Diffusion-weighted Imaging–Fluid Attenuated Inversion Recovery Mismatch in Nocturnal Stroke Patients with Unknown Time of Onset

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Background: More than a quarter of patients with ischemic stroke (IS) are excluded from thrombolysis because of an unknown time of symptom onset. Recent evidence suggests that a mismatch between diffusion-weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) imaging could be used as a surrogate for the time of stroke onset. We compared used the DWI–FLAIR mismatch and the FLAIR/DWI ratio to estimate the time of onset in a group of patients with nocturnal strokes and unknown time of onset. *Methods:* We used a prospectively collected acute IS patient database with MRI as the initial imaging modality. Nineteen selected nocturnal stroke patients with unknown time of onset were compared with 22 patients who had an MRI scan within 6 hours from stroke onset (control A) and 19 patients who had an MRI scan between 6 and 12 hours (control B). DWI and FLAIR signal was rated as normal or abnormal. FLAIR/DWI ratio was calculated from independent DWI and FLAIR ischemic lesion volumes using semiautomatic software. *Results:* The DWI–FLAIR mismatch was different among groups (unknown 43.7%; control A 63.6%; control B 10.5%; Fisher-Freeman-Halton test; $P = .001$). There were significant differences in FLAIR/DWI ratio among the 3 groups (unknown 0.05 ± 0.12; control A 0.17 ± 0.15; control B 0.04 ± 0.06; Kruskal–Wallis test; $P < .0001$). Post-hoc pairwise comparisons revealed that FLAIR/DWI ratio from the unknown group was significantly different from the control B group ($P = .0045$) but not different from the control A group. DWI volumes were not different among the 3 groups. *Conclusions:* A large proportion of patients with nocturnal IS and an unknown time of stroke initiation have a DWI–FLAIR mismatch, suggesting a recent onset of stroke. **Key Words:** Acute ischemic stroke—circadian pattern—diffusion-weighted imaging—fluid attenuated inversion recovery—sleep.

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Intravenous tissue plasminogen activator is the only proven treatment for acute ischemic stroke (AIS), and it improves neurologic outcome when administered within 4.5 hours of symptom onset.[1] Approximately one quarter of patients with AIS present upon awakening from sleep.[2] These patients are denied thrombolytic therapy and excluded from acute clinical trials because the time of symptom onset is uncertain. To date, there is no specific biomarker to age stroke, and clinicians still depend on the information provided by patients or bystanders to decide if the patient is eligible for thrombolysis.

Recent studies have revealed that a "mismatch" between an abnormal diffusion-weighted imaging (DWI) signal and a normal fluid-attenuated inversion recovery (FLAIR) on magnetic resonance imaging (MRI) scans of the brain may function as a surrogate for determining the age of the stroke in patients with AIS with an uncertain time of symptom onset, permitting reperfusion therapies.[3-7] These methods have a high specificity and positive predictive value for identifying patients within 4.5 hours of symptom onset; however, adequate sensitivity has not been proved.[6] Most of these recent studies used a visual inspection of the MRI scans to determine the DWI–FLAIR mismatch. Nonetheless, volumetric analysis of the diffusion–perfusion mismatch has been shown to be more accurate than simple visual assessment in determining the ischemic penumbra.[8]

In this study, we used visual inspection and volumetric analyses of the DWI–FLAIR mismatch to estimate the age of AIS in patients who presented with stroke symptoms upon awakening from sleep. We also studied whether the ratio of calculated volumes from hyperintense FLAIR and DWI signals would be a better method than the DWI–FLAIR mismatch for estimating the age of a stroke of unknown time onset.

Methods

Patients

A prospectively collected imaging database of patients with AIS who presented within 12 hours of the stroke onset was screened for patients who had undergone MRI as the initial brain imaging modality. We chose a group of patients with unknown time of onset who had a high probability of having their stroke while they were asleep. The selection criteria for these patients included presenting with AIS symptoms, unknown time of stroke onset, last seen normal >6 hours ago, with an arrival to the emergency department (ED) between 4 AM and 10 AM and having an initial brain MRI scan performed within 3 hours from ED arrival. Two patient control groups (A and B) with known time from stroke onset were chosen as controls. Control A received MRI scans of the brain within 6 hours from stroke onset, and control B received MRI scans of the brain between 6 and 12 hours from stroke onset. Signed consent to provide imaging data was obtained from patients or the patient's surrogates. The study was approved by the University of California San Diego Institutional Review Board.

Magnetic Resonance Protocol

All patients underwent MRI scans of the brain (1.5-T; Siemens Medical System, Malvern, PA) before any type of recanalization therapy. The MRI protocol included DWI (b = 1000), gradient-recalled echo, FLAIR, and perfusion-weighted imaging sequences, with previously described MRI methodology.[9] Only FLAIR and DWI (b = 1000) sequences were used for this study.

Imaging Analysis

Four stroke physicians (B.H., B.C.M., T.H., and B.M.M.) with ample experience in analyzing acute stroke MRI scans were blinded to all clinical data and independently interpreted FLAIR and DWI sequences. For rating images, the dichotomized choices were the presence or absence of abnormal hyperintense signal suggestive of acute brain ischemia. Raters were allowed modify the contrast level to display images with optimal contrast for lesion identification. They were instructed to judge lesion visibility using the DWI signal to identify only the changes of FLAIR parenchymal hyperintensity, disregarding other possible imaging signs of AIS, such as hyperintense vessels on FLAIR. For the volumetric analysis, first areas of abnormal DWI and FLAIR signal were obtained semiautomatically using maximal entropy threshold (Image J software version 1.42; developed by Wayne Rasband and available from http://rsbweb.nih.gov/ij/; Fig 1). Manual thresholds were used in cases when the software was not able to depict the correct area (0% in DWI and 30% in FLAIR sequences). The FLAIR and DWI lesion volumes were calculated by adding all areas of abnormal hyperintense signal and multiplying by the distance between the slices. The FLAIR/DWI ratio was defined as the FLAIR lesion volume divided by the DWI lesion volume. DWI-FLAIR mismatch was considered present when subjects displayed DWI lesions >0 "positive DWI" and normal FLAIR imaging "negative FLAIR" on the same MRI. Patients with DWI volumes equal to 0 were excluded from the mismatch and imaging analysis. FLAIR imaging with extensive leukoaraiosis and imaging sequences with significant motion or artifacts were also excluded from the analysis. Neither small strokes nor lacunar strokes were excluded.

Statistical Analysis

Associations were assessed using the Kruskal–Wallis (KW) test for continuous data with Holm-adjusted pairwise Wilcoxon rank sum (WRS) test for multiple pair comparisons and the Fisher-Freeman-Halton (FFH) test for categorical data. The final lesion score was obtained