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SAS CARE 1: Sleep architecture changes in a cohort of patients with Ischemic Stroke/TIA

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ABSTRACT

Objective: Changes in sleep architecture following ischemic stroke have been poorly investigated. Our objective was to explore changes of sleep structure in patients with ischemic stroke or transient ischemic attack in order to verify a possible predictive value of sleep with respect to clinical outcome.
Methods: Patients recruited in the prospective SAS-CARE study received two polysomnographies (PSG) in the acute and chronic phases after stroke/TIA. Sleep parameters were compared between the two time-points and matched with a non-stroke population randomly selected from the HypnoLaus cohort.
Results: Of the 169 patients investigated with PSG in the acute phase, 104 were again studied 3 months after stroke symptom onset and compared with 162 controls. The acute phase of stroke/TIA was associated with sleep disruption, which significantly improved in the chronic phase, but remained worse than controls (total sleep time improve from 318.8 ± 90.8 to 348.4 ± 81.5 min, compared to 388.2 ± 71.3 in controls, sleep latency from 49.9 ± 58.4 to 27.9 min, compared to 20.2 ± 22 in controls, sleep efficiency from 58.2 ± 18.1% to 27.9 ± 36.4 min, compared to 83.4 ± 10.3% in controls, wakefulness after sleep onset percentage from 36.5 ± 17.3 to 29.3 ± 15.6, compared to 13.2 ± 9.2 in controls). The percentage of REM sleep was negatively associated with stroke severity, whereas stroke topography did not correlate with sleep parameters.
Conclusions: This study confirmed a severe sleep disruption in the acute phase of stroke. Although a significant improvement of sleep quality was observed during the three months after stroke, sleep architecture did not normalize. In particular, sleep efficiency and REM sleep seem to be particularly affected by stroke in the acute phase, with a relative preservation of NREM sleep. We suggest that these sleep architecture changes represent a persistent marker of brain damage due to stroke. Further studies are needed to assess the relationship with stroke topographic and outcome.

1. Introduction

The analysis for the Global Burden of Disease Study 2017 showed that not only are neurological disorders the third most common cause of disability and premature death in the European Union, but their prevalence and burden will likely increase with the progressive ageing of the European population. Greater attention to neurological diseases must be paid by health authorities for prevention and care of ageing populations [1]. In particular, stroke is the most common source of disability-adjusted life-years (7.3 million, 35%) [1]. Globally, stroke is one of the leading causes of morbidity and mortality in adults [2].

Main strategies in managing stroke encompass the control of known risk factors for cardio-vascular disease (CVD), identification and treatment of associated conditions, and acceleration of

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systemic and intra-arterial interventional approaches [3,4]. Although sleep disorders are common in most neurological disorders but often poorly recognized as adjunctive risk factors [5], the American Heart Association and American Stroke Association stroke guidelines recommend screening for obstructive sleep apnea for the prevention of recurrent stroke or transient ischemic attack (TIA) [6]. Observational data show a high prevalence of OSA among patients with acute ischemic stroke, and small trials suggest that treatment may improve several important outcomes, supporting the hypothesis that early detection and treatment of OSA may be helpful for selected patients [6]. Sleep-disordered breathing (SDB) has been recognized as an independent risk factor for stroke [7]. Other sleep disorders, including insomnia, periodic leg movement during sleep (PLMS), and restless leg syndrome (RLS), have also been associated with an increased stroke risk [7]. However, the bidirectional impact of non-apnoea related sleep disorders, sleep architecture disruption, and endogenous circadian rhythm dysfunction in ischaemic stroke remains unclear [8].

Relationships between stroke and sleep may occur on three different levels: sleep and sleep disorders as a risk factor for stroke; stroke as a risk factor for new sleep disorders or worsening of pre-existing ones; transient sleep alterations impacting stroke outcome (Duss et al. Curr Neurol and Neurosci Rep 2018). The latter relationship remains poorly investigated.

Epidemiological studies suggest a link between sleep duration and sleep quality with CVD. Many studies and meta-analyses showed that short sleep duration is associated with an increased risk of heart diseases, diabetes mellitus, hypertension, cardiovascular diseases, coronary heart disease, obesity and mortality (Itani et al., 2016; Xialoin Gu, 2017) [48]. In particular, short sleepers (e.g., sleep duration<6 h) and poor sleepers showed a higher risk for CVD like coronary heart disease and stroke, and for mortality for CVD [9–11]. Several hypotheses have been advanced to understand how sleep disruption might favor CVD and, in particular, stroke. Among them, sympathetic activation, procoagulatory and inflammatory pathway activation, acceleration of atherosclerosis, and consequent changes in brain hemodynamics and oxygenation are the ones mostly debated in literature [12–14].

