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ASPECTS in patients with wake up Stroke

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Abstract

Background—One quarter of ischemic strokes occur during sleep and they are excluded from thrombolytic therapy due to an unknown time of stroke onset. It has been suggested that early ischemic changes in CT are similar between acute stroke patients and patients who recently awoke with stroke. We compared head CT scans using the Alberta Stroke Program Early CT Score (ASPECTS) in patients who were likely to suffer their stroke during sleep (AWOKE) to a control group of patients with stroke of known onset time.

Methods—Patients were recruited from a prospectively collected acute stroke database. The "AWOKE" group was defined as all ischemic stroke patients who were "last seen normal" more than 4 hours ago, arrived between 4AM and 10AM and had a head CT within 15 hours from last seen normal. The control group was randomly selected using patients who had a head CT within 4 hours from stroke onset. The ASPECTS evaluations were performed blinded to patient group and time of onset. In 15 AWOKE and 46 control patients a mRS at 90 days after stroke was available.

Results—Twenty-eight AWOKE and 68 control patients had suitable imaging for the ASPECTS. Baseline demographics and risk factors were similar in both groups. The dichotomized ASPECTS analysis (≤7 versus 8–10) showed no significant differences between groups. In the AWOKE group 89.3% had an ASPECTS of 8–10, while for controls 95.6% scored 8–10 (p= 0.353). There was a trend toward better 90 day mRS (0–1) in the AWOKE group (73%) versus control (45%) p=0.079.

Conclusion—Initial ASPECTS were similar between patients with wake-up strokes and those with documented onset within 4 hours of symptoms.

Background

Fifteen to 25% of ischemic strokes occur during sleep.[1–5] These patients are denied thrombolytic therapy and excluded from acute stroke clinical trials because the actual time from onset is often unknown.[6] In many patients, the stroke may occur shortly before or after awaking. Two previous studies using head CT have suggested that early ischemic changes (EIC) in CT do not differ in acute stroke patients with known onset and patients who recently awoke with stroke.[7,8] However, EIC on CT have never been shown to correlate with any differential outcomes, either death/disability or hemorrhage and it does not contraindicate the use of thrombolytics in the appropriate patients[9]. The Alberta Stroke Program Early CT Score (ASPECTS) is a 10-point scale that grades early ischemic changes on head CT within the middle cerebral artery (MCA) territory in patients with acute ischemic stroke.[9] ASPECTS is

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Authors' contributions

BH conceived of the study, participated in its design carried out the ASPECTS evaluations and drafted the manuscript. GT, AS and BM carried out the ASPECTS evaluations. RR and KE carried out the statistical analysis. TH carried out the ASPECTS evaluations, coordination of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

a reproducible clinical scale for rating early ischemic changes on CT and it has shown reliability between real-time and expert ratings.[10] One point is subtracted for an area of EIC; a normal CT scan represents a score of 10 and a score of cero represents diffuse ischemia within the MCA territory.

We hypothesize that there is no difference in the ASPECTS score between wake-up stroke patients and patients with head CT within 4 hours from documented onset of symptoms.

Methods

We used an acute stroke database which prospectively collects demographics, process of care, safety, and 90-day outcomes of all consented patients. A limited dataset from all registered patients with Institutional Review Board (IRB)-approved waiver of consent was used to investigate patients from January 2005 to June 2009 (http://spotrias.ucsd.edu). Our database captures patients with wake-up strokes as "last seen normal". We defined patients with wake – up strokes as the "AWOKE group" using the following criteria: All ischemic stroke patients who were "last seen normal" more than 4 hours ago, arrived to the Emergency Department between 04:00 to 10:00 hours and with a head CT within 15 hours from last seen normal. Controls were randomly selected from patients who had a known or documented time of stroke symptom onset and had a head CT within 4 hours from stroke.

ASPECTS were used to evaluate all the initial CT scans from the AWOKE and control groups. Five different stroke neurologists performed ASPECTS on all initial head CT, blinded to patient groups and time of onset. Patients with lost or unavailable head CT or studies with considerable motion artifact were excluded for the ASPECTS analysis. A pre-specified dichotomization of ASPECTS, >7 versus ≤**7**, was planned for the analysis.

Patient characteristics, 90-day mRS score and dichotomized ASPECTS scores were compared between the AWOKE and Control groups using the Wilcoxon Rank Sum test for continuous outcomes and the Fisher's Exact test for categorical outcomes. Multivariable regression analyses, as appropriate, were performed to control for any observed confounding factors. Variables were considered to be confounders and included as covariates in the multivariable model if found to be associated with gender ($p<0.1$) and moderately associated with response ($p<0.15$) based on univariate analysis. All analyses were done with the statistical software R 2.9.1. Since this is an exploratory study, no adjustments for multiple comparisons were be made and a p-value of 0.05 was considered statistically significant.

