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ORIGINAL COMMUNICATION

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Does sleep protect against ischemic stroke? less frequent ischemic strokes but more severe ones

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Abstract *Background and objective* Stroke occurrence follows a circadian curve, with a higher frequency in the morning. This curve changes if the hours of sleep also change. Our aim was to evaluate the characteristics, risk factors, and prognosis associated with sleep stroke. *Methods* Patients with ischemic stroke (n = 813), consecutively assessed in our hospital for 2 years, were recorded with the time of clinical onset, pathological antecedents, severity (NIHSS), clinical classification, etiologic TOAST classification, and functional outcome at 3 months (modified Rankin scale). When clinical disturbance appeared during night sleep time it was considered as sleep stroke (SS). The rest were considered wakefulness stroke (WS). Differences SS–WS were analyzed with χ^2, *t*-student, Mann–Whitney *U*, and logistic regression tests. *Results* From 813 patients included, 127 were SS (15.6%). The SS frequency was less than expected for the corresponding interval of hours. After the univariate analysis and posterior logistic regression, obesity was a factor associated with SS. Adjustment for age and gender revealed that atrial fibrillation (AF) was less frequent in the SS group. There were no differences for other risk factors or in the etiologic distribution. SS had a greater initial clinical severity and a worse functional outcome at 3 months. This functional outcome was dependent on the initial clinical severity. *Conclusions* Whilst sleep could be associated with a lesser stroke occurrence, it could also be associated with a higher severity. Obesity appears as a factor related to SS whilst AF appears related to WS.

Key words cerebrovascular · circadian rhythms · ischemia · sleep stroke

Introduction

Ischemic stroke incidence not only changes according to the different seasons of the year [29, 37], and probably the different weather conditions [11], but also the time of onset along the 24 h of a day.

Several hospital-based and community-based studies [3, 12, 24, 35, 39] have examined the time of onset of ischemic stroke. A meta-analysis identified a 55% excess risk for ischemic stroke in the time period between 6:01 am and 12:00 noon [10]. A circadian curve has also been described for the onset of the stroke clinical symptoms, with a frequency peak in

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the hours after awakening [7, 17, 20, 21]. Stroke frequency during the nocturnal hours changes in different reports. Most studies, however, agree in finding a lower frequency than expected for this time [8, 33]. Some mechanisms have been postulated as an explanation for this pattern, especially the circadian variation in arterial pressure [13, 18, 30]. The circadian pattern of stroke onset may be related not only with the clock hour, but also with the fact of sleeping. The hours of the morning peak of incidence are later at the weekend [23]. It is suspected that night sleep could have a protective effect against ischemic stroke.

The aim of this study is to analyze the frequency, characteristics, prognosis, and associated factors or possible triggers of sleep ischemic stroke in a hospital-based series.

Methods

Subjects

Data from 962 patients with ischemic stroke, consecutively assessed at our hospital from 2003 to 2005, were analyzed in this study. Both those that required hospitalization and those discharged from the emergency department were included. Patients where it was not clear whether stroke had occurred during night sleep or not (90 patients) were excluded. Those patients that could not be followed up at 3 months, either by visit or by phone, (59 patients) were also excluded. These excluded groups did not show differences in age, gender, initial severity or 3 month outcome with regard to the included group.

Classifications and variables

From the 813 patients included, those patients who already presented clinical impairment at the moment of awakening were classified as sleep stroke (SS). The rest of the patients were classified as wakefulness stroke (WS), the exact hour of clinical onset was recorded whenever possible.

An acute basic etiologic study was carried out in all patients: a blood analysis (hemogram, ionogram, renal function, hemostasis), an electrocardiogram (EKG), a computer axial tomography (CT), and an intra and extracranial doppler. The following variables were recorded: age, gender, anthropometric data, previous functional situation, pathologic antecedents, vascular risk factors (VRF), previous antiaggregant or anticoagulant treatment, clinical and etiologic classification, clinical severity at the moment of admission, and functional outcome after 3 months. The number of patients who received thrombolysis (24 patients, all of them WS) was also recorded.

