Sleep-Related Breathing Disorders in Cerebrovascular Stroke and Transient Ischemic Attacks: A Comparative Study

Saly H. ElKholy, Hanan A. Amer,† Mona M. Nada,* Mona A. F. Nada,† and Amira Labib**

Summary: Sleep-related breathing disorders are said to be common in patients with established cerebrovascular accidents. The aim of this study was to assess the frequency and characteristics of sleep-related breathing disorders in ischemic stroke and transient ischemic attacks. All patients were subjected to neurologic assessment, Berlin questionnaire (Arabic version), brain computed tomographic scan, and polysomnography along 6 to 8 hours overnight with special emphasis to apnea/hypopnea indices. All assessments were done for 30 patients who had stroke and transient ischemic attacks as well as 20 age- and sex-matched controls. Overall, 13.3% of patients had mild sleep apnea (apnea/hypopnea index, >5), 13.3% had moderate sleep apnea (apnea/hypopnea index, >15), and 34% had severe sleep apnea (apnea/hypopnea index, >30). The sensitivity and specificity of Berlin questionnaire for obstructive sleep apnea diagnosis were 55% and 100%, respectively, for mild sleep apnea, 56.3% and 85.7% for moderate sleep apnea, 66.7% and 83.3% for severe condition. Berlin questionnaire is a moderate sensitive but highly specific screening test for sleep apnea in cerebrovascular diseases. Those who scored high risk should consider polysomnography to specify the type and severity of apnea.

Key Words: Stroke, TIAs, Berlin questionnaire, Polysomnogram, Apnea hypopnea index.

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Sleep-related breathing disorders have been identified as one of the risk factors for cardiovascular diseases, such as coronary heart disease and arterial hypertension (Hung et al., 1990). Sleep-related breathing disorders include obstructive sleep apnea (OSA), central sleep apnea (SA) syndrome, mixed type, and other less common respiratory abnormalities. From a prognostic point of view, it seems that long-term mortality is higher in patients with sleep-related breathing disorders associated with acute cerebrovascular disease (CVD) (Dyken et al., 1996; Good et al., 1996).

Polysomnography (PSG) has been used to study respiratory parameters in patients with CVD. It is able to detect apnea and hypopnea events, thus measuring apnea index, hypopnea index, apnea/hypopnea index (AHI), and detecting oxygen desaturation. Also, Berlin questionnaire, a screening tool that was first used at Berlin on April 1996, is currently used to identify high-risk patients and could be used before the PSG recording (Netzer et al., 1999).

The objective of this study was to analyze the frequency, characteristics, and difference of sleep-related breathing disorders in patients with recent ischemic stroke and with recurrent transient ischemic attacks (TIAs) and to find the relationship between these vascular disorders and the presence of breathing problems during sleep, in an attempt to improve the impact and outcome of the disease on such patients.

From the *Department of Neurophysiology; and †Department of Neurology, Faculty of Medicine, Cairo University, Egypt.

Address correspondence and reprint requests to Saly H. ElKholy, MD, 15-106 Street, Maadi, Cairo 11431, Egypt; e-mail: elkholysaly@yahoo.com.

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PATIENTS AND METHODS

Study Design

A prospective case–control study carried out on patients with recent ischemic stroke or recurrent TIAs, and age- and sex-matched healthy controls. All patients were selected from Neurology Department and Outpatient Clinic of the Kasr El-Aini Hospital, Cairo University, Egypt, during the period from February 2007 to October 2008.

Patients

Thirty patients (18 men and 12 women) with age ranging from 25 to 76 years (mean, 50.67 ± 14.94 years) were divided into 2 groups: Group I and Group II. Group Ia included 15 patients (9 men and 6 women) with acute recent ischemic stroke (8 with thrombotic and 7 with embolic stroke) within 1 to 4 weeks after stroke onset, provided that the patient remains conscious. Their age ranged from 25 to 69 years, with a mean age of 51.07 ± 13.25 years. Group Ib included 15 patients (9 men and 6 women) with recurrent TIAs with age between 25 and 76 years and a mean age of 50.27 ± 16.62 years. Group II included 20 age- and sex-matched healthy controls (8 men and 12 women) with age ranging from 25 to 70 years (mean, 50.15 ± 14.38 years) (Table 1).