Besides prediction, sleep might also have a prognostic value for stroke outcome. Evidence demonstrates a negative effect of sleep loss/sleep fragmentation on stroke outcome, mostly when sleep disruption is secondary to major sleep disorders, such as sleep-disordered breathing (SDB) and restless legs syndrome (RLS), with the latter much less investigated than the first one. Sleep duration after stroke has been assessed in few studies (e.g. in patients with paramedian thalamic stroke), whereas a correlation between short sleep duration measured by actigraphy and stroke was observed [15]. Not only may sleep disruption negatively affect stroke recovery, but brain lesions associated with a worse outcome may also involve critical structures responsible for sleep generation such as the thalamus or brainstem [15,16]. Based on few studies, REM sleep seems to be reduced in patients with brainstem lesions, as well as NREM sleep in those with hemispheric lesions [16–18]. In a single study, a reduction of REM sleep was reported in cerebellar strokes [19]. Recently a topographical sleep EEG analysis revealed a large significant cluster of 88 electrodes in which low slow wave activity was reduced in thalamic compared to extrathalamic stroke. This reduction was related to increased daytime sleepiness in patients with thalamic stroke [20]. Other studies observed no significant differences in sleep architecture between patients with brainstem (infratentorial) lesions vs those with hemispheric (supratentorial) lesions [19,21].

Notwithstanding topographical brain location, it appears that acute post-stroke changes in sleep architecture (lower total sleep, lower sleep efficiency, and reduced amounts of NREM sleep stages 2–4) correlate with negative outcome in humans [22]. Abnormalities of REM sleep have been found during the acute phase (within 3 days) of stroke [22]. Recently, we have demonstrated that acute ischemic stroke is followed by a significant transient reduction of REM sleep in both animals and humans, and that the reduction of REM sleep and an increase in REM latency is associated with poor prognosis in humans [23].

The main aim of the present study was to prospectively explore sleep structure in a cohort of patients with stroke/TIA both in the acute and chronic phase to confirm our previous data, while adding a comparison with a control healthy population, and to evaluate changes of sleep architecture over time. Secondary aims were to investigate possible associations between sleep parameters and severity of stroke, type and location of stroke, and whether sleep parameters recorded in the acute phase and subacute phase of stroke may aid in predicting recovery from stroke.

2. Material and methods

2.1. Participants

This analysis is based on data obtained from the prospective multicenter study SAS-CARE (Sleep Disordered Breathing in Transient Ischemic Attack (TIA)/Ischemic Stroke and Continuous Positive Airway Pressure (CPAP) Treatment Efficacy (SAS-CARE); NCT01097967). The study (Clinical-Trials.gov identifier: NCT01097967) was performed in Switzerland (Bern, Lugano), Germany (Münster) and Italy (Milano). It was approved by the local ethics committees and conducted in accordance with the principles of good clinical practice and local regulations, and an informed consent was obtained from all participants.

. The design of the international SAS-CARE investigator-initiated study has been reported elsewhere [24]. Briefly, the SAS-CARE cohort includes 35–75 year old patients with clinical diagnosis of TIA or ischemic stroke, admitted at the Stroke Unit within 2 days from onset of symptoms. Exclusion criteria were the following: unstable clinical condition (cardio-respiratory or life-threatening medical conditions); current or CPAP treatment use during the last 3 months before stroke; non-ischemic events (intracerebral/subarachnoid haemorrhage); coma/stupor.

Patients underwent a full-night polysomnographic (PSG) investigation in the acute phase of stroke/TIA (within 7 days from the onset of symptoms) and a second PSG and clinical evaluation 3 months after the onset of symptoms. For the analysis of the evolution of sleep structure and stroke outcome, we included all patients who received full PSG recordings at baseline and after 3 months. In addition to PSG data, the following parameters from SAS-CARE database were considered: age, BMI, medical history (dislipidemia, diabetes, hypertension, previous cerebrovascular events, smoking and snoring), etiology of stroke according to the criteria of the TOAST-study [25], stroke severity as assessed with the National Institute of Health stroke scale [26] at admission and 3 months after stroke. Functional outcome was assessed by the modified Rankin Scale (mRS). The scale ranges from 0 (no symptoms) to 6 (death). A score of 2 indicates a slight disability (unable to carry out all previous activities, but able to look after own affairs without assistance). A score of 3 indicates a moderate disability, with requirement of some help [27]. Both short- (at discharge) and long-term (3 months after stroke) outcome were assessed.

