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Frequency and evolution of sleep-wake disturbances after ischemic stroke: A 2-year prospective study of 437 patients

Simone B. Duss [a, b, *], Stefan A. Bauer-Gambelli [a, b], Corrado Bernasconi [a], Martijn P.J. Dekkers [a, b], Corina Gorban-Peric [a, b], Doris Kuen [a], Andrea Seiler [a, b], Michael Oberholzer [a], Filip Alexiev [a, b], Julian Lippert [a], Anne-Kathrin Brill [b, c], Sebastian R. Ott [c, d], Frédéric Zubler [a], Thomas Horvath [a], Markus H. Schmidt [a, b], Mauro Manconi [e, f, a], Claudio L.A. Bassetti [a, b, g, **]

[a] Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland
[b] Interdisciplinary Sleep-Wake-Epilepsy-Center, Inselspital, Bern University Hospital, University of Bern, Switzerland
[c] Department of Pulmonary Medicine and Allergology, Inselspital, Bern University Hospital, University of Bern, Switzerland
[d] Department of Pulmonary Medicine and Thoracic Surgery, St. Claraspital, Basel, Switzerland
[e] Sleep Medicine Unit, Neurocenter of Southern Switzerland, EOC, Ospedale Civico, Lugano, Switzerland
[f] Faculty of Biomedical Sciences, Università della Svizzera Italiana, Lugano, Switzerland
[g] Department of Neurology, Sechenov First Moscow State Medical University, Moscow, Russia

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ABSTRACT

Objective: In the absence of systematic and longitudinal data, this study prospectively assessed both frequency and evolution of sleep-wake disturbances (SWD) after stroke.
Methods: In 437 consecutively recruited patients with ischemic stroke or transient ischemic attack (TIA), stroke characteristics and outcome were assessed within the 1st week and 3.2 ± 0.3 years (M±SD) after the acute event. SWD were assessed by interview and questionnaires at 1 and 3 months as well as 1 and 2 years after the acute event. Sleep disordered breathing (SDB) was assessed by respirography in the acute phase and repeated in one fifth of the participants 3 months and 1 year later.
Results: Patients (63.8% male, 87% ischemic stroke and mean age 65.1 ± 13.0 years) presented with mean NIHSS-score of 3.5 ± 4.5 at admission. In the acute phase, respiratory event index was >15/h in 34% and >30/h in 15% of patients. Over the entire observation period, the frequencies of excessive daytime sleepiness (EDS), fatigue and insomnia varied between 10–14%, 22–28% and 20–28%, respectively. Mean insomnia and EDS scores decreased from acute to chronic stroke, whereas restless legs syndrome (RLS) percentages (6–9%) and mean fatigue scores remained similar. Mean self-reported sleep duration was enhanced at acute stroke (month 1: 07:54 ± 01:27h) and decreased at chronic stage (year 2: 07:43 ± 01:20h).
Conclusions: This study documents a high frequency of SDB, insomnia, fatigue and a prolonged sleep duration after stroke/TIA, which can persist for years. Considering the negative effects of SWD on physical, brain and mental health these data suggest the need for a systematic assessment and management of post-stroke SWD.

1. Introduction

There is increasing evidence that after stroke sleep-wake disturbances (SWD) such as sleep disordered breathing (SDB), insomnia, changes of sleep duration, restless legs syndrome (RLS), excessive daytime sleepiness (EDS) and fatigue are frequent [1,2]. Only limited data are available concerning the evolution of post-stroke SWD over time.

* Corresponding author. Department of Neurology, Bern University Hospital (Inselspital) and University Bern, 3010, Bern, Switzerland.
** Corresponding author. Interdisciplinary Sleep-Wake-Epilepsy-Center, Bern University Hospital (Inselspital) and University Bern, Switzerland.
E-mail addresses: simone.duss@insel.ch (S.B. Duss), claudio.bassetti@insel.ch (C.L.A. Bassetti).

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Nonstandard abbreviations and acronyms

AHI	Apnea-Hypopnea Index
BDI-II	Beck Depression Inventory second edition
EDS	Excessive Daytime Sleepiness
ESS	Epworth Sleepiness Score
FSS	Fatigue Severity Scale
ICSD-3	international classification system of sleep disorders, 3rd edition
IRLS	International Restless Legs Scale
ISI	Insomnia Severity Index
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
PSQI	Pittsburgh Sleep Quality Index
REI	Respiratory Event Index
RLS	Restless Legs Syndrome
SDB	Sleep Disordered Breathing
SSR	Swiss Stroke Registry
SWD	Sleep-Wake Disturbances
TIA	Transient Ischemic Attack
TOAST	trial of ORG 10172 in acute stroke treatment

The best characterized post-stroke SWD is SDB, which has been assessed in more than 100 studies. Two recent meta-analyses - including 89 and 132 studies, respectively - reported similarly high frequencies with an apnea-hypopnea index (AHI, derived from polysomnography) or a respiratory event index (REI, derived from respirography not containing an electroencephalogram required for sleep staging) > 5/h in 2/3 and > 30/h in 1/3 of patients with a relative stability from acute to chronic stroke [3,4].