Information about demographic data, VRF, and medications was obtained from each patient or their caregivers, their next of kin, and from medical records. VRF were defined as follows: hypertension (reported systolic blood pressure over 160 mmHg, reported diastolic blood pressure over 90 mmHg, patient's self-report of hypertension, or use of antihypertensive drugs to treat it), diabetes mellitus (DM) (fasting blood glucose level over 120 mg/dl, patient's self-report of diabetes, or use of antidiabetic drugs), hyperlipidemia (reported cholesterol over 200 or tryglicerid over 150, patient's self-report of hyperlipidemia, or use of hypolipidemic drugs), smoking habits (current smoker), severe alcohol intake (>80 g/day), ischemic cardiac disease (history of myocardial infarction, coronary artery disease), atrial fibrillation (AF) (reported history of chronic or paroxysmal AF, or reported during the assessment in our hospital), obesity (body mass index BMI $\geq$ 30) and previous history of peripheral arterial disease or previous stroke.

The continuous doppler study (DWL multidop B+) in acute phase included analysis of the internal extracranial carotids and the ophthalmic arteries. The intracranial study was completed by the pulsed doppler. A stenosis >70% or an occlusion pattern in the symptomatic vascular territory was considered a pathologic result.

Patients were clinically monitored with the National Institutes of Health Stroke Scale (NIHSS) [14] during their stay at hospital and at the 3 month visit. Functional dependency was evaluated with the modified Rankin Scale (mRS). The previous mRS, the mRS at discharge and after 3 months, and mortality during this period were recorded. The change from a previous autonomic state (mRS = 0–1) to another of dependency at 3 months (mRS = 3–5), or the increase of 1 point in those patients with a previous dependency situation, was considered as *Functional Deterioration* (FD). This allows us to consider the previous functional state and to detect worsening in those patients with a previous dependency state with the same variable.

According to the etiologic study, following the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) etiologic criteria [1], strokes were classified as: *atherotrombotic*, *cardioembolic*, *lacuna*, *other*, *undetermined*, and *undetermined for double cause*. The *Other* group, with stroke etiologies such as heart catheterization, neoplasms, and arterial dissection, contained 10 patients (1 SS, 9 WS) and was not included in the etiologic analysis.

The initial clinical presentation was recorded following the Oxfordshire Community Stroke Project classification (Oxford) [4].

Statistical analysis

The SS percentage of total strokes was compared with a hypothetical expected rate by a non-parametric binomial test. According to the data of the year 2003 from the *Instituto Nacional de Estadística y Ministerio de Sanidad y Consumo de España*, the average of sleep hours in people >65 years is 7.54 h per day. The expected frequency from the corresponding rate of stroke occurrence for 7 h was 29.2%, assuming an equal distribution for the whole day. The univariate analysis was first performed followed by *T*-test, used to test differences in continuous variables, and Mann–Whitney *U*-test for analysing NIHSS. χ^2 test was used for those variables in proportions. In order to rule out the possible bias that sleep transient ischemic attack (TIA) could go unnoticed, the analysis of SS frequency, stroke classifications, clinical severity, and prognosis was also performed excluding TIA. A multivariate logistic regression analysis, performed without TIA, included the VRF, and the adjustment for age and gender. NIHSS, FD, and mortality were also adjusted for age and gender, thrombolytic treatment, and for the variables that had been statistically different between SS and WS in the first multivariate logistic regression analysis. All tests were 2-tailed, and statistical significance was determined at a α level of <0.05.

