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The estimation of excessive daytime sleepiness in post-stroke patients - a polysomnographic study

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ABSTRACT

Excessive daytime sleepiness (EDS) has been reported in stroke patients. EDS in acute stroke was studied repeatedly, but there is a modest amount of data in post-stroke patients. The aim of this study was to assess the frequency of EDS and characterize sleep architecture in patients > 3 months after stroke and identify factors which may affect EDS.

66 patients were enrolled, of which 33 had experienced stroke. All underwent a standardized overnight, diagnostic single night polysomnography, including electrocephalogram (EEG) leads, electrooculograms (EOG), chin electromyogram (EMG), and electrocardiogram (ECG). Epworth Sleepiness Scale (ESS) was used to measure subjects' level of daytime sleepiness.

We observed similar total ESS score, total sleep time (TST), sleep efficiency, as well as respiratory disturbance index /apnea-hypopnea index (RDI/AHI), oxygen desaturation index (ODI) and mean heart rate in both groups. We observed positive linear correlation between EDS and mean heart rate in the stroke group ($r = 0.46$, $p < 0.05$) as well as between EDS and REM duration ($r = 0.23$, $p < 0.05$). In the non-stroke group EDS didn't correlate with the heart rate or with the REM duration. In the non-stroke group EDS correlated positively with RDI/AHI and ODI index ($r = 0.46$; $p = < 0.05$ $r = 0.41$, $p < 0.05$ and maximal desaturation ($r = 0.55$, $p < 0.05$), this correlation was not observed in post-stroke group. In the both groups we observed negative linear correlation between BMI and saturation (stroke group - mean as well as minimal saturation ($r = -0.458$, $p < 0.05$; $r = -0.578$, $p < 0.05$), non stroke group - minimal but not mean saturation rate ($r = -0.544$, $p < 0.05$). We also noticed in both groups positive correlation between BMI and both AHI and ODI index (stroke group respectively: $r = 0.430$, $p < 0.05$; $r = 0.451$, $p < 0.05$; non-stroke group - BMI and ODI: $r = 0.405$, $p < 0.05$). The positive BMI correlation with RDI/AHI was not significant in the non-stroke group. We noticed that BMI correlates with non-REM sleep N1 ($r = 0.760$, $p < 0.05$) in post-stroke group, while it correlates negatively with REM sleep ($r = -0.709$, $p < 0.05$). There was no such correlation in the non-stroke group.

In summary, in stroke patients subjective daytime sleepiness is associated with heart rate, but not with the severity of OSA. Thus ESS (Epworth Scale Score) may be not as useful as a marker of obstructive sleep apnea (OSA) presence or severity in post stroke patient as in the general population.

1. Introduction

Stroke is the leading cause of disability in adults worldwide (Mukherjee and Patil, 2011). Excessive daytime sleepiness (EDS) is often reported in patients who experienced a stroke; however, it is also commonly reported in the general population (Suh et al., 2016; Bassetti and Hermann, 2016). EDS occurring at least 3 days per week has been reported in between 4% and 20.6% of the population, while severe EDS was reported in 5% (Ohayon, 2008). EDS has been defined by the American Academy of Sleep Medicine as an inability to maintain wakefulness and alertness during the major waking episodes of the day, with sleep occurring unintentionally or at inappropriate times almost daily (Berry et al., 2012). The most common causes of EDS are: sleep disorders, such as sleep-disordered breathing, restless legs syndrome and periodic limb movement disorder, use of sedating medication and improper sleep hygiene. Depression, food intake and probably some

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hormones or neuropeptides involved in the neuroendocrine regulation of sleep in humans may also affect EDS. Sleep disorders and EDS are common in stroke patients. Structural impairment of the central nervous system – subcortical stroke lesion location - has also been reported to be closely associated with post-stroke EDS (Bassetti and Hermann, 2016; Suh et al., 2014; Slater and Steier, 2012; Pack et al., 2006; Koutsourelakis et al., 2008).

