaction of leukoaraiosis and rt-PA.

In conclusion, the results from the present study do not support the concept that leukoaraiosis present on baseline noncontrast CT scan is critical to thrombolysis decision making in the first 3 h from symptom onset. No clear leukoaraiosis threshold was identified below which no benefit or harm could be seen from intravenous rt-PA therapy. Further, the nonsignificant increase in the symptomatic ICH rate in those with severe leukoaraiosis is overweighed by the benefit of thrombolysis, as reflected by the 3-month functional outcome.

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