Ethics

The data for the study were collected from our hospital's prospective clinical protocols that complied with the local ethical guidelines and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Results

From the 813 included ischemic stroke patients (415 men, 398 women), the recorded onset time is shown in Fig. 1. There were 127 (15.6%) stroke patients that already presented clinical alteration when they awoke. Excluding TIA, SS proportion was 17.9%. Comparing this last percentage against the expected proportion, the binomial test shows an undoubtedly significant difference ($p < 0.001$). Furthermore, each TOAST subtype shows a significant decrease ($p < 0.001$ for all) in the stroke frequency during night sleep (atherotrombotic SS: 13.7%; lacuna SS: 16.7%; cardioembolic SS: 15.9%; undetermined: 17.1%; undetermined double cause: 13.4%).

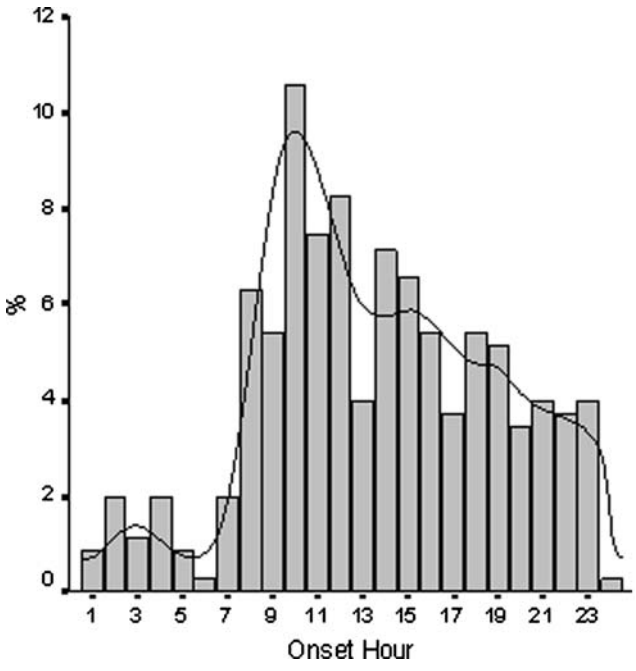

Fig. 1 Distribution of stroke onset along 24 h (TIA excluded)

The results shown in Table 1 are from the univariate analysis. Age, gender, and obesity were factors associated with SS. Older women with a higher BMI were more frequent in the SS group than in the WS.

The logistic regression study shows obesity as the only risk factor associated with SS (OR: 1.6, $p = 0.035$). After adjusting for age and gender, we found a lesser prevalence of AF in the SS group ($p = 0.027$), and that obesity, despite losing its significance ($p = 0.058$), still maintained a strong tendency associated with SS (Table 2).

There were neither significant differences in the etiologic distribution (Table 3) nor in the clinical subtypes. Patients with SS had a greater initial clinical severity (measured by NIHSS), a worse functional outcome after 3 months (measured by FD), and a tendency to a higher mortality during the first 3 months (Table 4). When we excluded TIA, and after adjusting for confounding variables, the 3 month worse outcome lost its significance, but not the initial NIHSS. Moreover, FD and mortality, when adjusted by initial NIHSS, also lost their significance.

Discussion

In the present study the sleep ischemic stroke occurrence is found to be lower than expected for the night period. Nevertheless, these strokes show a higher severity and a worse prognosis. It also appears