Methods

All patients were subjected to the following assessments:

1. Thorough history taking and clinical assessment with special attention to smoking, cardiac condition, the presence of diabetes mellitus, hypertension, dyslipidemias, previous chest problems or medications, and previous abnormal sleep events. Body mass index was measured for all participants.
2. Cardiological assessment included ECG, to assess the presence of myocardial infarction or ischemia, and echocardiography, to detect poor ejection fraction.
3. Laboratory investigations to exclude other causes of sleep-disordered breathing (SDB).
4. Radiological assessment: (1) Brain computed tomographic scan to confirm ischemic nature and exclude hemorrhagic cases. Size and site of infarction was also detected. (2) Chest X-ray to exclude cases with SDB as a result of any chest condition.
5. Assessment of sleep-related breathing disorders: (1) Berlin questionnaire (Netzer et al., 1999): Sleep apnea history was taken by means of the Arabic version of Berlin questionnaire

TABLE 1. Control and Patients Groups' Comparative Data

Variables	Control Group (Mean ± SD)	Patients Group (Mean ± SD)	P
Age (years)	50.15 ± 14.38	50.67 ± 14.94	>0.05
Males (%)	40	60	0.08
Smokers (%)	0.0	46.7	0.0001
BMI (% overweight)	45	50	0.72
MBP (% high)	0.0	50	0.001
Sleep efficiency (%)	68.31 ± 21.54	69.15 ± 23.61	0.45
Av. O_2 saturation (%)	96.23 ± 1.68	94.77 ± 4.22	0.09
Lowest O_2 saturation (%)	80.72 ± 13.69	83.53 ± 9.51	0.21
Apnea n. TST	10.95 ± 25.0	12.43 ± 24.55	0.11
Hypopnea n. TST	50.48 ± 40.25	49.37 ± 39.96	0.46
Apnea index in TST	7.24 ± 24.65	17.01 ± 8.49	0.09
Hypopnea index in TST	4.14 ± 5.69	12.1 ± 13.77	0.009
Apnea/hypopnea index	10.99 ± 27.51	29.11 ± 33.16	0.02

BMI, body mass index; MBP, mean blood pressure; Av.O_2 saturation, average oxygen saturation; TST, total sleep time; $P < 0.05$ is considered significant.

(Appendix 1). Final scoring results classified the patients into high risk for developing SDB (≥2 categories were positive) and low risk (only 1 or no categories were positive). (2) Polysomongraphic recording was performed for patients and controls for at least 6 to 8 hours overnight using Somnologica software (Somnologica version 3.1; Comlab sleep system; Flaga Schwarzer Epos 32 Gmpld medical diagnostic polysomnogram amplifier, Schwarzer, Germany). Polysomnography was scored according to the standardized Rechstchaffen and Kales (1968) criteria. Polysomnography measured sleep onset, sleep efficiency, the number of awakenings, apnea index, hypopnea index, AHI, and desaturation detection (Grigg–Damberger, 2006). Apnea/hypopnea index was graded as follows: normal, <5 events/hour; mild, 5 to 15 events/hour; moderate, 15 to 30 events/hour; and severe, >30 events/hour.

Statistical Methods

Data were statistically described in terms of range, mean (± SD), median, frequencies (number of cases), and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Kruskal–Wallis analysis of variance test. For comparing categorical data, χ^2 test was used. Exact test was used instead when the expected frequency was less than 5. A probability value (P value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs such as Microsoft Excel 2003 (Microsoft Corporation, NYh, Chicago, IL) and SPSS (Statistical Package for the Social Science; SPSS, Inc, Chicago, IL) version 15 for Microsoft Windows.

RESULTS

Groups were selected to be age and sex matched (Table 1). On comparing the different risk factors in the patient group and the control group (Group I and II), a highly significant statistical difference was found as regards smoking and mean blood pressure, whereas no statistical difference was found regarding fasting blood sugar, cholesterol level, triglyceride level, hematocrit value or body mass index.

Berlin Questionnaire

Berlin questionnaire identified 36.6% (n = 11) of the patients as being in the high-risk group for OSA and the remaining 63.3% (n = 19) in the low-risk group.

Polysomnography

Sleep efficiency and the number of apnea or hypopnea events during total sleep time were statistically nonsignificant as well as that of the mean apnea index, while the mean hypopnea index and apnea/hypopnea index in total sleep time showed significant differences (Table 1; Fig. 1).

For each of the two groups, the average O_2 saturation and the lowest O_2 saturation also showed no statistically significant differences (Table 1). On correlating BQ and PSG, most of the subjects scored as high-risk group in BQ [72.7% (n = 8)] had severe OSA, 18.2% (n = 2) presented mild OSA, and another 1 had moderate OSA in PSG.