The patient population was compared with a sample of age and gender matched non-stroke population belonging to the HypnoLaus cohort study [28].

Insomnia definition was based on the alteration of sleep parameters (decrease of sleep efficiency, increase of wakefulness after sleep onset and increase of sleep onset latency).

2.2. Nocturnal polysomnographic studies

All PSG recordings from Lugano, Bellinzona and Bern Centers were registered with EMBLA Titanium, while the PSG recordings from Italy and Munich were exported in European Data Format and scored by the same software of EMBLA. Recordings within the first 7 days after stroke were performed in the Stroke Units from 8-10 p.m. until 7–8 a.m. PSG after 3 months were recorded in the Sleep Laboratories from 9-11p.m. until 6–7.30 a.m. PSG recordings included 6 channels of electroencephalogram, submental electromyogram, electrooculogram, nasal airflow, 2 channels of breathing effort, pulse-oximetry, bilateral tibialis anterior electromyogram.

All the sleep recordings (including sleep macrostructure and arousals, cardiorespiratory parameters, and periodic limb movements) have been centrally scored according to the international criteria [29,30] by one blinded investigator (SM). Apnoea was defined as a drop of at least 90% of airflow from baseline lasting 10 s or longer, hypopnoea events were scored using the following criteria: ≥30% drop of airflow lasting at least 10 s with either an arousal or ≥3% oxygen saturation drop [30].

2.3. Control group

Controls were obtained from the HypnoLaus Sleep Cohort study, which included 2162 subjects (51.2% women, mean age 58.4 ± 11.1 years) randomly selected from the population based CoLaus/PsyCoLaus cohort. According with the protocol, all subjects received a full night-PSG at home between September 2009 and June 2013 in Lausanne, Switzerland. Certified technicians equipped the subjects with a PSG recorder (Titanium, Embla®Flaga, Reykjavik, Iceland) between 5 and 8 p.m. at the Center for Investigation and Research in Sleep of Lausanne. All recordings took place in the subject home environment. Two trained sleep technicians scored manually the PSG recordings. Each recording was reviewed by an expert sleep physician and a second sleep expert performed random quality checks. Sleep and related events were scored using American Academy of Sleep Medicine criteria [29,30]. PLMS were scored according to the official World Association of Sleep Medicine standards [31]. Apnoea was defined as a drop of at least 90% of airflow from baseline lasting 10 s or longer, hypopnoea events were scored using the following criteria: ≥30% drop of airflow lasting at least 10 s with either an arousal or ≥3% oxygen saturation drop [30].

2.4. Statistical analysis

Data are presented as mean ± standard deviation (SD). Data were check for normality, when indicated. All statistical tests were two-sided and p-values of less than 0.05 were considered statistically significant. Correlations between continuous variables were assessed by Pearson's product moment.

One-way ANOVA was performed to compare anthropometrics', sleep and stroke severity data between groups. Changes in sleep indices between acute and chronic phase were assessed by means of repeated measures ANOVA analysis (MANOVA). Tukey's honest statistical difference test for unequal sample sizes (Spjotvoll & Stoline test) and the Scheffe' test were used to compare differences between groups and within groups, respectively. Data were analyzed using the Statistica 10 package (StatSoft Inc., Tulsa, OK, USA).

3. Results

One hundred and sixty-nine patients (mean age 61.4 ± 9.4, males 72.3%) participated in the study and received a full PSG recording in the acute phase after stroke. One hundred and four of them (mean age 61.1 ± 9.3, males 78.9%) underwent a clinical and polysomnographic follow-up three months (chronic phase) after the onset of symptoms. The control population (Hypnolaus Cohort) consisted of 162 healthy subjects (mean age 62.1 ± 8.4, 72.2% males).

Table 1 shows clinical characteristic of the cohort of patients, no statistical differences were found between stroke and TIA patients. Tables 2 and 3 show respectively the comparison between PSG parameters of stroke patients in acute phase and controls and between the acute to the chronic phase of stroke. The acute phase of stroke was associated with sleep disruption, with patients showing a longer sleep latency, shorter total sleep time (TST), lower sleep efficiency (SE), higher percentage of slow wave sleep, a lower percentage of REM sleep and a longer REM latency than controls. No differences were found for LM or PLM index between these two groups, whereas a mild improvement of AHI was found (supplemental material table E1).