Despite the adverse impact on the overall outcome, EDS is commonly underdiagnosed in stroke patients. EDS in acute stroke has been studied repeatedly, but there is a modest amount of data in post-stroke patients (Bassetti and Hermann, 2016). There is little data concerning sleep architecture in chronic stroke as well. Decreased sleep efficiency, increased sleep latency, and decreased rapid eye movement sleep (REM) have been reported in stroke patients, as well as increased prevalence of the REM sleep behavior disorder (Bassetti and Hermann, 2016; Arzt et al., 2010; Arzt et al., 2006; Wessendorf et al., 2000). Alternatively, some studies reported decreased non-rapid eye movement sleep (non-REM) (Wu et al., 2016). Amongst the two main sleep stages, non-REM is characterized by a reduced global brain activity, and REM is characterized by global brain activity similar to that of wakefulness (Chouchou and Desseilles, 2014). There is opposite autonomic nervous system activity during REM and non-REM (Chouchou and Desseilles, 2014). There is growing evidence suggesting an important role for sleep architecture shifts in stroke recovery and outcome, associated with the uniqueness of sleep stages (Bassetti and Hermann, 2016; Hodor et al., 2014).

The aim of this study was to assess the frequency of EDS and characterize sleep architecture in chronic stroke patients > 3 months after stroke as well as identify factors which may affect EDS.

2. Material and methods

A total of 66 patients were enrolled in the study, of which 33 had experienced ischemic or hemorrhagic stroke at least three months (90 days) before admission to hospital. The subjects were selected for the sample through purposive sampling based on the case to case method. All patients were admitted to hospital because of suspected sleep apnea (ESS > 10 or STOP-BANG score ≥3). No patient has diagnosed OSA, whereas hypertension was diagnosed in 95.5%. Males constituted 68.2% of the patients and females constituted 31.8%. The control group had no history of stroke. Thus, the inclusion criteria were experienced ischemic or hemorrhagic stroke at least three months before admission to hospital, age > 18 yo, absence of contraindications for PSG examination, and willing to participate in the study. The exclusion criteria were: myocardial infarction < 4 weeks, decompensated congestive heart failure, acute respiratory insufficiency or acute exacerbation of chronic obstructive pulmonary disease (COPD), severe mental illness and significant mental (including genetic) disorders, inability to undergo PSG, including severe mental retardation or Alzheimer's disease, presence of active malignancy and severe mental disorders. Hypertension and smoking were not exclusion criteria. Baseline clinical characteristics were recorded on admission.

The ESS has good construct validity for use in stroke and is reliable at the cutpoint of 10 (Mills et al., 2013). Total ESS scores ≥11 are considered indicative of clinically significant excessive sleepiness. The control group was selected in consideration of gender, age (difference < 5 y), body mass index (BMI) (difference < 3 kg/m2), hypertension and smoking to avoid the influence of these confounding factors. The prevalence of hypertension and smoking was similar in the study group and in the controls to avoid the influence of confounders.

All patients underwent a standardized overnight, single night polysomnography. Sleep recording included EEG leads (C3, C4, and O2, O3), 2 electrooculograms (EOG), chin electromyogram (EMG), and electrocardiogram (ECG). Thoracoabdominal movement was measured by an inductance plethysmogram, and arterial oxygen saturation (SpO2) by finger pulse oximetry. Sleep was staged manually according to standard criteria (Berry et al., 2012). The following parameters were obtained: AHI (the number of apneas and hypopneas per hour of sleep time); oxygen desaturation index (ODI; the number of oxygen desaturations > 3% per hour of sleep time); and percentage of sleep time below 90% oxygen saturation, total sleep time (TST), sleep efficiency (EF), sleep architecture (%N1, N2, N3 and REM). Abnormal respiratory events were evaluated according to the standard criteria of the American Academy of Sleep Medicine Task Force (Berry et al., 2012).

The study was approved by the Local Ethics Committee.