Studies on non-apnoeic SWD are less frequent and inconsistent. In a recent meta-analysis, Baylan and colleagues estimate the pooled prevalence of post-stroke insomnia to be 38% with a great variability (12–68%) across the 22 included studies [5]. To our knowledge, there is only one prospective longitudinal study which reported a stable point-prevalence of insomnia from subacute (28 days post-stroke) to chronic stroke (1 year post-stroke) ranging between 30% and 37% [6]. This is in contrast to a recent meta-analysis, including 28 studies with retrospective and prospective designs, revealing a slight decrease of insomnia prevalence from acute (41%) to chronic stroke (36%) [4].

The same meta-analysis also reported a pooled post-stroke/TIA RLS prevalence of 10.4% (95% CI: 6.4–16.4) and 13.7% (95% CI: 2.3–51.8), respectively, summarizing 13 retrospective and prospective studies, in the acute and only 2 studies in the chronic phase following the event [4].

The majority of studies investigating sleep architectural changes following stroke compared to control participants report a reduction of total sleep time and sleep efficiency in stroke patients [7]. An increase of post-stoke sleep duration that seems to normalize over time has been described in severely affected patients with large hemispheric or thalamic lesions [8,9].

The most frequent daytime symptoms following stroke appear to be EDS and fatigue, but with largely varying frequencies depending on the method of assessment. The reported frequency of post-stroke EDS in the most currently available review ranged from 6 to 49.5% in 18 studies using the Epworth sleepiness scale (ESS) as the method of assessment (the mean ESS score ranged between 7.7 and 12) [10]. The estimated pooled prevalence of fatigue in a recent meta-analysis including 22 studies was 50% (95% Confidence Interval: 43–57%) and was reported to remain stable from acute to chronic stroke [11].

Looking at multiple SWD within the same population of stroke/TIA patients is important, since SWD are frequently comorbid and new data suggests that the presence of multiple SWD, rather than isolated SWD, is associated with a higher cardiovascular risk in the general population [12,13]. In the absence of prospective and longitudinal studies assessing the frequency and long-term course of multiple SWD in stroke and TIA patients, the aim of this paper was to assess systematically and prospectively the frequency and evolution over 2 years of six types of SWD (SDB, insomnia, fatigue, EDS, changes of sleep duration and RLS) in a single cohort of patients with ischemic stroke and TIA. Since ischemic stroke and TIA share the same pathophysiological mechanisms and in order to facilitate the comparison with other studies with similar populations, we decided to investigate both conditions performing joint and separate analyses.

2. Patients and methods

2.1. Patients

In this prospective cohort study, patients with ischemic stroke or TIA admitted to the stroke units of the Departments of Neurology at the Bern University Hospital (recruitment period: 7/2015-1/2018) and at the Neurocenter of Southern Switzerland of the Ospedale Regionale di Lugano (recruitment period: 11/2015-7/2016) were included and followed-up over a total time period of 3 years (last patient follow-up February 2021). The study was registered at ClinicalTrials.gov (NCT02559739) and approved by the local ethics committees of Bern and Lugano (Switzerland).

Patients were eligible for inclusion if they had a confirmed ischemic stroke or TIA, were 18–85 years of age and were able to give informed consent. Clinical unstable patients (e.g. coma/stupor, severe heart failure, persisting oxygen-dependency) and those with primary hemorrhagic stroke were not eligible. Further exclusion criteria were pregnancy and drug/alcohol abuse. Inclusion was performed consecutively during the acute hospitalization (VISIT 1, day 1–7, M±SD = 2.1 ± 1.5 days). Follow-up visits took place at 5 predefined time-points: 1 and 3 months post-stroke (VISIT 2 and 3), as well as 1, 2 and 3 years post-stroke (VISIT 4–6). The study schedule is shown in Table 1.

3. Methods

During the acute hospitalization (VISIT 1, day 1–7) patients' demographics, level of education, height, weight and neck-, waist- and hip-circumferences were assessed.

Stroke and TIA characteristics including stroke severity by National Institute of Health Stroke Scale (NIHSS), time of stroke onset, stroke localization, aetiology according to TOAST criteria [14] and acute reperfusion therapy (intravenous thrombolysis and/or mechanical thrombectomy) were determined. Patients underwent brain neuroimaging within clinical routine and lesion location was documented according to vascular territories. When no lesion could be detected in neuro-radiological imaging, as per definition is the case for TIA, localization was inferred from the clinical symptoms, whenever unambiguously possible or otherwise classified as not known.