In general sleep improved from the acute to the chronic phase of stroke, but without a complete normalization. An increase of TST, SE, and a decrease of REM latency and AHI were found in stroke patients after 3 months with respect to the acute phase (Table 1). No differences were found in AHI, LM or PLM index between acute and chronic phase (supplemental material table E2). At baseline, patients with lacunar infarct had a lower SE (50.7 ± 12.5%) compared to patients with partial anterior circulation infarct (58.6 ± 19.1%), and with posterior circulation infarct (64.7 ± 17.1%) (ANOVA $p = 0.02$). No other differences in clinical and sleep parameters were found, at baseline among stroke patients.

Table 4 shows the differences in age and sleep parameters between 3 subgroups of patients clustered according to the first (<263 min), second/third and fourth quartile of TST distribution (>385 min, lower limit of 4° quartile of 385 min). Patients in the lower quartile were older, had longer sleep onset and REM latencies, a longer WASO and a lower REM sleep percentage. No differences between these three subgroups were found in gender, BMI and severity of stroke, measured by NIHSS and Rankin scales.

Table 5 shows the differences in age, sleep parameters and NIHSS between three subgroups of patients clustered according to the first (<13.3%), second/third and fourth quartiles (>22.5%) of REM sleep percentage. Patients in the first quartile (lowest REM%) were older and had a lower TST and SE, a longer REM latency, a higher WASO, a higher percentage of N2 and N3, and a higher arousal index and AHI compared to the other subgroups. In addition, patients with lower REM percentage showed a higher NIHSS at

Table 1
Clinical characteristics of the stroke/Transient Ischemic attack (TIA) cohort.

	TIA	Stroke
Age	62.8 ± 6.7	61.1 ± 9.7
Body mass index kg/m²	25.3 ± 3.9	28.1 ± 5.1
Smokers (%)	35.7	30.6
Diabetes (%)	20	14.1
Atrial Fibrillation (%)	0	9
Hypertension (%)	55.6	65
Stroke etiology (TOAST)		
No Information	1	5
Large artery	1	19
Cardioembolic	2	31
Small artery	5	17
Dissection or other	0	6
Unknown - evaluated	6	33
Unknown - in evaluation	3	9
>one	0	3
Patent foramen ovale only	1	22
Atherosclerosis < 50%	0	3
Aorta plaque	1	1

Table 2
Sleep polysomnographic and clinical parameter recorded at baseline, and after 3 months.

	Acute Stroke (n = 169), males: 72.3%)	Controls (n = 162), males:72.2%)	P value
Age, year	61.4 ± 9.4	62.1 ± 8.4	n.s.
TIB min	572 ± 98.7	488.7 ± 77.4	<0.0001
TST .min	320.9 ± 93.7	388.2 ± 71.3	<0.0001
SOL min	50.9 ± 58	20.2 ± 22	<0.0001
REM Latency	120.6 ± 89.9	93.3 ± 60.9	0.001
SE(%)	58.2 ± 18.1	83.4 ± 10.3	<0.0001
WASO (%)	38.4 ± 20.9	13.2 ± 9.2	<0.0001
N2 (% TST)	44.7 ± 10.1	47.2 ± 11.2	0.03
N3(% TST)	26.7 ± 11.3	18.3 ± 8	<0.0001
REM(% TST)	17.7 ± 7.4	21.3 ± 6.4	<0.0001
NIHSS score admission	4.2 ± 5.1		n.a.
NIHSS score after 24 h	2.9 ± 3.9		n.a.
NIHSS score at discharge	1.7 ± 3.1		n.a.

Abbreviations: NIHSS=NIH Stroke Scale; SE = sleep efficiency; SOL = sleep onset latency; TIB = total bed time; TST = total sleep time; WASO = wake after sleep onset.

Table 3
Sleep polysomnographic and clinical parameter recorded after 3 months.

Total number of subjects:104	Acute Phase	Chronic Phase	p
TST (min)	318.8 ± 90.8	348.4 ± 81.5	<0.00
SOL(min)	49.9 ± 58.4	27.9 ± 36.4	<0.00
Sleep Efficiency (%)	58.9 ± 18.2	67.1 ± 16.7	<0.00
WASO (%)	36.5 ± 17.3	29.3 ± 15.6	<0.0001
NIHSS score	3.9 ± 4.4	0.7 ± 1.1	<0.001

Abbreviations: NIHSS=NIH Stroke Scale; SE = sleep efficiency; SOL = sleep onset latency; TIB = total bed time; TST = total sleep time; WASO = wake after sleep onset.

discharge with a similar trend observed for NIHSS after 24 h (4 ± 5.5 vs 2.5 ± 3.1 and 2.5 ± 3.2, respectively) but which did not reach statistical significance (p = 0.09). No differences were found in gender, BMI or Ranking scores.