Regarding the patients in the low-risk group, the majority [52.6% (n = 10)] had no apnea, followed by those [21.1% (n = 4)] who experienced severe SA (Table 2).

The global agreement between BQ score and AHI was 36.6% (n = 11). The sensitivity and specificity of BQ were 55% and 100%, respectively, for an AHI ≥ 5, 56.3% and 85.7% for an AHI > 15, and 66.7% and 83.3% for an AHI > 30. A small change in the probability of not having moderate or severe OSA [negative likelihood ratio of 0.5 (AHI > 15) and 0.4 (AHI, > 30)] was found in subjects with a BQ low-risk score. In the remaining situations, BQ score demonstrated only a little or no change in the disease probability (Table 3).

DISCUSSION

There are several studies that reported a higher frequency of SDB among patients with CVDs. This observation increases the evidence of the presence of some pathophysiological links. The prevalence after stroke was varying between 43% and 72% (Dziewas et al., 2005; Parra et al., 2000; Sandberg et al., 2001).

Community stroke screenings are a commonly used strategy to improve recognition of stroke warning signs. They tend to attract a highly motivated older population containing both the "worried well" (who seem highly interested in staying healthy) and the "worried sick," who are looking for free health advice. However, the benefits of such questionnaires in changing health behaviors remain unknown, may be because larger samples are needed. Also improved communication between screening teams and physicians may boost follow-up and build up more gains (DeLemos et al., 2003).