Pre-stroke medical history included medication and treatments, as well as pre-existing cardiovascular risk factors such as family history, arterial hypertension (blood pressure ≥140/90 mmHg measured ≥3 times before stroke or patients under treatment for hypertension), diabetes (fasting glucose level ≥140 mg/dL or patients treated for diabetes), smoking status, alcohol intake, hypercholesterolemia (cholesterol level ≥250 mg/dL or previously under treatment), previous history of coronary heart disease or heart

Table 1
Study schedule.

	Day 1–7 (VISIT 1)	Month 1 (VISIT 2)	Month (VISIT 3)	Year 1 (VISIT 4)	Year 2 (VISIT 5)	Year 3 (VISIT 6)
Demographics, stroke characteristics, medical history incl. Respirography Assessed by clinical interview, patients records and neuroimaging	X					
Frequency & type of sleep-wake-behaviour/disturbances Assessed by clinical interview and validated questionnaires (ESS, FSS, PSQI, Berlin Questionnaire, ISI, Becks Depression Inventory revised (BDI-II))	X [1]	X [2]	X	X		
Functional stroke outcome & quality of life Assessed by validated scales (Barthel Index (BI), mRS, EQ-5D-3L (www.euroquol.org))	X [1] (BI, mRS only)		X	X	X	
Subsequent cardio-cerebrovascular events & death Assessed by clinical interview & patients records		X	X	X	X	X
Additional assessment [3] Including assessment of endothelial function, blood pressure, actigraphy, respirography, cognitive dysfunction (MoCA)	X		X	X		

1: retrospective assessment of pre-stroke period.
2: no PSQI, FSS and BDI-II.
3: About one fifth of the recruited patients took part in the additional assessment group undergoing objective measurements of endothelial function, blood pressure, actigraphy, respiratory events and cognitive function (Montreal Cognitive Assessment, MoCA) during acute hospitalization (VISIT 1) and after 3 months (VISIT 3) and 1 year (VISIT 4) following the event. In order to increase adherence to these extensive follow-up assessments, we stopped randomly assigning patients in a 1:5 ratio after inclusion of 260 patients and started assigning all patients that were willing to perform the additional assessments into the additional assessment subgroup. In total, 121 (28%) patients were assigned to this group.

failure.

During the acute hospitalization, patients were screened for SDB by respiratory polygraphy (using the NoxT3 device, Nox Medical, Inc., Reykjavik, Iceland) or nocturnal oximetry (using ApneaLink™, ResMed, Bella Vista, Australia). In a subset of patients respiratory polygraphy was repeated at 3 months and 1 year post stroke/TIA (VISITS 3 & 4, see study schedule, Table 1).

To assess patients' pre- and post-stroke sleep-wake behaviour and disturbances, patients were interviewed and asked to complete questionnaires (see Table 1). The following assessments were performed from VISIT 1 to 5:

1) Insomnia was assessed using the Insomnia Severity Index (ISI) [15]. According to a more recent study by Morin and colleagues, a cut-off score of ≥10 was determined to be most specific and sensitive to define the presence of insomnia [16]. For reasons of comparability with other studies we also report the percentage of participants presenting with an ISI ≥15, the initially suggested cut-off score for clinical insomnia. To investigate the frequency of use of any type of sleep medication, we analysed the following item of the Pittsburgh sleep quality index questionnaire: "During the past month, how often have you taken medicine to help you sleep (prescribed or over the counter)" [17].
2) Restless legs syndrome (RLS). The diagnosis was defined according to the international RLS criteria (ICSD-3, [18]). RLS severity was assessed using the International Restless Legs Scale (IRLS) [19].
3) Subjective sleep-wake-behaviour including the usual bed- and rise-times, sleep latency, sleep duration, daytime napping at week- and weekend-days during the last month. Sleep duration was classified into normal, long, very long, short and very short based on the population reference of 6:58 h with a standard deviation of 1:08 h obtained from the study of Kerkhof and colleagues [20]. Normal sleep duration was defined as the population mean ±1SD (05:50–08:06), short sleep duration and very short sleep duration as less than 1 and 2 SD from the population mean and long and very long sleep duration as more than 1 and 2 SD from population mean.
4) Daytime sleepiness. This was estimated by the Epworth Sleepiness Scale (ESS) [21]. The cut-off score for excessive daytime sleepiness was defined by an ESS score >10.
5) Fatigue. This was estimated by the Fatigue Severity Scale (FSS) [22]. The cut-off score for fatigue was defined by a FSS score ≥4.
6) Severity of depressive symptoms using the Becks Depression Inventory 2nd edition [23].

3.1. Statistics

The analysis of this study was exploratory and included all evaluable patients who met the eligibility criteria. It was primarily based on descriptive statistical methods and no imputation of missing values was performed. To compare changes in mean sleep questionnaires scores and SWD frequencies over the different assessment time points, we used the Wilcoxon signed-rank tests for continuous and the McNemar tests for categorical variables. Tests were conducted at the two-sided 5% significance level and no adjustment for multiplicity was performed. The planned sample size for this study was about 520 patients. The final number of patients enrolled in the pre-determined recruitment period end evaluable for this analysis (437 patients) is still considered adequate in the context of assessing the frequency and evolution of post-stroke/TIA SWD.