No differences were found for polysomnographic parameters and age between patients classified according to the stroke location (table E3), in the acute phase.

NIHSS at admission was higher in females than males (6.3 ± 6.1vs 3.5 ± 4.4; F = 11.3, p < 0.0001). The trend of NIHSS from admission to discharge was significantly different between sex, as shown in Fig. 1. Post-hoc analysis demonstrated a higher NIHSS at admission in females, while no differences were found at discharge. A significant positive correlation was found between NIHSS at 24 h and N2% (r = 0.20, p = 0.01) and between NIHSS at discharge and N2% (r = 0.18, P = 0.026) while showing a negative correlation respectively with REM% (−0.19, p = 0.02) in the acute phase and REM % (r = −0.25, p = 0.001) at discharge. Differences were found between genders, with females having a NIHSS at 24 h and at discharge that showed a significant positive correlation with N2%

Table 4
Comparison between sleep parameters and age between subgroups according to quartile of total sleep time (TST) at baseline, upper limit 1° quartile: 263 min, lower limit 4° quartile 385 min (see Fig. 2a).

	TST quartile 1 (n = 43)	TST quartile 2–3 (n = 87)	TST quartile 4 (n = 39)	p<
Age, year	65.1 ± 7.7	60.9 ± 9.5	58.3 ± 9.8	0.00
SOL, min	79.8 ± 80.5	46.3 ± 48.8	29.2 ± 29.7	0.00
REM Latency	151.2 ± 75.2	118.3 ± 90.2	94.5 ± 95.3	0.02
SE, %	38.1 ± 14.8	60.6 ± 12.4	74.9 ± 10.4	0.00
WASO, %	56.7 ± 14.6	35.8 ± 17.8	24.2 ± 19.4	0.00
REM, %	14.1 ± 8.1	18.4 ± 6.2	20.2 ± 7.7	0.00
ΔNIHSS (0–3 months)	−3±3.7	−3.5 ± 4.5	−3.7 ± 5.1	n.s.

Abbreviations: SE = sleep efficiency; SOL = sleep onset latency; TIB = total bed time; TST = total sleep time; WASO = wake after sleep onset.

Table 5
Comparison between sleep parameters and age between subgroups according to quartile of REM% at baseline, upper limit 1° quartile 14.8%, lower limit 4°quartile 23.2% (Fig. 2b).

	First Quartile (n = 43)	2nd-3rd Quartiles (n = 79)	4th Quartile (n = 47)	p =
Age, year	64.7 ± 8.5	61.6 ± 8.7	58.1 ± 10.5	<0.00
TST, min	268.3 ± 99.2	299.9 ± 89.1	353.5 ± 76.2	<0.00
REM Latency	189.4 ± 113.4	109.1 ± 65.7	81.6 ± 69.8	<0.00
SE, %	46.2 ± 17.2	60.7 ± 16.9	64.9 ± 16	<0.00
WASO, %	51.9 ± 20	34.7 ± 16.1	32.3 ± 23.7	<0.00
N2, %	50.1 ± 13	44.4 ± 8.5	40.4	<0.00
N3, %	29 ± 14.4	27.4 ± 10.3	23.3 ± 9.1	0.04
Arousal Index (n/h)	27.2 ± 16.4	22.4 ± 10.7	8.8 ± 9.8	<0.01
AHI, (n/h)	28.3 ± 24.7	20.2 ± 16.3	16.4 ± 15.2	<0.01
NIHSS score after 24 h	4 ± 5.5	2.5 ± 3.1	2.5 ± 3.2	0.09
NIHSS score at discharge	2.9 ± 4.7	1.4 ± 2.4	1.2 ± 1.5	0.01
ΔNIHSS (0–3 monts)	−3.7 ± 4.2	−2.9 ± 4.6	−4±4.4	n.s.

Abbreviations:NIHSS=NIH Stroke Scale; AHI = apnea/hypopnea index; desaturation index; SE = sleep efficiency; SOL = sleep onset latency; TST = total sleep time; WASO = wake after sleep onset.