The software used to perform the statistical analysis was STATISTICA 12 (StatSoft). For quantitative variables, the arithmetical mean and standard deviation values were calculated for the parameters analyzed in the groups. The Lilliefors test and the Shapiro-Wilk test were used to verify the distribution of variables. Quantitative independent variables with a normal distribution were further analyzed by means of an independent t-test. The variables whose distribution was beyond normal were analyzed by means of the Mann-Whitney U test for independent quantitative variables. A correlation analysis was performed to define the relationships between the analyzed variables. Pearson correlation coefficients were established for quantitative variables with normal distributions, and Spearman's rank correlation coefficients for quantitative variables with non-normal distributions. The adopted level of statistical significance was $p < 0.05$.

3. Results

The group consisted of 66 patients: 33 non-stroke and 33 post-ischemic or post-hemorrhagic stroke individuals. The participation of hypertensive subjects in both groups was similarly predominant (94%). The precise clinical characteristics of both groups are presented in Table 1.

We observed a similar total ESS score, total sleep time (TST), sleep efficiency, as well as AHI, ODI index and mean heart rate in the non-stroke and the post-stroke group. However, we noticed a trend to non-significantly less REM total sleep duration in stroke patients than in the non-stroke subjects. The precise results of the polysomnographic sleep architecture analysis are presented in Table 2.

EDS defined as ≥ 11 in ESS score was reported in 33% of the stroke group (n = 11) and in 42% of the control group (n = 14). The ESS score was 7.43 ± 5.17 in the post-stroke group and 8.84 ± 6.42 in controls. We observed a positive linear correlation between EDS and mean heart rate during sleep in the stroke group ($r = 0.46$, $p < 0.05$) as well as between EDS and REM duration ($r = 0.23$, $p < 0.05$). On the contrary, in the non-stroke group, EDS did not correlate with the heart rate or with the REM duration. In the non-stroke group, EDS correlated positively with RDI/AHI and ODI index ($r = 0.46$; $p < 0.05$; $r = 0.41$, $p < 0.05$) and maximal desaturation ($r = 0.55$, $p < 0.05$), while this correlation was not observed in the post-stroke group. AHI > 5 was observed for 13.3% in the post -stroke group and for 26.6% in the controls ($p > 0.05$).

Table 1
Clinical characteristics of the both groups.

	Post-stroke (n:33)		Non-stroke (n:33)		p value*
	mean value	SD	mean value	SD	
Age (years)	61.03	11.43	60.33	10.48	0.797
Height (cm)	170.54	10.09	170.19	6.54	0.866
Weight (kg)	95.12	21.98	96.20	15.87	0.821
BMI	32.52	6.07	33.17	5.51	0.656
Smoking (years)	24.71	4.27	26.25	10.61	0.727
Cigarettes /day	16.00	4.52	17.25	11.27	0.803

BMI- body mass index.

* variables with a normal distribution: independent t-test; variables with non-normal distribution: Mann-Whitney U test.

Table 2
ESS score and results of polysomnographic sleep architecture analysis in the both groups.

	Post-stroke (n:33)		Non-stroke (n:33)		p value*
	mean value	SD	mean value	SD	
ESS score	7.43	5.17	8.84	6.42	0.325
TST (min)	352.08	141.89	361.38	134.09	0.896
latency N1 (min)	41.16	47.28	26.35	27.46	0.475
Sleep efficiency (%)	71.77	24.24	74.17	19.31	0.834
AHI	21.95	17.21	22.96	23.85	0.855
Mean saturation (%)	93.78	2.67	93.22	2.76	0.458
Min. saturation (%)	82.03	6.84	79.53	11.64	0.343
ODI	17.85	19.07	18.84	21.66	0.860
Max. desaturation (%)	14.72	7.24	16.35	11.23	0.603
Mean desaturation (%)	4.60	1.02	3.86	0.80	0.189
Mean HR (beats/min)	62.83	9.22	60.57	8.08	0.349
TST N1 (% sleep time)	14.87	11.44	11.77	7.07	0.540
TST N2 (% sleep time)	46.62	21.96	49.90	24.41	0.782
TST N3 (% sleep time)	25.43	25.05	18.14	31.02	0.611
TST REM (% sleep time)	14.67	7.36	20.18	17.97	0.440

ESS - Epworth Sleepiness Scale, TST- total sleep time, AHI-apnea- hypopnea index, ODI- oxygen desaturation index, HR- heart rate, REM- rapid eye movement.

