The Stroke Patient Who Woke Up

Clinical and Radiological Features, Including Diffusion and Perfusion MRI

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Background and Purpose—Time of stroke onset is uncertain for patients who wake from sleep with stroke. Functional imaging techniques may allow estimation of benefit and risk of acute stroke therapy. We compared the clinical and multimodal MRI findings of patients with uncertain stroke onset with those with known onset time.

Methods—Patients imaged within 24 hours of ischemic stroke onset between January 1997 and June 2000 were identified from a prospective stroke registry. Clinical and imaging data from patients with known stroke onset (group I) were compared with those who woke with stroke (group II).

Results—A total of 364 patients were identified, of whom 100 (27%) woke from sleep with stroke. Group I and group II did not differ in age, gender, National Institutes of Health Stroke Scale, or TOAST (Trial of Org 10172 in Acute Stroke Treatment) diagnoses. Time from stroke onset was shorter in group I (mean 6.0 versus 13.3 hours, $P<0.001$); time from detection did not differ between groups (6.0 versus 5.9 hours). Within 3 hours, diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) lesion volumes were similar in both groups; DWI-PWI mismatch was present in 82% of group I and 73% of group II patients. Mean apparent diffusion coefficient of water (ADC) of group I patients was negatively associated with DWI volume ($\beta=-0.324$, $P=0.004$) and time from stroke onset ($\beta=-0.238$, $P=0.031$) in multivariate analysis. The mean ADC of group II patients was lower than that of group I patients within 3 hours of stroke detection (mean 556 *versus* 665 $\mu m^2/s$, $P<0.01$), but individual group II patients had ADC values as high as 742 $\mu m^2/s$, in addition to a DWI-PWI mismatch pattern.

Conclusions—Onset time is uncertain in over one quarter of acute ischemic stroke patients. Clinical features of these patients do not differ significantly from those with known onset time. Some patients who wake with stroke seem to have favorable imaging characteristics for acute stroke therapy. Further study is needed to determine whether criteria for therapy based on imaging parameters can safely be applied to these patients. **(*Stroke*. 2002;33:988-993.)**

Key Words: cerebral infarction ■ diagnosis ■ magnetic resonance imaging

Approximately one quarter of patients with ischemic stroke wake from sleep with their deficits, having gone to sleep in their normal state of health.[1–3] Because the exact time of stroke onset cannot be determined for patients who wake with stroke, they are ineligible for established acute stroke treatments such as thrombolysis with recombinant tissue plasminogen activator[4] and are generally excluded from trials of acute stroke therapies. The automatic exclusion of a significant proportion of patients with stroke from potentially beneficial therapy limits the impact of these treatments on the burden of stroke in the community.[5] Although it is possible that some patients who wake from sleep with stroke may wake at the time of the stroke itself and may otherwise be good candidates for thrombolysis or acute stroke trials, investigation of methods to identify such patients has been lacking.

Methods that could be used to identify these patients are limited. Imaging techniques that possess a functional component are required to determine whether tissue at risk of infarction is still present and whether there is increased risk of hemorrhage. Among currently used methods, it is possible that CT-based techniques such as CT perfusion imaging,[6] positron-emission tomography,[7] single photon emission computed tomograph,[8] and multimodal MRI techniques[9–21] could fulfill some of these requirements.

We have used multimodal MRI to determine parameters that may be important for therapeutic decisions. The combination of diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) can identify patients who might have the greatest benefit from thrombolytic therapy, such as those with hypoperfused but still viable brain tissue.[10–15,22] Assessment of the apparent diffusion coefficient of water

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(ADC) within ischemic lesions may give us an estimate of the risk of hemorrhage after thrombolysis. In experimental models, the severity of ADC abnormalities detected by DWI imaging predicts the severity of histopathological changes[23,24] and areas of reversible or irreversible infarction within DWI lesions.[25] In humans, the severity of ADC changes has been associated with the risk of hemorrhage after thrombolysis, with hemorrhagic changes primarily associated with regions within the DWI lesion that have ADC values less than 550 $\mu m^2/s$.[18–20]