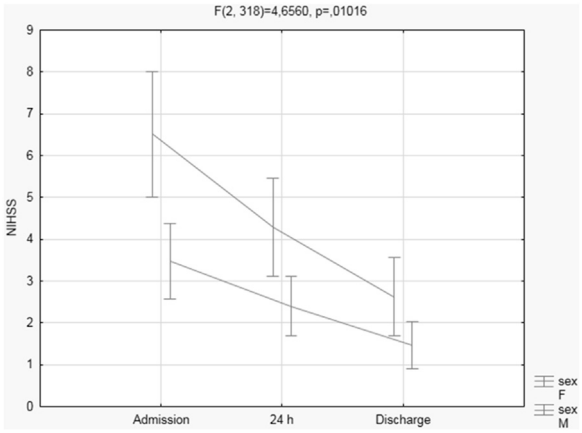

Fig. 1. Trends of NIHSS in the acute phase from admission to discharge separately for males and females.

(r = 0.44, p = 0.003; r = 0.43, p = 0.004) and negative correlation with N3% (r = −0.2, p = 0.02; r = −0.47, p = 0.001); while in males, both NIHSS at 24 h and at discharge negatively correlated only with REM% (r = −0.47, p = 0.001; r = −0.27 p = 0.003). Taken together, the data suggest that strokes with a higher NIHSS in the acute phase or at discharge tend to result in more sleep fragmentation as reflected by a decrease in REM sleep and N3 sleep and a corresponding increase in N2%.

As shown in Fig. 2a, the improvement of TST from the acute to the chronic phase of stroke was significant only for patients with TST in the lower quartile at baseline (MANOVA p < 0.0001). Similarly, changes over time of REM sleep percentage improved in patients in the lowest quartile of REM percentage at baseline and decreased in patients in the highest quartiles (MANOVA p < 0.0001), as shown in Fig. 2b.

Changes of NIHSS from admission to 3-months follow-up was significantly influenced by sex and quartiles of TST in the acute phase (MANOVA p = 0.01), as shown in Fig. 3.

At baseline, differences were not found between patients with TIA or Stroke for sleep indices except for REM Latency (167 ± 77.5 vs 115 ± 90 min, p = 0.01) and Arousal index (29.5 ± 18.6 vs 21.6 ± 11, respectively p = 0.007). At follow-up, a statistically significant difference was found only for Arousal index, still higher in patients with TIA (33.5 ± 15.7 vs 22 ± 9.9, respectively; p = 0.001) (see table E4).

4. Discussion

The present prospective polysomnographic study investigated changes in sleep architecture in a large cohort of patients with ischemic stroke. This study confirms a severe sleep disruption in the acute phase of stroke, as well a significant improvement of sleep quality during the three months after stroke, without reaching, however, a complete normalization. In particular, sleep efficiency and REM sleep are particularly reduced in the acute phase and associated with a negative impact on stroke outcome. On the other hand, a significant amelioration of stroke severity in terms of NIHSS, was associated with improvement of sleep parameters. The amelioration of sleep quality seems to be more significant in a subgroup of older patients with a more severe sleep loss in the acute phase. In particular, a lower REM sleep percentage (lower than 14%) was accompanied by a higher severity of stroke, and a lower sleep efficiency. Interestingly, this subgroup of patients also had a higher AHI, consistent with the hypothesis that sleep is altered globally in this group. Furthermore, a gender difference was found in terms of sleep quality and stroke outcome. Specifically, the reduction of TST correlated with worse outcomes in females, whereas a reduction in REM sleep correlated with worse outcome in males. These gender differences have never been reported and are challenging to understand. We hypothesize that the well-known increased incidence of insomnia and OSA in women and men, respectively, may play a role before the occurrence of stroke.

The observed alterations of sleep architecture are in agreement with the high prevalence of acute insomnia in stroke patients that tend to improve over time [7]. The acute insomnia may be a direct consequence of either the infarct, the result of environmental factors (light, noise on stroke units), or comorbidities (SDB, depression, pain) described in up to half of all patients during the first month [7,32,33]. Reduced sleep duration has been shown to be strongly associated with poor functional outcomes and neurocognitive dysfunction among stroke survivors [34]. A recent metanalysis confirmed that prevalence of insomnia is considerably higher in stroke survivors compared to the general population (ranging from 32.2 to 40.7% of cases depending on the tools of investigation). Greater insomnia symptoms were indicated in those with comorbid depression and anxiety [35]. Interestingly, a prospective cohort study with continuous full band electroencephalography in a small sample of patients with acute cortical ischemic stroke recorded at stroke units with similar criteria of inclusion, found a disruption of sleep architecture in these patients with sleep stages alternating in a random manner, both during day