4. Results

4.1. Patients

A total of 447 ischemic stroke/TIA patients, 90% at the Bern University Hospital and 10% at the Neurocenter of Southern Switzerland in Lugano, were included. Ten patients were excluded from our analysis dataset because of nonfulfillment of an inclusion criterion or uncertain diagnosis of ischemic stroke or TIA resulting in 437 patients with confirmed ischemic stroke (87%) or TIA (13%) at visit 1. Out of the 437 patients, 363 (83%) could be contacted at month 1, 367 (84%) at month 3, 349 (80%) at year 1, 326 (75%) at year 2 and 287 (66%) at the year 3 visit following the event.

The mean age of patients was 65.1 ± 13.0 years with male predominance (63.8%). The demographic data is shown in Table 2.

4.2. Stroke characteristics and risk factors

Stroke severity at admission was mild to moderate

Table 2
Demographic data and stroke characteristics separate for TIA and stroke patients.

	TIA (N = 56, 13%)	Stroke (N = 381, 87%)
Sex [% male]	60.7%	64.3%
Age [years] (M±SD, range)	68.6 ± 11.0, 30.8–85.4	64.6 ± 13.2, 20.8–85.8
BMI [kg/m^2] (M±SD, range)	26.2 ± 4.6, 19.1–47.8	26.9 ± 4.6,16.1–44.1
NIHSS at admission (M±SD, range)	0.9 ± 1.1, 0-5	3.9 ± 4.7, 0-40
NIHSS at discharge (M±SD, range)	0.1 ± 0.4, range 0–3	1.5 ± 2.2, range 0–18)
Wake-up-symptoms/stroke: % yes	17.9%	20.7%
Previous stroke/TIA: % yes/no/not known	35.7%/62.5%/1.8%	20.2%/79.5%/0.3%
Aetiology according to TOAST		
- % Large artery atherosclerosis	23.2%	20.8%
- % Cardioembolism	33.9%	38.9%
- % Small vessel occlusion	8.9%	7.6%
- % Other determined aetiology	1.8%	4.3%
- % Undetermined aetiology	32.1%	28.4%
Localization in relation to tentorium		
- % supratentorial	32.1%	76.9%
- % infratentorial	5.4%	19.2%
- % both	1.8%	3.1%
- % not known	60.7%	0.8%
Affected hemisphere:	Information available: N = 20	Information available: N = 368
% left/right/both	65%/30%/1%	42%/47%/11%

(NIHSS = 1–15) in most cases (76.9%) and severe (NIHSS ≥16) in 4.2% of stroke patients. TIA patients presented asymptomatic or with mild symptoms (NIHSS ≤4) except for one patient. Cardioembolism (38%) followed by large artery atherosclerosis (21%) constituted the most commonly identified stroke aetiologies in both stroke and TIA patients, whereas in 29% of cases the aetiology remained unknown. Apart from the NIHSS score, stroke characteristics including the aetiology did not differ significantly between stroke and TIA patients. Most ischemic strokes were supratentorial (77%) with an equal affection of the left and the right hemisphere. A good outcome (mRS ≤2) at 3 months was found in 95% of the patients and at 2 years in 88% of the patients. For slightly more than one third of the TIA patients and a fifth of the ischemic stroke patients, the observed acute event was a recurring event. The stroke characteristics are summarized in Table 2.

The three most frequently observed stroke risk-factors were arterial hypertension (61%), dyslipidaemia (58%) and current smoking (25%). Twenty-four percent of the ischemic stroke and TIA patients reported a family history of stroke and 22% indicated to be physically inactive. In 321 out of the 437 included patients an echocardiography was performed as part of the clinical routine during hospitalization and revealed a left ventricular ejection fraction <45% in 4% of patients and a patent foramen ovale in 36%.

4.3. Pre-stroke sleep-wake-disturbances

Ten percent of patients had a diagnosis of SDB made before stroke or TIA and about one third thereof was undergoing positive airway pressure treatment.

Pre-existing insomnia was present in 26.5% of patients according to an ISI score ≥10 and in 9.6% of patients if the more specific but less sensitive cut-off score of ≥15 was used (N = 396). The majority of the patients reported not having used medication to help them sleep during the past month (84.8%, N = 389).

A total of 10.5% of the patients (N = 427) fulfilled the RLS criteria according to the international classification system of sleep disorders (ICSD-3 [18]) prior to stroke admission. Patients fulfilling the RLS diagnostic criteria suffered more often from insomnia compared to patients not fulfilling the RLS criteria (44% vs. 24%, p < 0.01).

The self-reported pre-stroke mean sleep duration was 07:21 ± 01:22h (N = 428). Short (04:42–05:49h) and very short sleep duration (≤04:41h) was reported by 6.3% and 4.4%, respectively. A long (08:07–09:14h) and very long sleep duration (≥09:15) was reported by 15.9% and 6.5% of the patients, respectively.