An MRI sequence that could accurately determine the age of a stoke would be of great advantage in the assessment of patients who wake from sleep with stroke. The evolution of ADC abnormalities over time may enable some estimation of lesion age.[26–28] A profound reduction in ADC occurs within minutes of ischemia in experimental models,[25,29–31] but there is a tendency for further reduction in the mean ADC over the next several hours until a nadir is reached.[31,32] The nadir may be as early as 3 to 6 hours in experimental stroke but has not been well documented in humans because of the difficulty in performing multiple sequential measurements during the first 24 hours of stroke. One prospective study suggested the time until minimum ADC is reached is heterogeneous, averaging 33 hours after stroke onset.[12] The mean ADC rises subsequently, reflecting increasing loss of cell membrane integrity and tissue necrosis within the lesion.[23,31,32]

It has been suggested that these imaging modalities may be able to expand the current therapeutic window for thrombolysis for carefully selected patients beyond the current 3-hour time window by identifying patients with a favorable benefit-risk ratio for treatment.[14] The functional imaging characteristics of patients who wake from sleep with stroke require characterization before any further steps can be made to determine whether similar criteria could be applied to this group of patients. The purpose of this study was to compare the clinical and MRI findings of patients who woke with stroke with those with defined stroke onset time.

Subjects and Methods

This is a retrospective study of patients with acute stroke who were seen by our stroke service between January 1997 and June 2000. Patients were identified from a prospectively collected computerized stroke registry of consecutive patients. Patients with ischemic stroke who were evaluated by the stroke team within 24 hours of stroke onset were eligible for inclusion. Onset time was defined as the last time the patient was known to be well. Patients with transient ischemic attack were excluded. Patients with defined stroke onset were designated group I, and patients who woke from sleep with stroke were designated group II.

Prospectively recorded data for each patient in the stroke registry included demographic details, stroke risk factors, time of stroke onset (or time last known well), National Institutes of Health Stroke Scale (NIHSS) score at acute presentation immediately before imaging, type and time of imaging studies performed, treatments given, and stroke mechanism according to the TOAST[33] (Trial of Org 10172 in Acute Stroke Treatment) classification system. The NIHSS score was recorded by accredited stroke fellows. The hospital records of patients who woke from sleep with stroke were examined retrospectively to determine the time and circumstances of waking or detection by a witness. During the study period, multimodal MRI including DWI and PWI was a routine part of the evaluation of all acute stroke patients, unless contraindications to MRI existed or a scanner was unavailable. Acute DWI was performed in 134 (50%) group I patients and 54 (54%) group II patients. PWI was performed in addition to DWI in 88 (33%) group I patients, 42 within 3 hours of stroke onset, and 34 (34%) group II patients, 12 within 3 hours of stroke detection.

Imaging Protocol

MRI studies were performed on a Siemens Vision 1.5-Tesla echo-planar imaging system (Siemens Medical Systems). The imaging protocol included a diffusion-weighted sequence with 2 b-values (0 and 1000), susceptibility-weighted (T2*) images and conventional spin-echo T1- and T2-weighted images, and magnetic resonance angiography (MRA). Perfusion MRI (PWI) was performed on patients who were tolerating the scanning well, with a special effort to perform PWI on patients presenting within 6 hours of stroke detection. The details of the imaging parameters have been published previously.[10,26]

Imaging Analysis

Patients with small-vessel infarction according to TOAST criteria were excluded from further imaging analysis. These patients typically had diffusion lesion diameters $<$1.5 cm and normal PWI and MRA. Detailed analysis was performed on the imaging of patients who presented within 12 hours of stroke onset (group I) or within 12 hours of stroke detection (group II). Volumetric assessment of lesion size was performed using custom-made software implemented in the Advanced Visualization Systems software package running on a Hewlett-Packard workstation, as previously described.[10] DWI volumes were measured by 1 experienced blinded observer on 2 occasions, the mean value being used. The intraobserver correlation between measurements was $>$0.95. The volume of the perfusion abnormality was assessed on relative mean transit-time maps, calculated as previously described.[10] Measurements were made by 1 experienced observer who was blinded to clinical data and DWI volumes. P$>$D mismatch was considered present when the PWI lesion was $>$120% of the DWI lesion volume.