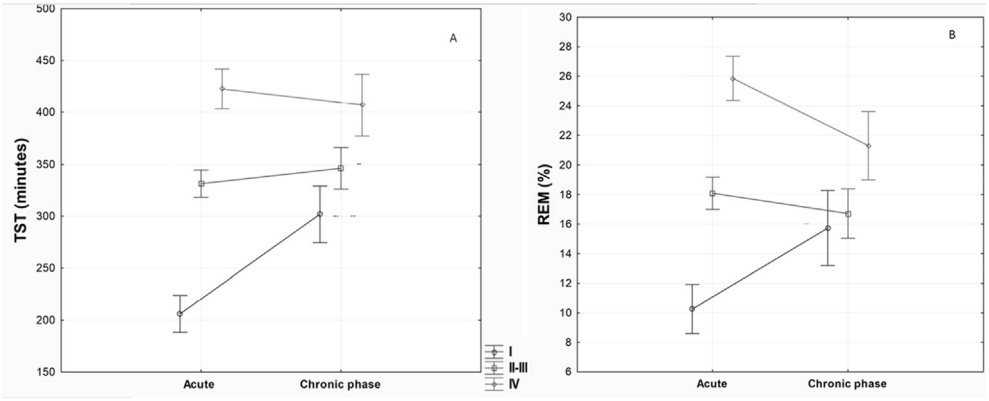

Fig. 2. a: Changes in Total Sleep Time (TST) from acute to chronic phase in the three subgroups of patients classified according to the quartile of TST distribution at baseline evaluation. Post-hoc comparison: <0.001 for all the tests. Fig. 2b: Changes in REM sleep percentage from acute to chronic phase in the 3 subgroup of patients classified according to the quartile of REM distribution at baseline evaluation. Post-hoc comparison: <0.001 for all the tests.

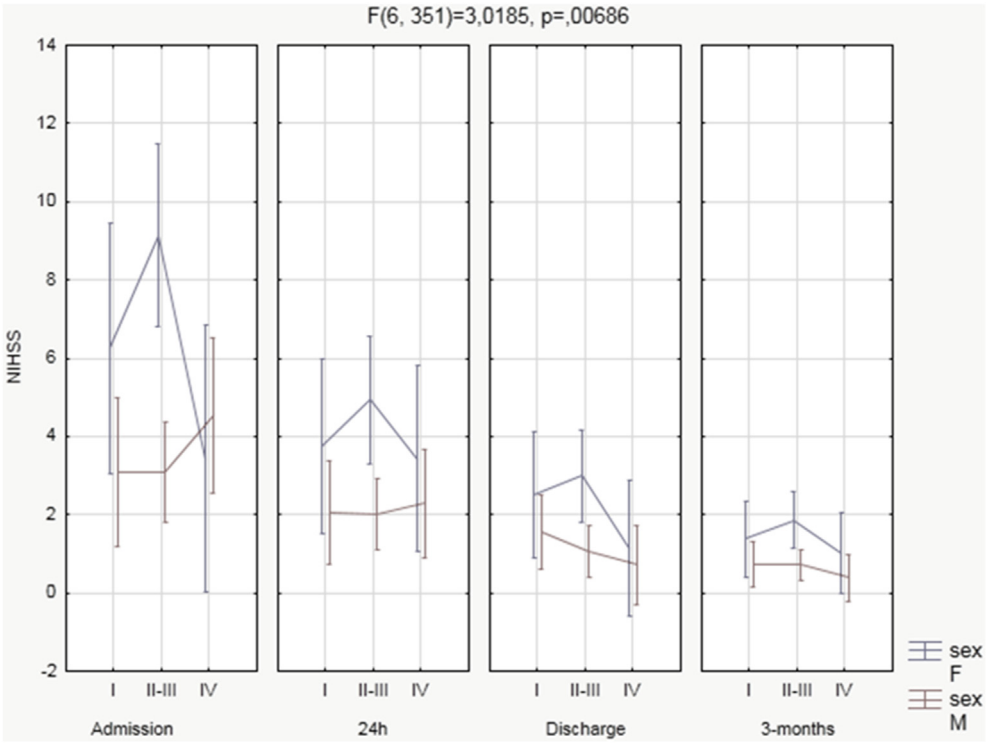

Fig. 3. Trends of NIHSS from the acute phase to 3-months follow-up separately for sex and quartiles of TST distribution (I, II-III-IV) at baseline evaluation. Post-hoc comparison: <0.001 for all the tests.