Pre-stroke EDS (ESS score >10) was found in 12.9% of patients and the mean ESS sum score was 6.2 ± 3.7 (N = 396).

Pre-stroke fatigue (FSS score ≥4) was present in 23.7% of patients (M±SD: 2.9 ± 1.5, N = 388).

4.4. Frequency and evolution of sleep-wake-disturbances post-stroke/TIA

One third of patients suffered from moderate to severe SDB (REI>15/h) in the acute phase of stroke and the REI showed some dependence on age (Spearman's correlation 0.25, p < 0.01). The mean REI was 14.4 ± 15.9/h (M±SD, N = 394) and did not change markedly at 3 months (12.9 ± 11.4/h, N = 70) and 1 year (16.3 ± 14.2/h, N = 59) post stroke (as assessed in a subset of patients). Results are summarized in Fig. 1 and displayed in detail in Table 3.

The prevalence of insomnia (i.e. ≥10 points on the ISI questionnaire) was 28.3% after 1 month and declined to 26.2% at 3 months and to approximately 20% at 1 and 2 years post stroke/TIA, respectively. The comparison of the mean ISI scores at month 1 with all other follow-up time points revealed a significant decrease of the ISI score (Wilcoxon signed-rank tests, all $p < 0.05$, Table 3).

The presence of insomnia was associated with higher scores of the BDI-II (indicating severity of depressive symptoms) at all points in time, but not with comorbid SDB (REI >15/h or REI >30/h). The majority of patients reported not having consumed medication to help them sleep during the past month at any of the follow-up visits (month 3: 88.0%, N = 325, year 1: 86.9, N = 272, year 2: 89.1, N = 236).

One month following stroke/TIA, 9.3% of the participants fulfilled the diagnostic criteria of RLS. The observed decrease to 6.4% at 3 months and subsequent prevalence of 8.7% and 6.9% at 1 and 2 years post stroke/TIA was not statistically significant when compared to month 1 (see Table 3). After 1 month, patients who fulfilled diagnostic criteria of RLS had significantly higher rates of insomnia compared to those not fulfilling the criteria (63% vs 26%, p < 0.01). After 3 months (32% vs 25%, p = 0.55) and one year (25% vs 20%, p = 0.55), insomnia was still more frequent in patients with RLS, but this was not statistically significant.

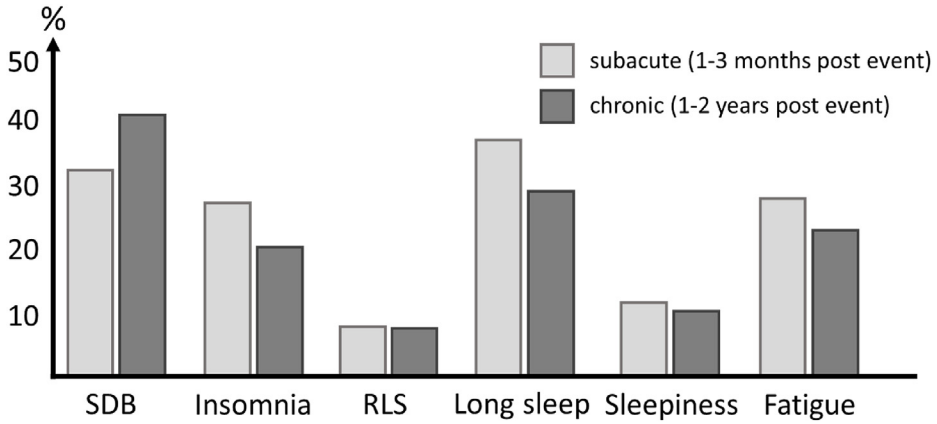

Fig. 1. Frequency of sleep-wake disturbances and prolonged sleep duration after stroke/TIA
Legend: SDB as assessed by REI>15/h; Insomnia as assessed by ISI ≥10; RLS fulfilment of diagnostic criteria; long sleep as defined as ≥08:07h; Sleepiness as assessed by ESS>10, Fatigue as assessed by FSS ≥4. Subacute assessments represent average frequencies from study VISIT 1 to 3, i.e. hospitalization to 3 months post event and chronic assessments represent the average frequencies from year 1–2 following the event (VISIT 4 & 5). SDB was assessed in a subgroup of patients at 3 months (VISIT 3) and 1 year (VISIT 4) following stroke and not at year 2 following stroke (VISIT 5). In the subacute phase of stroke fatigue was assessed only at 3 months following stroke (VISIT 3).

Table 3
Frequency and evolution of post-stroke/TIA SWD.