Table 1 Univariate study Comparison of SS against WS

	Total cases (n = 813)	SS (n = 127)	WS (n = 686)	p[a]
Women (%)	49	58.3	47.2	*0.022*
Men (%)	51	41.7	52.8	
Age (year)[c]	73.59 (12.07)	75.39 (9.96)	73.26 (12.40)	*0.035*
Arterial hypertension (%)	65.8	68.8	65.2	0.44
Diabetes mellitus (%)	32.9	36.8	32.1	0.309
Hyperlipidemia (%)	39	35.2	39.7	0.34
Atrial fibrillation (%)	27.8	23.8	28.6	0.273
Current smoking (%)	22.3	20.8	22.5	0.671
Alcoholism (≥80 g/day) (%)	8.3	5.6	8.7	0.241
Obesity (%)	33.2	41.1	31.7	*0.041*
Ischemic heart disease (%)	16.6	16.9	16.6	0.925
Previous stroke (%)	7.8	4.1	8.4	0.13
Peripheral arterial disease (%)	10.7	8.9	11	0.476
Previous antiplatelet treatment (%)	33.2	34.6	32.9	0.708
Previous anticoagulant treatment (%)	8.7	5.5	9.3	0.162
Glycaemia (mmol/l)[c]	7.84 (3.38)	8.06 (3.48)	7.80 (3.36)	0.809
NIHSS at admission[b]	4 (2–9)	5 (3–15)	4 (2–8)	*<0.001*
Functional deterioration at 3 months (%)	28.8	36.6	27.4	*0.038*
Mortality at 3 months (%)	13.5	16.3	13	0.324

[a]p value for the comparison between SS and WS
[b]Median (q1–q3)
[c]Mean (SD)

Table 2 Multivariate logistic regression of SS risk against WS[a]

	p	OR	95% CI	
			Low	Up
Arterial hypertension	0.667	1.108	0.694	1.769
Hyperlipidemia	0.183	0.734	0.466	1.157
Diabetes mellitus	0.280	1.276	0.820	1.987
Obesity	*0.058*	*1.489*	*0.992*	*2.262*
Alcoholism	0.383	0.660	0.260	1.677
Smoking	0.202	1.525	0.797	2.916
Ischemic heart disease	0.428	1.254	0.716	2.197
Previous stroke	0.765	0.922	0.544	1.564
Peripheral arterial disease	0.697	0.866	0.418	1.791
Atrial fibrillation	*0.027*	*0.566*	*0.342*	*0.936*

[a]Model included VRF and the adjustment for age and gender. Analysis performed without TIA

for the first time that obesity is associated with sleep ischemic stroke whilst AF is related to wakefulness ones.

Several studies [3, 6, 12, 16, 22–24, 32–24, 35–24, 39], with varied methodology, have analyzed the circadian variation in ischemic stroke onset. Most of them are in agreement with finding a frequency peak during the morning (6:01 am–12:00 noon). There are also studies that analyze whether strokes occurred during sleep. Some of them do not only describe a morning peak, but also a decrease of stroke frequency in the night sleep hours [36]. It is significant that one study [16] finds that during weekdays the period of greatest stroke frequency is from 6 am to 8 am, at weekends, however, the timing shifts to 8–10 am. It seems that the circadian pattern may be related not only with the clock hour, but also, and specially, with the fact of sleeping and being awake.

Our study confirms a similar curve of hour distribution that has been previously described. In terms of sleep/non-sleep stroke occurrence, the SS occurrence is less than expected, even if we exclude the possible TIA bias. There could be, therefore, a protective effect associated with night sleep or an activator effect in awakening. The mechanism is not still clear, but several explanations have been proposed: a circadian pattern in blood pressure, with a nocturnal fall in its levels [13, 25]; a higher rates of aggregation during the morning hours [34]; a tendency to fall of blood viscosity at night and to peak in the morning hours [19]. Moreover, endogenous tissue plasminogen activator (TPA) activity shows to be lowest in the

Table 3 Etiologic distribution (TOAST classification)

	Total cases (803)	SS (126)	WS (676)	OR	p	95% CI	
						Low	Up
Atherotrombotic (%)	15.5	13.5	15.9	0.825	0.493	0.475	1.432
[a]	–	–	–	0.909	0.738	0.519	1.591
Lacuna (%)	27.7	29.4	27.3	1.105	0.641	0.727	1.680
[a]	–	–	–	1.212	0.380	0.789	1.864
Cardioembolic (%)	27.5	27.8	27.5	1.015	0.947	0.663	1.552
[a]	–	–	–	0.832	0.426	0.528	1.310
Undetermined (%)	19.0	20.6	18.7	1.129	0.616	0.703	1.811
[a]	–	–	–	1.154	0.557	0.716	1.860
Undet. double cause (%)	10.3	8.7	10.5	0.811	0.537	0.417	1.578
[a]	–	–	–	0.842	0.616	0.431	1.648
Total stroke subtypes (%)	100	100	100				