and during night-time sleep. The authors also found an absence of REM sleep during night-time in 10 out of 13 patients and lack of N3 sleep in those with secondary deterioration [32]. Our results showed a negative correlation between NIHSS and N3%, especially in patients with the highest sleep disruption, and in females. These results might be explained by EEG changes induced by stroke, hampering correct classification of sleep stages. These include a reduction of sleep spindles and an increase of non-physiological slow wave activity in both hemispheres [36]. Increased SWA after stroke may be the result of altered synchronization within the damaged area and/or of reduced innervation due to severed inputs, rather than because of neuroplasticity [37]. Moreover, increased poststroke SWA could simply be a result of disturbed sleep–wake patterns [37]. While interpreting the results of our study several limitations should be considered: the three different environments for recording may have an impact on the outcomes, although the sample size of the 3 groups mitigates these differences. Moreover, it is impossible to study the acute phase of sleep, in patients in a place different from a stroke unit. The relatively low number of EEG channels did not allow a complete analysis of sleep alterations. Moreover, the comparison between patients in their acute phase and controls is limited by the absence of information about sleep habits before polysomnographic evaluations.

Less commonly, acute insomnia may be directly related to brain damage [38]. Patients with strokes within the paramedian thalamus can also develop insomnia due to an inability to generate sleep spindles due to the disruption of the thalamoreticular system [39]. On the other hand, in our large sample of patients, also taking into consideration the exclusion of the most severe cases, no significant differences in sleep architecture between patients with brainstem (infratentorial) lesions vs those with hemispheric (supratentorial) lesions were found, confirming other previous studies [19,21,40]. We found a significant association between lacunar stroke and low sleep efficiency. An association between asymptomatic cerebral small vessel disease of white matter hyperintensity (WMH), silent lacunar infarction and OSA was reported by a recent metanalysis (Chokesuwattanaskul et al., 2019) [43]. Although we did not find a higher AHI in the subgroup of patients with lacunar stroke, the lower sleep efficiency in these patients may be in part mediated by sleep disordered breathing at baseline. Moreover, an association between poor sleep quality and WMH severity already has been reported and greater waking after sleep onset as determined using actigraphy was related to WMH among midlife women (Thurston et al., 2019) [52].

We have reported in both animals and in this group of patients a significant reduction of REM sleep in the acute phase of stroke, and that this reduction of REM sleep, together with a prolonged REM sleep latency, is linked with poor outcome in humans [23]. Compared with other studies in the field, our study adds information about the changes over time from the acute to subacute/chronic phase. In addition to the improvement of SDB, we found an amelioration of sleep quality after 3 months; these findings validate the idea that during the acute phase of stroke, there is a significant and transitory alteration of sleep architecture. On the other hand, sleep efficiency and TST were still reduced compared to normal controls, and the reduction of REM sleep percentage did not improve across time. We may hypothesize that these changes, mostly reflected by insomnia or sleep fragmentation and a reduction of REM sleep, may signify a persistent marker of the brain damage due to stroke. However, these results need to be replicated by other prospective studies in general population. The origin of the observed acute reduction of REM sleep remains speculative at this point. Since stroke topography is not relevant, other stroke-related changes may be implicated [23]. For example, acute stroke causes the secretion of cytokines from activated microglia at the infarct center during the acute phase of stoke, and cytokines have been shown to suppress REM sleep [23]. These effects could also explain the transitory nature of REM sleep reduction after stroke and the

lack of a link with stroke topography [23].

Moreover, animal models of stroke demonstrate that acute sleep disruption has a detrimental impact on long-term functional recovery and on endogenous brain restorative processes, including axonal sprouting, synaptogenesis, neurogenesis, and angiogenesis [41]. Intervention studies in hyper-acute stroke are lacking. On a fundamental level, effects of sleep on recovery after brain infarction remain enigmatic. However, accumulating evidence suggests that healthy sleep enhances neuroplasticity and recovery after ischemic or haemorrhagic stroke (Duss et al., 2017) [44]. Siengsukon et al. [42] have shown that stroke patients, but not healthy controls, improve their performance in an implicit and explicit motor learning task following a period of sleep and that the magnitude of improvement is associated with the amount of time spent in REM sleep.

In conclusion, in our prospective study, the type of stroke (lacunar vs the others), age and sex seem to be associated with differences in sleep macrostructure and outcome. We confirm a severe and acute insomnia, including difficulty with sleep onset and sleep maintenance, mostly in the oldest patients and in females, while reduction of REM sleep is a persistent and negative prognostic marker of stroke outcome. Further studies investigating the incidence and changes in insomnia over time are needed to employ tailored treatments. In summary, strategies to promote sleep quality following stroke and their subsequent impact on stroke outcome should be a focus of future investigations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2022.06.002.

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