* variables with a normal distribution: independent t-test; variables with non-normal distribution: Mann-Whitney U test.

In both groups, we observed a negative linear correlation between BMI and saturation (stroke group - mean as well as minimal saturation ($r = -0.458$, $p < 0.05$; $r = -0.578$, $p < 0.05$), non-stroke group - minimal but not mean saturation rate ($r = -0.544$, $p < 0.05$); and positive correlation between BMI and maximal desaturation (stroke group $r = 0.568$, $p < 0.05$; non-stroke group $r = 0.459$, $p < 0.05$).

We also noticed in both groups a positive correlation between BMI and both AHI and ODI index (stroke group respectively: $r = 0.430$, $p < 0.05$; $r = 0.451$, $p < 0.05$; non-stroke group - BMI and ODI: $r = 0.405$, $p < 0.05$). The positive BMI correlation with AHI was not significant in the non-stroke group (Table 3).

We noticed that BMI correlates with non-REM sleep N1 ($r = 0.760$, $p < 0.05$) in the post-stroke group, while it correlates negatively with REM sleep ($r = -0.709$, $p < 0.05$). There was no such correlation in the non-stroke group.

4. Discussion

The study provides a few novel observations regarding EDS and sleep architecture in post-stroke patients. The most interesting result of this study is the lack of correlation between the total ESS score and the severity of OSA (AHI and ODI) in the post-stroke group in contrast to the control group. Such a correlation was described repeatedly in the non-stroke and the general population. In a large study sample of 886 men and 938 women, Gottlieb concluded that sleep disordered breathing (SDB) is associated with excessive sleepiness in community-dwelling, middle-aged and older adults, not limited to those with clinically apparent sleep apnea (Gottlieb et al., 1999). Also, in the community sample without stroke, Arzt observed that ESS correlates with the AHI and with objective measures of sleepiness as the MSLT (multiple sleep latency test) (Arzt et al., 2010). This is with agreement with our observation of the non-stroke group: in our non-stroke group, EDS correlated positively with RDI/AHI and ODI index ($r = 0.46$; $r = 0.41$) as well as with the maximal desaturation ($r = 0.55$), while surprisingly we have not observed this correlation in the post-stroke group. However, there are also contrary data suggesting no correlation between sleep apnea and sleepiness (Sharkey et al., 2013). Thus, the results on AHI and sleepiness are not consistent. It is worth noting that several investigations indicated that the ESS is inapplicable in patient with sleep apnea syndrome because of the low sensitivity and specificity for the diagnosis of OSA (Silva et al., 2011; Hesselbacher et al., 2012).

Table 3
The correlations between BMI and polysomnographic parameters in the both groups.

	Post- Stroke		Controls	
BMI- SatO2	r = −0.458,	p < 0.05	p > 0.05	
BMI- minimalSatO2	r = −0.578	p < 0.05	r = −0.544	p < 0.05
BMI- maximal desaturation	r = 0.568	p < 0.05	r = 0.459	p < 0.05
BMI- AHI	r = 0.430	p < 0.05	p > 0.05	
BMI- ODI	r = 0.451	p < 0.05	r = 0.405	p < 0.05
BMI- Non REM N1	r = 0.760	p < 0.05	p > 0.05	
BMI- REM	r = −0.709	p < 0.05	p > 0.05	

BMI- body mass index, Sat O2- oxygen saturation, AHI- apnea-hypopnea index, ODI- oxygen desaturation index, REM- rapid eye movements.
variables with a normal distribution: Pearson correlation coefficients; variables with non-normal distribution: Spearman's rank correlation coefficients.

Similarly to our observation, Arzt previously reported the dissociation of OSA from hypersomnolence in patients with a stroke (Arzt et al., 2010). He has shown that patients with a stroke had less daytime sleepiness and a lower body mass index than subjects without stroke and that there was no significant correlation between the EDS score and OSA. Thus, these results are in agreement with our study. We showed that patients who experienced stroke less frequently reported daytime sleepiness than the non-stroke patients: 33% vs 42%. This observation was also described in other communications, low mean ESS score in patients with stroke: ESS 5,8 and in moderate to severe OSA after stroke: ESS of 6,8 (Bassetti et al., 2006) to 7,2 (Wessendorf et al., 2000; Wessendorf et al., 2001). Wu reported in patients with acute minor thalamic stroke that hypersomnia was more prevalent (Wu et al., 2016).