[a]Adjustment by age and gender

Table 4 Initial clinical severity and 3 month outcome in SS and WS

	Total cases	SS	WS	OR	p	OR 95% CI	
						Low	Up
Initial NIHSS[d]	4 (2–9)	5 (3–15)	4 (2–8)	1.045	*<0.001*	1.019	1.073
[a]	4 (2–11)	5 (3–17)	4 (2–10)	1.032	*0.013*	1.004	1.060
[b]	–	–	–	1.036	*0.020*	1.006	1.068
FD[e] (%)	28.8	36.6	27.4	1.529	*0.038*	1.021	2.290
[a]	34.1	38.1	33.3	1.236	0.312	0.819	1.866
[c]	–	–	–	1.197	0.429	0.766	1.870
Mortality[f] (%)	13.5	16.3	13.0	1.304	0.324	0.769	2.213
[a]	15.8	16.9	15.5	1.109	0.703	0.651	1.891
[c]	–	–	–	1.035	0.905	0.587	1.826

[a]TIA excluded
[b]TIA excluded and adjusted for age, gender, obesity and atrial fibrillation
[c]Same as ''b'' including thrombolytic treatment in the adjustment
[d]Median (q1–q3)
[e]Functional deterioration at 3 months
[f]Mortality at 3 months

morning [2] and there also seems to be a decrease in endothelial function in the early morning [27]. Therefore, sleep may exert significant effects on the autonomic nervous system, systemic hemodynamics, cardiac function, endothelial function, aggregation and coagulation.

No evident associations between classical FRV and SSs have been described [31]. We find, however, that obesity seems to be related to SS and, to our knowledge this is the first study that reports this association. It might be explained by the fact that obesity has a greater association with primary and secondary sleep abnormalities, especially with obstructive sleep apnoea (OSA) [40]. Patients with these sleep abnormalities suffer a greater frequency of disturbances of intrathoracic pressure, cardiac arrhythmias, endothelial dysfunction, and alterations in nocturnal blood pressure patterns, promoting an increase in the risk of cardiovascular events [9, 38]. Obese patients, thus, may lose the supposed protective effects of sleeping and could suffer more SSs than the non-obese. Future prospective studies in obese patients, recording respiratory pathology and analyzing stroke incidence, may support these hypothesis.

On the other hand, patients with SS are more frequently women and older than WS patients. AF prevalence is associated with older people [28]. After adjusting VRF by age and gender, AF arises as a factor associated with WS. Patients with SS have less AF for the same age and gender or, in other words, AF may trigger stroke mainly in wakefulness. It has been described that heart rate also has a circadian variation, as well as an occurrence of falls in AF [5, 15]. Both follow a curve with a lower rate and less falls in AF

during sleep, and a peak in the morning after awakening, which could explain the relatively higher prevalence of AF in WS.

In spite of some differences being proposed [21, 23, 29] neither we, nor some of the latest studies [31], found any etiologic or clinical differences.

With respect to severity and evolution, there is no agreement in previous studies [6, 26]. However, we find that severity (initial NIHSS) is higher in SS even when it is analyzed excluding TIA, though FD at 3 months and mortality does not show a statistically significant increase after adjustments. Thrombolytic treatment benefit may only reinforce the lack of differences in prognosis.

The strength of this study is based on a consecutive and well documented sample of patients including both those that required hospitalization and those that did not. Likewise, it is supported by the representative character of the study design, the adjustment for several important confounders, and the inclusion of most of the characteristics and risk factors that might be involved.

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