Results

Among 867 patients with diagnosis of acute ischemic stroke form our database, 36 patients met the AWOKE group definition and 83 patients were randomly selected as control group. Baseline demographics and risk factors were similar in both groups, including age, gender, diabetes, hypertension, and baseline mRS with the exception of the initial NIHSS that was higher in the AWOKE group. From the control group 34(40.96%) were treated with rt-PA and no patients from the AWOKE group were treated. There was a trend of a shorter time of arrival to head CT in the control group. (Table 1)

Only 28 AWOKE and 68 DOCUMENTED patients had suitable head CT imaging for the ASPECTS evaluation. Among these patients the mean ASPECTS in the AWOKE group was 9.0±1.9 versus 9.8±0.7 in the control group ($p= 0.0019$). Using the dichotomized ASPECTS analysis 89.3% of the AWOKE versus 95.6% of controls had an ASPECTS of 8 to 10 ($p= 0.35$). (Table 2)

The dichotomized ASPECTS analysis (≤7 versus 8–10) showed no significant differences between groups; in the AWOKE group 89.3% had an ASPECTS of 8–10, controls 95.6% (p= 0.35). (Table 2)

Fifteen AWOKE and 46 control patients had 90 day mRS available. There was a trend toward better 90 day mRS (0–1) in the AWOKE group (73.3%) versus controls (45.7%) p=0.079. (Table 3)

Discussion

In our analysis, we found that ASPECTS from stroke patients presenting within 4 hours of stroke onset did not significantly differ from patients with wake up strokes. Two prior retrospective studies found that early ischemic changes on CT from wake-up strokes were similar to acute ischemic stroke patients with known symptoms onset.[7,8] In a subgroup analysis from the Abciximab in Emergency Stroke Treatment Trial-II (AbESTT-II), more new strokes were detected in head CTs from the wake-up stroke group compared with the group presented from 0 to 6hrs from the onset of the symptoms; but the difference did not reach statistical significance.[11] (Table 4) The sensitivity of CT detecting EIC in acute ischemic stroke depends on the severity and duration of the focal cerebral ischemia.[10] However, reporting EIC on CT lack of clinical any importance when an extension of those CT changes are not given; therefore EIC on CT have never been shown to correlate with any type of stroke outcomes neither guide medical treatment in acute stroke patients[9]. Conversely, ASPECTS performed in real time, is a reliable method for quantification of EIC.[10] We chose dichotomized ASPECTS of >7 versus ≤7 because EIC on CT measured by ASPECTS of ≤**7** correlate well with clinical outcomes, and although not proved, it has been suggested as predictor of thrombolytic treatment response. In the 0 to 3 hour time window, there is a suggestive evidence of a greater magnitude of treatment benefit among patients with favorable ASPECTS > 7.[13] However, in patients from 3 to 6 hours from stroke onset, ASPECTS of ≤**7** has predicted a poor response to intra-arterial rt-PA treatment.[14]

We chose patients within 4 h of the onset of symptoms as control group because they could be suitable to thrombolytic therapy by using ECASS III time criteria.[15] Although head CT cannot determine time of onset in wake-up strokes and patients with unknown stroke onset, early hypodensity correlates well with irreversible infarct.[16] The diffusion and FLAIR mismatch in MRI have been suggested as a better surrogate of time of onset in stroke patietns.[17] MRI perfusion imaging have aided to the better understanding of brain tissue changes over time after ischemia.[18,19] Brain perfusion studies have been used to select patients for intravenous (IV) thrombolysis beyond 3 hours.[20,21] Using brain MRI, Fink et al showed that 73% of patients who woke up with stroke symptoms had a favorable perfusion and diffusion mismatch pattern. This was similar to stroke patients presenting within 6 hours of known onset of symptoms.[22] Based on these MRI findings,[22] prior CT studies,[7,8,11] and our current work, we could postulate that a significant subset of patients who awake with stroke suffer ischemia shortly before or after waking.

In previous studies, baseline clinical characteristics and stroke severity of wake-up strokes compared with stroke-while-awake patients have not shown significant differences.[23,24] In our sample, however, AWOKE patients had a significantly higher initial NIHSS compared to controls. Despite of the control group had lower initial NIHSS and a subset of them received IV rt-PA, we found a trend towards better 90 day mRS in the AWOKE group, though this did not meet statistical significance. Data of clinical outcome in wake-up stroke is scarce. One previous study suggested that patients who awake with stroke have poorer outcomes than patients with stroke during waking.[24] This data, however, was derived from an incomplete stroke registry, missing 60% of stroke admissions and included patients with transient ischemic

attack or intracranial hemorrhage. When focusing on ischemic stroke, there were no significant differences between groups.[24]

Our AWOKE group likely underestimates the real number of wake-up strokes in our hospitals. In fact the number of patients included in the AWOKE group using our selection criteria is by far lower than 20 or 25% reported by others.[1–5,23,24] Due to the uncertainty of time onset, it is likely that wake-up strokes were put off by the emergency physicians failing to activate the acute stroke code; therefore, not captured in our acute stroke database. A trend of longer time from arrival to CT in the AWOKE patient group compared with the controls might suggest this less priority given to wake-up strokes compared to the acute ischemic stroke patients with known onset time.