Regions of interest (ROI) drawn for ADC calculation were delimited just within the boundary of the visible DWI lesion to avoid partial-volume effects at the boundary of the lesions and inadvertent inclusion of cerebrospinal fluid spaces or normal brain within the region. These regions were drawn by 2 independent observers on a subset of 20 patients; because the interobserver agreement for mean ADC was extremely high (r=0.97), the remainder of ROI were drawn by a single observer whose results were used for the data analysis. ADC values were calculated on a voxel-by-voxel basis within the ROI. The mean lesional ADC value for each patient was determined, along with the absolute number of voxels with an ADC value of $<$550 $\mu m^2/s$. This threshold was chosen because of prior studies, and our own preliminary work has indicated that ischemic regions with an ADC value of $<$550 $\mu m^2/s$ are associated with an increased risk of hemorrhagic transformation after thrombolysis with tissue plasminogen activator.[18–20]

MRA were analyzed by an experienced observer, blinded to clinical information apart from the side of the stroke. MRA were graded as “occlusion” when there was an abrupt loss of all signal in a vessel; “stenosis or attenuation” when lesser but definite focal abnormalities were present on the symptomatic side; or “no lesion.” For anterior circulation strokes, internal carotid artery and proximal M1 middle cerebral artery lesions were considered “proximal;” all others were considered “distal.”

Statistical Analysis

The clinical and imaging findings for group I were compared with group II. The Student’s t test was used for comparison of continuous variables, Wilcoxon rank sum test for nonparametric data, and χ^2 test for categorical comparisons, except when the Fisher exact test was used for 2$\times$2 tables. For group I, linear regression analysis was used to test association between mean ADC and time from stroke onset, DWI lesion volume, PWI volume, and NIHSS score. Variables with a P value less than 0.2 on univariate analysis were tested in a

TABLE 1. Demographic and Clinical Features

	Group I Defined Stroke Onset	Group II Wake With Stroke	
Number of patients	264 (73%)	100 (27%)	
Sex (M/F)	138/126	54/46	$P=0.81$
Mean age (yr)	71.0	71.3	$P=0.85$
TOAST diagnosis			
Cardiac	110 (42%)	31	
Large artery	58 (22%)	26	
Small vessel	54 (20%)	31	
Other	14 (5%)	3	$\chi^2=6.84$, $P=0.08$*
Unknown	28 (11%)	9	
Time from onset	6.0	13.3	$P\ll0.001$
Time from detection	6.0	5.9	$P=0.83$
NIHSS score (median)			
All cases	7	5	$P=0.06$
Exclude small vessel	10	10	$P=0.63$
Imaging performed			
DWI	134 (51%)	54	$P=0.64$
DWI+PWI	88 (33%)	34	$P=0.90$

TOAST indicates Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale; DWI, diffusion-weighted imaging; PWI, perfusion-weighted imaging.
*Cases with unknown stroke mechanism excluded.

multivariate linear regression model. Statistical analysis was performed using SPSS for Windows (Release 10.0.7, SPSS Inc).

Results

Clinical Characteristics

A total of 364 patients fulfilled the study criteria. Two hundred sixty-four had known stroke onset time (group I), and 100 (27%) woke from sleep with stroke (group II). Demographic and clinical features are summarized in Table 1. Groups I and II did not differ in age, gender, or NIHSS. Time from stroke onset to imaging was greater in group II. Time from stroke detection was similar in both groups overall; however, fewer group II patients were imaged within 3 hours of stroke detection (29% versus 45%, $P=0.006$). There was a trend toward a greater number of lacunar strokes among patients with known cause of stroke who woke up, but the result was not significant ($\chi^2=6.84$, $P=0.08$). If the number of patients with and without lacunar stroke were compared, the result became marginally significant ($P=0.04$, Fisher exact test).

