Leukoaraiosis and Early Neurological Recovery after Intravenous Thrombolysis

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Background: Early neurological recovery after intravenous thrombolysis (IVT) is associated with favorable outcome after acute ischemic stroke. Leukoaraiosis, a marker of chronic ischemia, is a possible negative predictive factor of early recovery. However, its negative attenuating effects remain inadequately studied, leading to uncertainty in the prediction of outcomes after IVT. We aim to determine the influence of leukoaraiosis on early neurologic recovery. *Methods:* We included consecutive acute ischemic stroke patients who received IVT between 2007 and 2011. The following data were included: demographics, vascular risk factors, stroke type, National Institutes of Health Stroke Scale (NIHSS) at onset, and at 24 hours after IVT. Baseline computed tomography (CT) brain scans were analyzed. Two blinded assessors rated the CT scans using the van Swieten scale for leukoaraiosis. Median regression was used to assess the relationship between leukoaraiosis and neurologic recovery. *Results:* We included 158 patients. The median (interquartile range [IQR]) age was 77 (68-84) and 71 (45%) were female. The median (IQR) NIHSS was 13 (7-18.75) at baseline and 7.5 (2-16) at 24 hours. After taking into account variables independently associated with leukoaraiosis, median regression analysis failed to demonstrate the association between the presence of leukoaraiosis and early neurologic recovery (NIHSS relative one) after IVT, for either of the 3 prespecified dichotomization-based definitions of leukoaraiosis. *Conclusions:* In our sample, there was no evidence of the association between the degree of leukoaraiosis and early neurological recovery after IVT. **Key Words:** Leukoaraiosis—stroke—recovery—thrombolysis—white matter hyperintensity of presumed vascular origin.

Introduction

Ischemic stroke is a significant cause of morbidity and mortality in the community.[1] Intravenous tissue plasminogen activator is the mainstay of current treatment, and has vastly improved outcomes for stroke patients presenting within 4.5 hours of ictal onset.[2-5]

However, there is significant variation in patient response to thrombolytic therapy. Between 18% and 33% experience early neurological recovery,[6-12] which is associated with reduced mortality rate and the likelihood of a favorable functional outcome at 3 months.[6,7,8-,11,13] There is increasing interest to identify clinical and radiological factors, which might predict clinical outcome.

It has been demonstrated that leukoaraiosis is an important factor for determining outcome after cerebral infarct.[14,15] This is evidenced by the pathologic correlates of leukoaraiosis, which include structural vascular abnormalities such as vessel wall thickening and by clinical studies, which demonstrate that patients with leukoaraiosis show a poorer outcome after infarct.[16-18] The clinical effects of leukoaraiosis may be

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substantial. Podigorska et al[17] reported 1 year poststroke mortality rate of 28% in those without leukoaraiosis and 45.8% with leukoaraiosis. It follows that leukoaraiosis may be included as part of an algorithm to determine suitability for thrombolytic therapy.[15]

In the setting of thrombolytic therapy for ischemic stroke, patients with baseline leukoaraiosis have been shown to have a poorer functional outcome at 3 months.[14,19] However, it has been proposed that this discrepancy in functional recovery is not because of the thrombolytic therapy itself, but more likely a reflection of the higher prevalence of comorbidities in patients with leukoaraiosis and the subsequent susceptibility of these patients to complications after stroke.[14] Therefore, concern remains that leukoaraiosis may negate the beneficial effects of intravenous thrombolysis (IVT) on clinical outcomes. It is possible that early neurologic recovery is a more sensitive measure of determining the influence of leukoaraiosis on the efficacy of IVT in these patients.

The present study aims to investigate the relationship between the degree of leukoaraiosis and early neurologic recovery after IVT. We hypothesize that severe leukoaraiosis present on baseline computed tomography (CT) is associated with lack of early recovery after IVT and with poor clinical outcomes.