Limitations of our study are that the patient sample was relatively small and included patients from a single stroke center. Our acute stroke database captures wake-up as “last seen normal” but it does not distinguish between patients of unknown time from onset and patients who suffered stroke while asleep. However, the inclusion criteria for the AWOKE group is based on our best estimate of sleep pattern and presentation of stroke patients. We believe it is unlikely capturing a non wake-up stroke using these restrictive selection criteria. ASPECTS is limited to the territory of the MCA and our population was not selected based on anterior circulation strokes, however there were new ischemic lesions within the MCA territory in 70% on following imaging in both patients groups. Furthermore, only 15 or 28 AWOKE and 46 of 83 control patients received a follow-up exam 90 days after stroke. This limits the information about clinical outcome significantly and only a prospectively collected cohort with close to 100% follow-up can determine clinical outcome in patients with stroke while asleep and validate if good ASPECTS can predict outcome after reperfusion therapy in this patient group. Because of these limitations, our study is considered hypothesis-generating.

Interventional studies in patient with wake-up strokes are scant. To our knowledge only one trial (AbESTT-II), which used intravenous administration of Abciximab with a window treatment of 6 hrs, had included patients with wake up strokes. The trial did not demonstrate either safety or efficacy of the treatment in any subgroup of patients.[25] Other recent report described patients with wake-up strokes treated with IV t-PA, has suggested feasible treatment and acceptable rates of symptomatic intracranial hemorrhages.[26] Certainly more data and research is needed in wakeup stroke patients.

In conclusion, a significant subgroup of patients present with stroke symptoms upon awaking. Brain imaging and clinical data suggest that some of these patients may be have the brain ischemic event close upon awaking. Further studies are needed to clarify clinical outcome, imaging characteristics and treatment options in patients with stroke during sleep.

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Disclosures

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Table 1

Baseline characteristics

	AWOKE N = 36	CONTROLS N= 83	p value
Age (mean±SD)	69.86 ± 17	69.06 ± 13.8	0.486#
Baseline NIHSS (mean±SD)	10.47 ± 8.7	8.05 ± 8.3	0.041#
Time from onset or "last seen normal" to CT (mean±SD)*	573.3 ± 179.92	63.5 ± 50.29	<0.001#
Time from arrival to CT *	63.5 ± 50.29	45.34 ± 24.76	0.089#
Gender (% female)	50%	49.4%	>0.999 π
Hypertension (%)	61.11%	69.88	0.398 π
Diabetes (%)	11.11%	18.07%	0.422 π
Pre stroke mRS (%)			
0–1	26 (72.22)	72 (86.74)	0.219 π
2–4	10 (27.78)	11(13.24)	
rt-PA treatment (%)	0%	34(40.96)	<0.001 π

*Time given in minutes.

#Wilcoxon-Rank Sum test.

πFisher's Exact test

Table 2

ASPECT scores (0–7 vs. 8–10), between stroke time documentation groups

	CONTROLS (%)	AWOKE (%)	OVERALL (%)	P-value*
≤7	3(4.4)	3(10.7)	6(6.3)	0.353
8–10	65(95.6)	25(89.3)	90(93.8)	
Overall	68(100)	28(100)	96(100)	

*Fisher's exact test

Table 3

Day 90 mRS scores (0–1 vs. 2–6) between stroke time documentation groups

	CONTROLS (%)	AWOKE (%)	OVERALL (%)	P-value*
0–1	21(45.7)	11(73.3)	32(52.5)	0.079
2–6	25(54.4)	4(26.6)	29(47.5)	
Overall	46(100)	15(100)	61(100)	

*Fisher's exact test

Table 4

CT changes in patients with wake – up strokes. Series reported in the literature.

Author, year	Type of Cohort	CT Interpretation	N:WUS/Controls	CT Changes %*
Serena[7], 2003	Stroke registry: BADISEN	Early CT changes. Controls from 0–6hrs	124/530	WUS: 52% Controls: 46.5%
Todo[8], 2006	Supratentorial cardioembolic strokes from retrospective single hospital.	Early CT changes. Controls from 0–3hrs	17/46	WUS: 77% Controls: 70%
Adams[10], 2008	Randomized clinical trial: ABeSTT II	Read as “new stroke” by enrolling doctor. Controls from 0–6 hrs	42/758	WUS: 40.4% Controls: 28%
Current study	Prospective Acute stroke database.	Dichotomized ASPECTS Controls from 0–4hrs	28/64	WUS: 10.7% Controls: 4.4%

*No statistical difference was found in any study.

WUS: Wake-Up Stroke

BADISEN=Stroke Data Bank of the Spanish Neurological Society