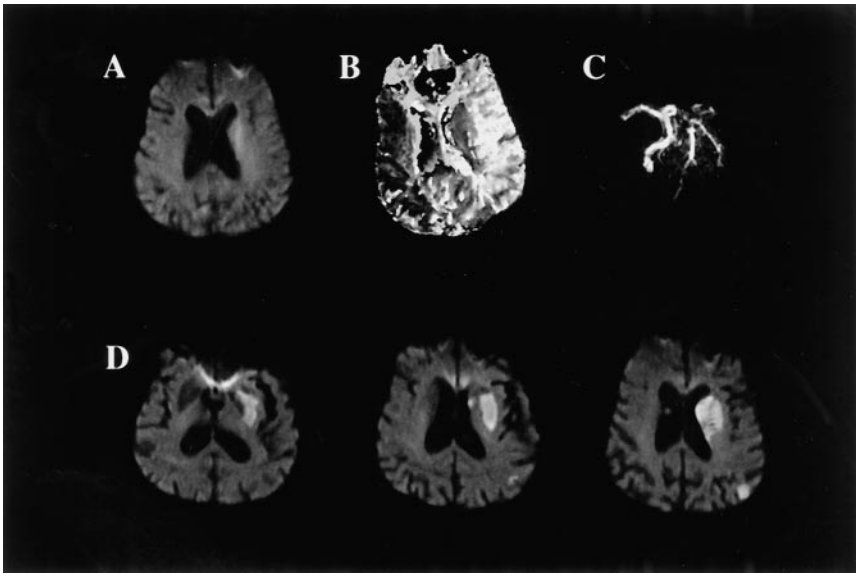
DWI, PWI, and ADC

Imaging data are summarized in Table 2. Within 3 hours of detection, DWI and PWI lesion volumes were similar in group I and group II; DWI-PWI mismatch was present in 82% of group I and 73% of group II patients ($P=0.4$). The

TABLE 2. Imaging Data

	Group I			Group II	
Time From Detection	<3 h	3–6 h	6–12 h	All (<12 h)	<3 h
DWI volume (cm^3)	26.8	22.8	8.3†	17.0	19.6
Number with analyzable DWI images	51	20	19	35	18
PWI volume (cm^3)	107.7	70.1	78.5	77.8	82.7
Number with analyzable PWI images	42	14	12	22	12
Mean lesional ADC ($\mu m^2/s$)	665	654	603*	602*	566†
Mean number of voxels with ADC<550 $\mu m^2/s$	1874	1606	609*	1278	1335
Patients with mean ADC<550 $\mu m^2/s$	10 (20%)	5 (25%)	6 (32%)	12 (34%)	9 (50%)*
NIHSS median	15	7†	6	9*	13.5

ADC indicates apparent diffusion coefficient of water; other abbreviations as in Table 1.
Group I patients<3 h were the reference group for all statistical comparisons.
*$P<0.05$; †$P<0.01$. Unmarked comparisons were nonsignificant.



Case example of a patient who woke from sleep with aphasia and flaccid right hemiplegia. The patient was imaged within 2 hours of detection: A, diffusion-weighted imaging (DWI) showing faint internal capsule abnormality only; B, perfusion-weighted imaging (PWI) (mean transit time map) showing large left hemisphere perfusion deficit; C, magnetic resonance angiography showing little flow in the left internal carotid artery and left middle cerebral artery occlusion. Thrombolysis was not given because of uncertain time of stroke onset. Repeat DWI 3 days later (D) shows progression to large capsular stroke; the aphasia improved but moderate hemiparesis persisted.

