Computed Tomography–Verified Leukoaraiosis Is a Risk Factor for Post-thrombolytic Hemorrhage

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Background: Is computed tomography (CT)–verified leukoaraiosis (LA) a risk factor for post-thrombolytic hemorrhagic transformation and symptomatic hemorrhage? *Methods:* (1) Retrospective analysis based on a prospectively planned single-center registry of consecutive tissue plasminogen activator (tPA)–treated patients within 4.5 hours from symptom onset. Standard work-up included baseline noncontrast CT and CT angiography and next day follow-up noncontrast CT. Baseline noncontrast CT LA was graded using Fazekas' score and dichotomized as the absence (Fazekas, 0) or the presence (Fazekas, 1-3). Hemorrhagic transformation was rated using European Cooperative Acute Stroke Study (ECASS) criteria. Symptomatic intracerebral hemorrhage was defined as hemorrhage and deterioration of National Institutes of Health Stroke Scale (NIHSS) of 4 or greater within 36 hours from symptom onset. Endovascularly treated patients were excluded. (2) Pooled analysis with 1312 tPA-treated patients from literature. *Results:* In all, 311 tPA-treated patients were included between April 2009 and July 2012. LA was present in 113 (36%). Twenty-three (7%) showed hemorrhagic transformation. LA positive patients had significantly higher hemorrhagic transformation frequency (11.5%, $P = .04$). LA doubled hemorrhagic transformation risk (odds ratio [OR], 2.4; 95% confidence interval [CI], 1.4-5.8). Only 4 patients developed symptomatic intracerebral hemorrhage, 3 with LA. LA was not an independent risk factor for hemorrhagic transformation ($P = .2$). Pooled analysis of 1623 patients in total, hereof 479 LA positive patients, showed significantly higher symptomatic intracerebral hemorrhage frequency in 35 (7.3%) LA positive than that in 44 (3.8%) LA negative patients, ($P = .005$) and doubled symptomatic intracerebral hemorrhage risk in LA positives (OR, 1.97; 95% CI 1.22-3.19). *Conclusions:* LA doubles the risk of post-thrombolytic hemorrhagic transformation and symptomatic hemorrhage; this finding does not support withholding thrombolysis from patients with LA. **Key Words:** Leukoaraiosis—thrombolytic therapy—brain hemorrhage—computed tomography.

Symptomatic intracerebral hemorrhage (sICH) is a major cause of deterioration after intravenous tissue plasminogen activator (IV-tPA)-treatment in acute ischemic stroke.[1] High leukoaraiosis (LA) burden is also associated with increased complication rate after anticoagulation with warfarin.[2,3] LA (Fig 1) is associated with microbleeds on T2*-weighted images.[4] Symptomatic hemorrhage has been reported in old microbleeds after tPA treatment.[5-7] LA and brain atrophy are computed tomography (CT) signs of neurodegeneration, and could therefore present predictors of higher risk of tPA-related hemorrhaging. LA itself is more common in the elderly population and

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is associated with increased risk of stroke and poor long-term outcome.[8] Studies on the risk of intracerebral hemorrhage after tPA have raised the question of LA as an independent risk factor, but literature on the subject remains ambiguous; 2 studies[9,10] with 849 patients support and 3 studies[11-13] with 669 patients oppose the hypothesis. These studies were retrospective re-evaluation of baseline CT or magnetic resonance imaging (MRI) scans, which graded the level of LA in patients who received tPA.

Cerebral atrophy is more frequent with age and vascular risk factors,[14,15] as is LA. We found no studies investigating the association between atrophy and hemorrhage in tPA-treated ischemic stroke. But as atrophy displays some of the same characteristics as LA, we find it interesting to look for both in our group of patients.

The aim of this study was to establish if LA and brain atrophy as diagnosed on baseline CT contributed to the risk of symptomatic or asymptomatic hemorrhage after IV-tPA treatment.