Methods

Data Collection

This was a single center retrospective study undertaken at Royal Melbourne Hospital between 2007 and 2011. This study received approval by the Human Research Ethics Committee at the hospital. Cases included in the present study were selected from a preexisting database containing data from consecutive patients who received IVT for ischemic stroke. Patients were included if they had presented within 4.5 hours of the onset of neurologic symptoms and had a baseline CT available for analysis. One hundred ninety-five patients met the inclusion criteria. Clinical data collected for the patient population included the following: (1) demographic data; (2) baseline characteristics; (3) risk factors including presence of hypertension, diabetes mellitus (DM), ischemic heart disease (IHD), atrial fibrillation (AF), and hypercholesterolemia; (4) National Institutes of Health Stroke Scale (NIHSS) quantifying stroke severity at baseline and 24 hours; (5) mRS (Modified Rankin Scale) at onset and at 3 months; (6) Oxford stroke scale classification; and (7) Trial of Org 10172 in Acute Stroke Treatment classification. mRS at 3 months was collected at clinic review. A total of 37 patients were excluded: 18 had no documented NIHSS 24, 14 with no mRS documented at 3 months, 1 without baseline NIHSS, and 4 as baseline CT undertaken at a different centre. The final number of patients included in this study was 158.

Imaging Data

Noncontrast CT images were obtained using the ischemic stroke protocol. Axial, nonhelical CT was performed using a Siemens Sensation 16 (Siemens Medical Solutions, Malvern, PA) using 120 kV, 320 mAs, 1.0 seconds rotation time, 4.5 mm slice thickness, and 12×0.75 mm detector combination.

Assessment of Scans

Leukoaraiosis was assessed using the van Swieten scale (vSS) for leukoaraiosis.[20] This simple scale is used regularly in leukoaraiosis research and has been verified for reliability.[14,18,19,21,22] The scale examines the severity of white matter changes on 3 sequential axial CT slices and is graded separately for the regions anterior and posterior to the central sulcus: 0 = no white matter hypodensity, 1 = hypodensity partly involving the white matter, and 2 = confluent white matter hypodensity extending up to the gray matter. The scores for the 2 regions are added together for the final vSS. Dicom images were analyzed from a single workstation by 2 independent raters. Assessors were blinded to the outcome of each patient.

Outcome Measures

Early neurologic outcome was defined as observed change in NIHSS score over 24 hours. This was defined in 3 alternative ways to reduce the likelihood of type II error:

(1) Absolute NIHSS change was determined by comparing NIHSS at baseline with NIHSS at 24 hours and was calculated as ($NIHSS_{24} - NIHSS_{bl}$), where $NIHSS_{bl}$ and $NIHSS_{24}$ are the observed NIHSS scores at baseline and at 24 hours, respectively. Absolute NIHSS change has been criticized as a measure of early neurologic recovery as it is vulnerable to the scale ceiling effect.[23]

(2) Change in NIHSS relative to the potential change in NIHSS over 24 hours. This could occur either toward 0 (if the patients are recovering) or toward 42 (if they are deteriorating). This measure takes into account the ordinal noninterval nature of the NIHSS score.[23] It was calculated as follows: $(NIHSS_{bl} - NIHSS_{24})/NIHSS_{bl}$ if $NIHSS_{24} < NIHSS_{bl}$ and $(NIHSS_{bl} - NIHSS_{24})/(42 - NIHSS_{bl})$ if $NIHSS_{24} > NIHSS_{bl}$.

(3) Change in NIHSS relative to NIHSS at baseline. It is calculated as follows: $(NIHSS_{bl} - NIHSS_{24})/NIHSS_{bl}$ if $NIHSS_{24} < NIHSS_{bl}$ and $(NIHSS_{bl} - NIHSS_{24})/NIHSS_{bl}$ if $NIHSS_{24} > NIHSS$.

The vSS for leukoaraiosis was used to grade baseline CT for presence of leukoaraiosis. As depicted in Figure 1 , scores are determined by a consistent change present on 3 consecutive CT slices and range from 0 (no