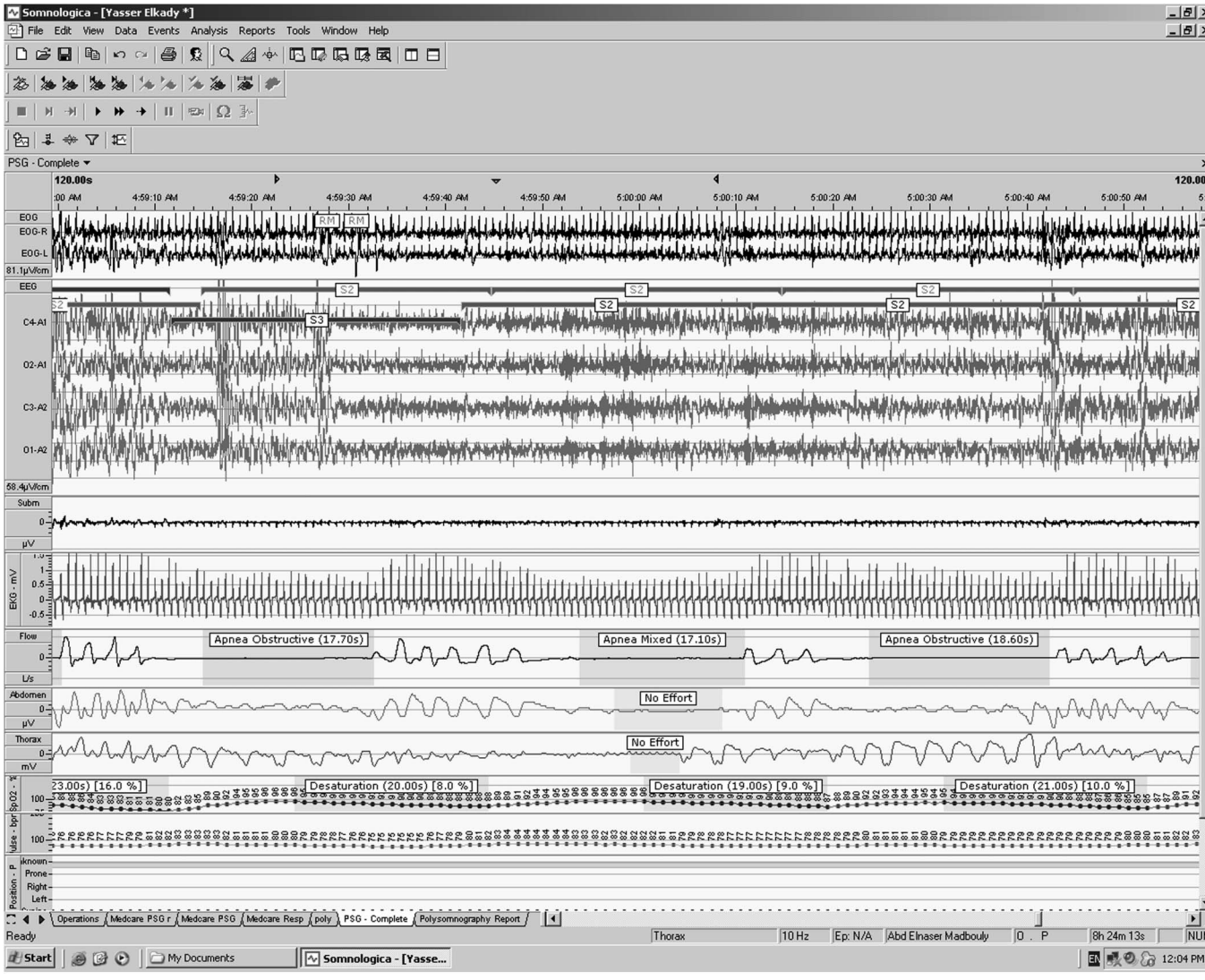

FIG. 1. Polysomnography of a 60-years old male patient with acute ischemic stroke.

Berlin questionnaire, an easily incorporated instrument into daily clinical practice, was our screening tool. It has more privilege above direct questioning about excessive daytime sleepiness and even above the Epworth sleepiness scale. Translation of the questionnaire into the mother language of patients (Arabic) facilitates easier communication and more valid results.

According to BQ, 11 of 30 (36.7%) CVD patients were at a risk of developing SDB. All of them had abnormal PSG of variable severity, presenting to different AHI cutoff moderate sensitivity (55%–66.7%) but a high specificity (83.3%–100%) with little or no change in the negative likelihood ratio. It shows high a positive predictive value but a mild to moderate negative predictive value. This illustrates the importance of performing PSG to high-risk patients detected by screening questionnaire and accentuates the importance of using a sleep questionnaire for screening patients with CVDs, before the overnight sleep record. On a larger scale, it accentuates the diagnostic value of screening questionnaires in neurologic patients in general.

TABLE 2. Relationship Between BQ Score and AHI

AHI/hour	Low-Risk Berlin, n (%)	High-Risk Berlin, n (%)
<5 (normal)	10 (52.6)	0 (0.0)
≥5 (mild)	2 (10.5)	2 (18.2)
>15 (moderate)	3 (15.8)	1 (9.1)
>30 (severe)	4 (21.1)	8 (72.7)
Total (30)	19	11

The patients in this study (whether stroke or TIA patients) were inpatient habituated to hospital atmosphere, so eliminating the first night effect on PSG. Still showed slightly higher tendency for sleep fragmentation than the control subjects, which goes with impaired sleep architecture of such patients because of the effect of CVD itself. Overall, we found no significant difference between sleep efficiency of each of the patients' groups and the control group.

Wessendorf et al. (2000) stated that their patients had a "first-night effect" sleep disruption, and this effect was always exaggerated depending on how elderly the subjects are.

TABLE 3. Diagnostic Value of BQ in Screening Sleep Apnea (Predictive Parameters)

Variables	AHI ≥ 5 (95% CI)	AHI > 15 (95% CI)	AHI > 30 (95% CI)
Sensitivity (%)	55 (50.6–59.4)	56.3 (52.4–60.1)	66.7 (63.5–69.9)
Specificity (%)	100 (100–100)	85.7 (83.2–88.3)	83.3 (80.2–86.4)
PPV (%)	100 (100–100)	81.8 (79.3–84.3)	72.7 (69.8–75.6)
NPV (%)	52.6 (48.4–56.9)	63.2 (59.0–67.3)	79.0 (75.5–82.4)
Positive LR	—	3.9 (5.0–3.1)	4.0 (3.4–4.7)
Negative LR	0.5 (0.3–0.8)	0.5 (0.3–0.9)	0.4 (0.2–0.9)
Accuracy	70.0 (65.1–74.9)	70.0 (65.1–74.9)	76.7 (72.1–81.2)

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; CI, confidence interval.

It is worth noting that Boselli et al. (1998) aimed at abolishing the "first-night effect" that caused biased results of PSG analysis and reported only the second night PSG data, discarding the first. No doubt that this was more accurate, but more time consuming. They found that this had a direct effect only toward lowering the number of awakenings and the arousal indices, whereas other sleep parameters were not significantly affected.

Disentangling the interrelations between SA and CVD remains a challenge, and the clinical significance of the data is still uncertain. However, many studies have proved the higher AHI was related to vascular events. This was simply attributed to causes common between both conditions, including male gender, old age, overweight, smoking, and lack of exercise. Moreover, there are several mechanisms that act to promote development of SA with vascular events. These include sympathetic overactivation, endothelial dysfunction, systemic inflammation, hypercoagulability, and metabolic disregulation (Bassetti and Aldrich, 1999*a*; Hui et al., 2002; Iranzano et al., 2002).