Method

Patients

We created a prospective registry based on consecutive IV-tPA–treated ischemic stroke patients within 4.5 hours from symptom onset. Our center is one of 2 thrombolysis centers serving the capital region of Copenhagen (approximately 1.7 million inhabitants) receiving referrals on even dates. Clinical data based on treating physicians' recordings were entered into the database. Results from this registry have previously been reported.[16]

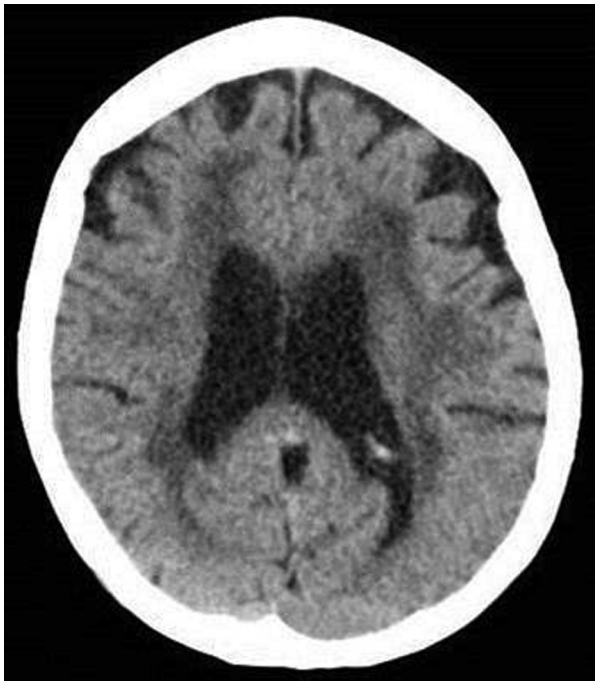

Figure 1. *Leukoaraiosis on noncontrast computed tomography.*

Imaging

All patients underwent standard neuroimaging with baseline noncontrast head CT (NCCT) and CT angiography from aortic arch to vertex as well as next day NCCT (22-36 hours after tPA) performed on 64-MDCT (Philips Brilliance-64, Philips Medical Systems, Best, the Netherlands). All imaging was reanalyzed by observers blinded to clinical information apart from side of neurologic deficits and primary radiologic diagnosis. LA was graded on baseline NCCT using the Age-Related White Matter Changes (ARWMC) rating scale for MRI and CT.[17] A score of 0-3 divided into periventricular white matter lesions and deep white matter lesions. We graded atrophy as central and cortical reduction is brain tissue according to the "CT and MRI basic reading form" developed by JM Wardlaw, University of Edinburgh; (http://www.bric.ed.ac.uk/documents/ctandmr%20reading%20form.pdf). The scores of LA (deep white matter lesion) and atrophy were dichotomized into no signs on CT (ARWMC 0 and no atrophy) or any LA and atrophy. On the next day NCCT, we graded hemorrhagic transformations (HTs) according to the ECASS criteria.[18] We defined sICH as hemorrhage on follow-up CT and deterioration of National Institutes of Health Stroke Scale (NIHSS) of 4 or more in the first 36 hours.

Literature Study

We performed a literature study searching PubMed/Medline, EMBASE, and Cochrane Library using free text searches and searches with medical subject headings with keywords "leukoaraiosis," "white matter lesions," "white matter hyperintensities," "thrombolysis," "thrombolytic therapy," "fibrinolysis," and "fibrinolytic agents." We also used article references. We included studies on post-thrombolytic hemorrhage with possible LA stratification into none versus any LA and with populations without age-related selection criteria to avoid selection bias. We excluded patients who had undergone thrombectomy as LA is an established risk factor for parenchymal hemorrhage after this procedure.[19] We excluded conference abstracts if they lacked details necessary for analysis.

Variables known to be associated to sICH were included into the regression analysis: NIHSS, blood pressure, age, platelet count, International Normalized Ratio (INR), blood glucose, early signs of ischemia on CT, and dense artery sign.

Statistics

Clinical characteristics were calculated by descriptive statistics and compared using t test and chi-square or Fisher exact test between groups. Binary logistics was used to compare the 2 groups. The multivariate model was created by identifying known factors from the literature. P values less than .05 were considered significant.