	Day 1–7 (VISIT 1)	Month 1 (VISIT 2)	Month 3 (VISIT 3)	Year 1 (VISIT 4)	Year 2 (VISIT 5)
REI (events per hour, M±SD, range)	14.4 ± 15.9 (0 −119.2) N = 394		12.9 ± 11.4 (0.4–52.6) N = 70	16.3 ± 14.2 (0.9–69.2) N = 59	
% <5	33.8		27.1	20.3	
% ≥5–15	32.7		42.9	39.0	
% >15–30	18.8		18.6	27.1	
% >30	14.7		11.4	13.6	
Insomnia severity (ISI sum score, M±SD, range)		6.6 ± 5.6 (0-25) N = 322	6.1 ± 5.2 (0-27) N = 324 **p=0.0495**	5.7 ± 5.2 (0-27) N = 313 **p=0.0003**	5.4 ± 5.0 (0-23) N = 284 **p=0.0021**
% ISI ≥10		28.3	26.2	20.1	20.8
% ISI ≥15		10.2	5.8	6.7	5.7
RLS		N = 311	N = 345	N = 312	N = 262
% yes		9.3	6.4	8.7	6.9
Sleep duration (hh:mm, M±SD, range)		07:54 ± 01:27 (03:30 −12:30) N = 335	07:41 ± 01:25 (02:00 −12:00) N = 350 **p=0.004**	07:32 ± 01:13 (04:00 −12:34) N = 336 **p<0.0001**	07:43 ± 01:20 (03:00 −12:45) N = 312 **p=0.0022**
% normal: 05:50–08:06		53.4	57.2	64.3	63.5
% long: 08:07–09:14		25.1	23.7	21.1	20.5
% very long: ≥09:15		14.0	11.4	6.0	10.6
% short: 04:42–05:49		5.7	5.4	7.4	3.8
% very short: ≤ 04:41		1.8	2.3	1.2	1.6
Sleepiness (ESS, sum score, M±SD, range)		5.7 ± 3.8 (0-20) N = 316	5.9 ± 4.1 (0-22) N = 325	5.6 ± 3.8 (0-23) N = 314 **p=0.067**	5.2 ± 3.7 (0-18) N = 286 **p=0.0012**
% ESS score >10		10.1	13.5	10.8	9.8
Fatigue (FSS score, M±SD, range)			3.0 ± 1.6 (1–7) N = 322	2.9 ± 1.5 (1–7) N = 308	2.8 ± 1.6 (1–7) N = 263
% FSS score ≥4			28.3	22.4	24.0

P-values are calculated based on a Wilcoxon signed-rank test for a comparison of each follow-up visit (month 3 until 2 years) to the 1 month visit. For fatigue and depression scores months 3 represented the baseline. McNemar test were used to compare RLS percentage of follow-up visits (month 3 to 2 years) to 1 month visit.

Mean self-reported sleep duration at 1 month following stroke was significantly longer than at 3 months, 1 year and 2 years following the event (Wilcoxon signed-rank test, $p < 0.01$, Table 3). The percentage of patients reporting longer sleep duration than 08:07 h (corresponding to >1 SD from the population mean reported in the study of Kerkhof [20]) was 39% at 1 month post-stroke/TIA and decreased to 35% 3 months post stroke/TIA. At the 1 and 2 years follow-up still 27% and 31% of the patients reported longer sleep duration than 08:07h (see Table 3).

The prevalence of EDS (ESS >10) from 1 month to 2 years post stroke ranged between 10 and 14%. Mean ESS scores remained substantially stable over one year post-stroke/TIA but significantly decreased at 2 years (compared to month 1) following the event (see Table 3).

Fatigue (FSS ≥4) decreased from 28.3% 3 months following the event to 22.4% and 24.0% 1 and 2 years post-stroke/TIA. However, mean fatigue scores remained stable over time (see Table 3).

5. Discussion

In the present paper we describe the frequency and evolution of SWD in 437 prospectively and consecutively recruited patients with acute ischemic stroke or TIA over a period of 2 years. The present study is unique because of its prospective design, the simultaneous investigation of 6 SWD, the use of standard and validated assessments, and the long follow-up period.

This study offers four main findings. First, we confirm a high frequency of SDB and insomnia (and to a lesser extent of fatigue) after ischemic stroke/TIA. Second, we find frequencies of RLS and EDS after stroke/TIA which are similar to those reported in the general population. Third, we provide (to our best knowledge first ever) evidence for a prolonged sleep duration after TIA and ischemic stroke. Forth, insomnia, prolonged sleep duration and EDS improve over the first 2 years following the acute event, while SDB, RLS, and fatigue remain rather stable from the acute to the chronic phase.

The cohort consisted of predominantly elderly patients (65 ± 13) of male sex (~2/3) consistent with the higher stroke incidence reported for men in this age range [24]. Regarding age (mean and dispersion) and sex, our cohort was comparable to the Bernese ischemic stroke/TIA stroke cohort hospitalized between February 2015 and December 2019 at the Stroke Unit of the Bern University Hospital, which is recorded in the Swiss Stroke Registry (SSR) of the Swiss Stroke Society (SSR N: 2102, age M±SD: 67 ± 14, 61% male patients, unpublished data). Our cohort included less severely affected patients when comparing mean NIHSS at admission and stroke outcome after 3 months as assessed by the mRS (SSR NIHSS M±SD: 5.7 ± 6.0, mRS ≤2 in 64% of the patients versus NIHSS M±SD: 3.5 ± 4.5 and mRS ≤2 in 95% of the patients). Consistent with the literature, also in our population hypertension, dyslipidaemia and current smoking were the most frequent risk factors for ischemic stroke and TIA [25].