However, EDS has been reported in acute stroke patients repeatedly (Suh et al., 2016; Suh et al., 2014; Klobučníková et al., 2016; Ding et al., 2016). EDS was present in 20.6% of subjects diagnosed with acute stroke (Klobučníková et al., 2016). EDS was reported in 28 of 199 stroke patients (14.4%) 3 months after stroke (Suh et al., 2016). In the study from 2014, 110 out of 282 acute stroke patients (39.0%) reported more daytime sleepiness than before the stroke (Suh et al., 2014). EDS prevalence observed in our study is similar to that highlighted in other communications. Some differences may emerge from different cut off criteria of EDS in different studies.

It is worth noting that following a stroke, enhanced functional activity has been reported, involving cortical and subcortical areas anatomically or functionally connected to the damaged ones (Grefkes and Fink, 2011). Although the functional meaning of those "hyper connections" is still debated (Rehme and Grefkes, 2013; Liu et al., 2015), it was postulated to represent compensatory neuronal plasticity phenomena (Koch et al., 2016), possibly affecting both arousal state and breathing during sleep (Sacchetti and Della Marca, 2014).

It is estimated that stroke survivors exhibit cognitive impairment, with many experiencing ongoing problems (Wu et al., 2016; Leśniak et al., 2008). The cognitive impairment may affect ability to complete the sleepiness scale and could be partially the explanation of our result. But interestingly, a similar lack of association between the severity of OSA and ESS score as well as less subjective daytime sleepiness compared with individuals from a community sample, despite a reduced sleep time, was observed in patients with heart failure (Arzt et al., 2006). This may suggest the presence of a more common mechanism disturbing the relationship between OSA and self-perception of sleepiness in both groups. Nevertheless, there is a need for more investigations in patients with stroke examining the relationship between ESS and objective measures of sleepiness.

We are in agreement with others that in patients with a stroke, ESS may not be a sensitive marker of hypersomnolence (Arzt et al., 2010). In this study, we show, for the first time, that in post-stroke patients, subjective daytime sleepiness is strongly correlated with the REM duration and heart rate, independently of the OSA severity. This association may be the missing link to explain the phenomenon of less subjective sleepiness in stroke patients. The reduction of REM sleep time after a stroke has been previously described. We noticed a non-significant trend to less REM total sleep duration in stroke patients than in the non-stroke subjects (14.67% vs 20.18%, p = 0.44), and this is in agreement with more strongly expressed reduction in REM sleep duration in the other communications (Arzt et al., 2010; Arzt et al., 2006; Wessendorf et al., 2000). In the study of Arzt, despite less subjective sleepiness and a similar total sleep time, stroke patients had less REM sleep compared with subjects from the community (Arzt et al., 2010). Wessendorf et al. reported that patients with a stroke and OSA had less REM sleep, thicker necks, and a more central type of obesity than non-stroke subjects (Wessendorf et al., 2000). A REM sleep reduction was reported also in people with heart failure (Arzt et al., 2006). After a stroke in the experimental model, the REM sleep of rats was also specifically and profoundly suppressed (Ahmed et al., 2011). Alternatively, the latest report of Wu et al. showed that compared to healthy controls, in patients with acute minor thalamic stroke, hypersomnia was more prevalent; however, the sleep architecture was disrupted by decreased non-REM sleep stages 2 and 3, but not REM (Wu et al., 2016). All observations describe objective disturbances in the sleep architecture and indicate poorer sleep quality.