DWI lesion volume, number of voxels with ADC <550 $\mu m^2/s$, and NIHSS score of group II patients were similar to those of group I patients imaged within 3 hours of stroke onset and were greater than for group I patients imaged between 6 and 12 hours of stroke onset. However, the mean ADC of group II patients was lower than that of group I patients within 3 hours of stroke onset and similar to the mean ADC of group I patients between 6 and 12 hours of onset.

Among group I patients imaged within 12 hours of stroke onset, univariate analysis revealed a significant negative association of DWI volume and mean ADC ($\beta=-0.285$, $P=0.011$). There was a trend toward a negative association between mean ADC and time from stroke onset ($\beta=-0.184$, $P=0.10$); there was no association of mean ADC and NIHSS score or PWI volume. Onset time was inversely associated with NIHSS score ($\beta=-0.337$, $P=0.002$) and DWI volume ($\beta=-0.170$, $P=0.12$). Multivariate analysis confirmed the association of mean ADC with both onset time ($\beta=-0.238$, $P=0.031$) and DWI volume ($\beta=-0.324$, $P=0.004$).

MR Angiography

After excluding patients with lacunar stroke, 159 group I and 49 group II patients had adequate-quality MRAs for review. In group I, 62 (39%) patients had a vascular occlusion and 25 (16%) had focal stenosis or attenuation on the symptomatic side. In group II, 25 (51%) had a vascular occlusion; 6 (12%) had stenosis or attenuation. If only patients presenting within 3 hours of stroke detection were considered, 49 (58%) of 85 group I patients and 12 (67%) of 15 group II patients had a vascular abnormality identified. There was no difference in the proportion of proximal or distal vascular lesions between the groups.

Clinical and Imaging Characteristics of Patients Presenting Early After Waking

Twenty-seven of the 100 group II patients either woke at an unusual time, mostly between 1:00 AM and 5:00 AM, or woke with a dramatic event such as palpitations or vomiting. However, only 3 of these 27 patients were imaged within 3 hours of detection with both diffusion and perfusion MRI (Figure). Of the 12 group II patients overall who were imaged with DWI and PWI within 3 hours of detection, 1 had lacunar stroke and was excluded from imaging analysis. P>D mismatch was present in 8 of 11 remaining patients, 7 of whom had vascular occlusion on MRA; attenuation or stenosis was present in 1. The mean DWI lesion volume of the patients with P>D mismatch was 15.0 cm^2; the mean PWI lesion volume was 108 cm^2. Mean lesional ADC ranged from 442 to 742 $\mu m^2/s$ (average 518 $\mu m^2/s$). The number of voxels with ADC <550 $\mu m^2/s$ ranged from 0 to 4819 (mean 1716). The NIHSS score ranged from 6 to 22 (median 13).

Discussion

To our knowledge, this is the first report to describe both the clinical and multimodal MRI characteristics of patients who wake from sleep with stroke. Analysis of the clinical characteristics of this group of stroke patients reveals little difference from patients with defined stroke onset time. Our finding that just over one quarter of ischemic stroke patients presenting to an acute stroke service woke from sleep with their deficits is consistent with previous series,[1–3] as is the finding of a trend toward a greater proportion of lacunar strokes among patients who woke with stroke.[2,3] Twenty-nine percent of patients waking with stroke were imaged within 3 hours of stroke detection. The imaging parameters of some of these patients who woke with stroke were comparable to others with known stroke onset who were eligible for acute stroke therapy or experimental trials.