5.1. Sleep disordered breathing

In the acute phase of ischemic stroke/TIA, REI was ≥5/h in 66%, >15/h in 34% and >30/h in 15% of patients. Whereas the frequency for mild SDB (REI ≥5/h) was comparable to the one reported in stroke/TIA patients in two current meta-analyses of Seiler (AHI/REI ≥5/h in 71%) and Hasan and colleagues (AHI/REI ≥5/h in 67%), the proportion of patients with moderate to severe SDB was lower in our cohort (Seiler et al. AHI/REI>30/h in 30%, 95% CI: 24.4–35.5%; Hasan et al. AHI/REI>30/h in 36%, 95% CI: 22.2–42.6%) [3,4]. Several factors may explain the lower SDB severity in our cohort, including oxygen supply during acute respirography in our study, the inclusion of more less affected patients, and the use of portable limited-channel devices instead of polysomnography. Consistent with Seiler and colleagues [3], the mean REI from the acute to the chronic phase of stroke as assessed in a subgroup of about 60–70 patients stayed relatively stable over time.

Comparisons of our results with those of the general population (~43–45% with at least mild SDB and ~12–15% with moderate to severe SDB [26,27]) suggest a higher prevalence of SDB in ischemic stroke/TIA patients. This underlines the necessity to systematically assess SDB in this population.

5.2. Insomnia

A little more than one fourth of the participants (26–28%) in our cohort scored ≥10 points on the ISI at 1 and 3 months following the ischemic event. At one and two years post-stroke/TIA, this prevalence decreased to only one fifth of the participants. We did not observe a significant increase in insomnia severity compared to the pre-stoke assessment, suggesting that insomnia does not occur de novo following stroke.

A recent meta-analysis of stroke and SWD, including 28 retrospective and prospective studies, revealed an overall prevalence of insomnia of 40.7% (95% CI: 31.8–50.3) for the acute phase, 42.6% (95% CI: 31.7–54.1) for the subacute phase, and 35.9% (95% CI, 28.6–44) for the chronic phase [4]. In general, assessing insomnia with single items reveals higher frequencies compared to assessments with multi-item scales or a diagnostic manual. We know of only one study that also used the ISI to assess insomnia and that recruited a comparable cohort of 241 acute ischemic stroke and TIA patients in terms of age, gender and stroke severity. Although Kim and colleagues [28] excluded stroke/TIA patients with known pre-existing sleep disorders or medication, they report a prevalence of 12% of stroke/TIA patients with moderate to severe insomnia symptoms (ISI ≥15.5) that is comparable to the 10% found in our cohort in the acute phase of stroke when applying the more restrictive cut-off of ≥15. While we find a significant decrease of insomnia severity from subacute to chronic stroke, Glozier and colleagues [6] report a stable course within the first year after stroke in a younger population also including haemorrhagic strokes.

Our results suggest a higher prevalence of insomnia in ischemic stroke and TIA patients than in the general adult population for both pre- and post-stroke assessments of insomnia. Nationwide health surveys in Germany and Switzerland report a prevalence of insomnia disorder of 6% [29], https://www.bfs.admin.ch. A current review by Morin and Jarrin [30] reported a prevalence of 10–15% when combining insomnia symptoms with daytime consequences (as also applies for the ISI questionnaire), corresponding to the average prevalence of 9–15% reported in the landmark review of Ohayon [31].

The proportion of participants indicating the use of sleep medication within the last month of assessment varies between 11 and 15% and is comparable to the proportion reported in the elderly general population (~8–16% [32–34]).

5.3. Restless legs syndrome

Six to 9% of the stroke/TIA patients fulfilled the diagnostic criteria of RLS at 1 month and up to 2 years post stroke. This percentage is slightly smaller than that observed in the few existing previous studies. Lee and colleagues found a prevalence of RLS in 12.4% of the 137 stroke patients at 1 month post stroke [35]; Schlesinger and colleagues in 15% out of 149 stroke patients [36] and Wu et al. in 13% out of 376 stroke and TIA patients [37]. RLS does not seem to be more frequent in stroke/TIA patients than in the general population when compared to data of Ohayon and colleagues who reported a prevalence of 3.9%–14.3% in the general population (based on the International Restless Legs Syndrome Study Group criterion) [38]. Moreover, in our population RLS does not seem to occur de novo following a stroke, since pre- and post-stroke reported frequencies are similar. This is in line with the study of Medeiros and colleagues reporting that all of the 12.5% (out of 96) of the consecutively recruited acute ischemic stroke patients meeting the diagnostic criteria for RLS already reported RLS symptoms before stroke [39]. Our findings and the one of Medeiros and colleagues [39] are in contrast with the study of Lee and colleagues describing that RLS symptoms initiate after stroke, especially after basal ganglia, pons and thalamic lesions [35].