Heart rate variability (HRV) analysis, used to assess autonomic cardiac activity, highlighted a higher sympathetic modulation during REM sleep. REM is marked by an increased heart rate (HR), and by low-amplitude, high-frequency electroencephalographic rhythms, muscular hypotonia, and brain activity more similar to wakefulness (Chouchou and Desseilles, 2014; Mendez et al., 2006; Cabiddu et al., 2012; Desseilles et al., 2006; Vandeborne et al., 1994). During REM, a strong connection has been identified between HRV and the activity of brain amygdala and insular cortex in positron-emission tomography (PET) imaging. This indicates a greater role of the central brain control of autonomous cardiac modulation during REM sleep (Chouchou and Desseilles, 2014; Desseilles et al., 2006). The observed positive association between daytime sleepiness and REM sleep may probably indicate sleepiness dependence on the central control of the brain regions known to be involved in autonomous modulation during wakefulness. The correlation between HR and excessive daytime sleepiness supports that connection. Thus, the key to changed sleepiness perception after a stroke might be the effect of a reduced activity of certain brain regions because of less REM sleep at night. REM is also associated with memory processes (Maquet et al., 2000; Siegel, 2001; Van Der Helm et al., 2011; Hornung et al., 2007). REM sleep duration can affect the relationship between expected as well as both concurrent and remembered unpleasantness; however, there is little data on REM duration and EDS to compare. We also noticed in post-stroke patients an impact of BMI on sleep architecture: promoting less REM sleep - expressed by a negative correlation ($r = -0.709$, $p < 0.05$), and associating with more sleep N1 ($r = 0.760$, $p < 0.05$). There was no such associations in the non-stroke group. The possible link - less REM sleep may mean less night sympathetic modulation controlled by less integrative brain activity during quasi-wakefulness at night, which results in changes in the subjective self-reported sleepiness and worse memory – needs further investigation. Recently, both reduced and increased sleep duration, as well as hypersomnia/EDS and insomnia, were suggested to increase stroke risk (Bassetti and Hermann, 2016; Harris et al., 2014).

In obstructive sleep apnea (OSA), repetitive sympaticotony will affect the HR variability in both the REM and non-REM periods, thus further studies are needed to estimate heart rate changes and their correlation separately in the REM and non-REM sleep.

Because OSA is a well-known risk factor for stroke, the result of similar AHI/RDI and ODI in the two groups may be considered surprising. However, in both studied groups, the BMI, age, prevalence of hypertension were similar and both groups had an increased risk of OSA based on STOP-BANG questionnaire (≥ 3).

The limitation of the study is a lack of studies on the mechanisms of sleepiness during a stroke. We have also not assessed post-stroke computed tomography (CT) or magnetic resonance imaging (MRI). Because stroke is not a homogenous disease and both the location and extent of lesion as well as background pathology will affect the clinical outcome on the level of sleepiness and fatigue, thus a lack of the above-mentioned information is an important limitation of the study. Further studies are needed to correlate the sleepiness with the localization, severity, background pathology of stroke. The low subject number is also a limitation; however, the selection of the control group in consideration as well as several possibly confounding factors like gender, age, BMI, hypertension and smoking explain the low number of participants. Another limitation of this study was a lack of measurement of objective sleepiness using (Multiple Sleep Latency Test) MSLT or Maintenance of Wakefulness Test (MWT) (Johns, 2000; Cai et al., 2013; Punjabi et al., 2003). There is controversy surrounding the usefulness of ESS as a marker to definite OSA in post-stroke patients. ESS may not be a useful screening tool for SDB in post-stroke patients (Šiarnik et al., 2018); however, we did not use ESS to predict OSA, but just as a marker of sleepiness. We also did not assess sleepiness depending on the type (central or obstructive) of sleep apnea; however, central sleep apnea can occur in severe obstructive sleep apneas because of a high loop gain, not necessarily as the consequence of a lesion in the central nervous system.

5. Conclusion

In stroke patients, daytime sleepiness according to the ESS score may be associated with heart rate, but not with the severity of OSA. The result of the study indicate that sleepiness is not related to OSA in post stroke patients; however, excessive daytime sleepiness may be related to heart rate, probably in the course of sympathetic hyperactivity. Thus, ESS may not be as useful as of a marker of OSA severity in post stroke patient as in the general population. Further studies are needed to explain the relationship between ESS, sympathetic activity and sleep architecture in post-stroke patients.

Declarations of interest

None.

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