The findings of our study do not suggest that the age of stroke can be estimated accurately within the first several hours of onset using currently available MRI techniques. We detected a significant reduction of mean ADC values with increasing time from stroke onset within the first 12 hours of stroke. However, the strength of the association was moderate, and the heterogeneity of results precludes any estimation of lesion age based on ADC time course within the acute time period. The heterogeneity of mean ADC results within the acute phase of stroke in this study is consistent with previous

series.[12,26] After the initial decline in ADC at the onset of ischemia, it is likely that the magnitude of any time-dependent changes of ADC within the first 12 hours of stroke is modest.[12,26,31,32] DWI lesion volume is associated with ADC reduction in the first hours of stroke, and other factors that were not examined in this study may also be important, such as severity of perfusion deficits and regional reperfusion.[16,34] Although our data are limited by the retrospective and cross-sectional nature of this study, no larger series of DWI and ADC changes in human stroke within 6 hours of stroke onset are available, and the data are similar to that which would be available in a clinical decision-making situation. Although ADC parameters may be valuable in the estimation of stroke lesion age within the first several days of onset,[12,26,28,35] the accuracy is unlikely to be sufficient to estimate lesion age within hours of acute stroke.

Although accurate estimation of lesion age of patients who wake with stroke is not possible with current methods, an estimation of potential benefit and risk of thrombolysis for these patients remains possible. Seventy-three percent of patients presenting with nonlacunar stroke within 3 hours of waking from sleep who had complete MRI studies were found to have P>D mismatch. This imaging pattern may be associated with potential benefit from thrombolysis beyond the current 3-hour window for treatment.[14,15,22] The region of P>D mismatch is likely to contain hypoperfused brain regions that are at risk of infarction in the absence of reperfusion.[9–11,13,15–17] Progression of ischemic lesions into the mismatch area has been documented to occur well beyond 3 hours of stroke onset.[9,11] Spontaneous or induced reperfusion of an area of initial PWI hypoperfusion has been associated with reduced infarct expansion and favorable clinical outcome.[11,16,17,22,36,37] Continuing development of MRI techniques to determine the severity of perfusion deficits based on parameters such as cerebral blood volume[10] or cerebral blood flow[13] might increase the accuracy of prediction of tissue outcomes for individual patients. Previous studies of perfusion imaging have not included patients who have woken from sleep with stroke, however. Further studies are required to determine whether predictive models of tissue outcome based on results from patients with defined stroke onset can be applied to patients waking from sleep.

The mean lesional ADC of patients who woke up with stroke was lower than that of patients within 3 hours of defined stroke onset and was similar to the levels seen among patients presenting beyond 6 hours of stroke onset. This finding is of concern, because low ADC values have been associated with hemorrhage risk,[18–21] and a higher average risk of hemorrhage could be present among patients waking with stroke than among those currently eligible for thrombolysis. However, within the group who woke with stroke, there were patients who had modest reduction of mean ADC and a relatively small volume of voxels with ADC below 550 $\mu m^2/s$, suggesting that individuals with lower hemorrhage risk may be present. Further studies of the ability of ADC parameters to predict hemorrhage risk after thrombolysis are required before criteria based on these parameters can be applied to patients who wake from sleep with stroke. In particular, it is uncertain whether ADC criteria established for patients presenting within several hours of stroke onset would apply to patients at later or uncertain time points, because there may be time-dependent cellular processes that confer an increasing risk of hemorrhage, such as progressive endothelial cell damage, which are not reflected in the ADC. Non-ADC parameters such as severity and persistence of perfusion deficits and disruption of the blood-brain barrier may also be important predictors of hemorrhage risk.[19,38]

Patients who wake from sleep with stroke are a large and heterogeneous group with similar clinical and imaging characteristics to other stroke patients with known onset time. Individuals who present rapidly to the hospital after waking with stroke may be appropriate candidates for thrombolysis; however, it will remain difficult to offer this treatment to any such patients without the development of criteria based on functional imaging studies. Accurate estimation of stroke age within the hyperacute phase does not seem plausible using current techniques. However, estimation of the presence of salvageable tissue and hemorrhage risk may be possible. There is now a particular need for accurate predictive models of hemorrhagic risk of thrombolytic treatment, before trials of acute stroke treatment can be extended to include patients who wake with stroke.

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