5.4. Sleep duration, hypersomnia, excessive daytime sleepiness, and fatigue

In our cohort, sleep duration and sleepiness were higher at 1 or 3 months post-stroke compared to one or two years after the event, whereas mean fatigue scores stayed stable over time. Our finding of higher sleepiness scores during the first 3 months following stroke that decrease on the long-term are in line with a previous study with thalamic stroke patients [9], which also observed higher sleep needs (hypersomnia) post stroke (as compared to self-reported pre-stroke sleep duration) recovering over time.

On the other hand, studies comparing sleep characteristics in

stroke patients versus controls using polysomnography are suggestive for a shorter sleep duration in the patient group during the early recovery phase of stroke [40]. Importantly, these studies do not consider the evolution of sleep duration and other sleep parameters over time. Comparing pre-with post-stroke values related to sleepiness, sleep-duration and fatigue, only sleep duration seems to increase post-stroke.

Looking at the overall frequency of sleepiness (10–14%) and fatigue (22–28%) pre- and post-stroke/TIA, we found rather lower frequencies than reported in the literature and also not markedly higher frequencies than reported for the general population, especially for sleepiness. Ohayon reports a prevalence of sleepiness of 4–21%, [41]. The validation study of the FSS in a Swiss cohort of 454 participants (age 13–94 years) and a recent population based survey of 2848 middle-aged men and women in Switzerland estimated the prevalence of fatigue to be 18.0% and 21.9% respectively [22,42]).

6. Limitations

The present study has some limitations. 1) Pre-stroke assessments of patients' SWD could be biased secondary to inaccurate memory and general health state just after an ischemic stroke/TIA and should thus be interpreted with caution. 2) The rate of patients lost to follow-up increased from about $1/5^{th}$ at 1 year up to $1/4^{th}$ or more depending on the type of assessment. 3) The REI was only reassessed in a subgroup of patients using respiratory polygraphy. 4) The study population mainly consists of mild to moderately affected stroke patients which may limit generalization of results to more severe cases. 5) The presence of mental disorders (except for depressive symptoms which were assessed with the BDI-II) and the use of medication, which both could influence the prevalence and the evolution of insomnia, fatigue and EDS, were not assessed systematically enough to perform quantitative analyses of the data. 6) The absence of a control population matched for age, sex and the cardio-cerebrovascular risk profile to assess whether ischemic stroke/TIA is associated with a higher prevalence of any of the investigated SWD, since stroke/TIA patients differ from the general population in the mentioned characteristics that might also be associated with the prevalence of SWD.

7. Conclusion

The current study shows that SWD in general, as well as SDB and insomnia in particular, are frequent after ischemic stroke and TIA. Since our sample consisted of patients less afflicted with respect to stroke severity but thus capable of giving informed consent and ability to follow the study procedures, we suspect that frequencies might be even higher in the full spectrum of the stroke population admitted to our tertiary center. SDB, RLS, and fatigue appear to persist over years, whereas insomnia, prolonged sleep duration/hypersomnia seem to improve faster over time. Considering the high frequency and the negative effects of SWD on cardiovascular risk, cognition, mental health and quality of life, our data suggest the need for a systematic assessment and management of post-stroke SWD.

CRediT authorship contribution statement

Simone B. Duss: Conceptualization, Writing – original draft, Visualization, Project administration, Data curation. **Stefan A. Bauer-Gambelli:** Writing – original draft, Investigation, Data curation. **Corrado Bernasconi:** Conceptualization, Formal analysis, Writing – review & editing. **Martijn P.J. Dekkers:** Investigation, Project administration, Writing – review & editing, Data curation. **Corina Gorban-Peric:** Investigation, Writing – review & editing. **Doris Kuen:** Investigation, Writing – review & editing. **Andrea Seiler:** Conceptualization, Investigation, Writing – review & editing. **Michael Oberholzer:** Conceptualization, Investigation, Software, Database Set-up, Writing – review & editing. **Filip Alexiev:** Investigation, Writing – review & editing. **Julian Lippert:** Investigation, Writing – review & editing. **Anne-Kathrin Brill:** Conceptualization, Writing – review & editing. **Sebastian R. Ott:** Conceptualization, Writing – review & editing. **Frédéric Zubler:** Conceptualization, Writing – review & editing. **Thomas Horvath:** Conceptualization, Writing – review & editing. **Markus H. Schmidt:** Supervision, Writing – review & editing. **Mauro Manconi:** Conceptualization, Supervision, Validation, Writing – review & editing. **Claudio L.A. Bassetti:** Conceptualization, Funding acquisition, Supervision, Validation, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest, neither financially nor non-financially.

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