66.7% of our patients had SA eventually distributed between stroke and TIA patients, mainly of the severe grade; it was predominantly of the obstructive type. Bassetti and Aldrich (1999*b*) showed a significantly higher AHI for their patients versus the control group. They also found no significant difference between SA severity in patients with stroke and those with TIAs. They argued that the equal severity of SA—whether the neurologic deficits were transient or permanent—suggested that SA after stroke probably predated the event and supported their argument that SA was not just a manifestation of stroke but more likely a cause or a risk factor rather than a consequence of stroke. Nocturnal apneas initiate a range of pathophysiological mechanisms that end up to promote CVDs, include presumably systemic inflammation, endothelial dysfunction, and hypercoagulability (Grigg–Damberger, 2006).

Bassetti et al. (1996) were the first to report that obstructive apneas were the predominant apnea type in patients with CVDs. Parra et al. (2000) supported the previous findings and added that central apneas were common in the acute poststroke phase, then became significantly lower in the stable phase, whereas the mean number of obstructive events remained unchanged throughout the two phases. This raised the argument that central apneas during the acute phase could be a consequence of the stroke, whereas OSA seems to be a condition that exists before and persists after the stroke.

Because SA is a treatable condition that, if left untreated, is associated with poor functional outcome and Berlin questionnaire (a moderate sensitive but highly specific screening test for SA in CVDs), we recommended such questionnaire to be used in large scale in all stroke units and as a comprehensive screening tool in high-risk groups. Those scored high risk should considered polysomnography to specify the type and severity of apnea.

APPENDIX 1

App (1) إستطـــلاع بـــرلـــين

إستطـــلاع بـــرلـــين

الإسم: .....
العنوان: .....
.....

تقييم النوم

المجموعة (1)

1 أكمل البيانات التالية:
الطول: ..... السن: .....
الوزن: ..... ذكر/أنثى: .....

2 هل تعاني من الغطيط؟
□ نعم
□ لا
□ لا أعرف

إذا كنت تعاني من الغطيط؟

3 صوت الغطيط يكون:
□ أعلى بنسبة بسيطة من النفس.
□ نفس درجة ارتفاع صوت الكلام.
□ أعلى من الكلام.
□ عالي جداً. يمكن سماعه في الحجرات المجاورة

4 ماهي معدلات الغطيط بالنسبة لك؟
□ تقريباً يومياً.
□ 4-3 مرات في الأسبوع.
□ 2-1 مرة في الأسبوع.
□ 2-1 مرة في الشهر.
□ لا يوجد نهائياً أو تقريباً.

5 هل يسبب صوت الغطيط إزعاج للآخرين؟
□ نعم.
□ لا.

6 هل لاحظ عليك أي شخص أنك توقف النفس أثناء النوم؟
□ تقريباً يومياً.
□ 4-3 مرات في الأسبوع.
□ 2-1 مرة في الأسبوع.
□ 2-1 مرة في الشهر.
□ لا يوجد نهائياً أو تقريباً.

المجموعة (2)

7 ماهو معدل شعورك بالتعب أو الإرهاق بعد النوم؟
□ تقريباً يومياً.
□ 4-3 مرات في الأسبوع.
□ 2-1 مرة في الأسبوع.
□ 2-1 مرة في الشهر.
□ لا يوجد نهائياً أو تقريباً.

8 في أثناء فترة استيقاظك هل تشعر بالتعب أو الإرهاق؟
□ تقريباً يومياً.
□ 4-3 مرات في الأسبوع.
□ 2-1 مرة في الأسبوع.
□ 2-1 مرة في الشهر.
□ لا يوجد نهائياً أو تقريباً.

9 هل سبق لك أن غفلت أو سقطت نائماً أثناء القيادة؟
□ نعم.
□ لا.

لو كانت الإجابة بنعم فما هي نسبة حدوث ذلك؟
□ تقريباً يومياً.
□ 4-3 مرات في الأسبوع.
□ 2-1 مرة في الأسبوع.
□ 2-1 مرة في الشهر.
□ لا يوجد نهائياً أو تقريباً.

المجموعة (3)

10 هل تعاني من ارتفاع في ضغط الدم؟
□ نعم.
□ لا.
□ لا أعرف.

BMI =

تسجيل الأسئلة: أي إجابة بداخل مربع تعد رد فعل إيجابي

تسجيل المجموعات: **المجموعة الأولى:** تعد إيجابية في حال وجود رد ين إيجابيين أو أكثر على الأسئلة 2 ← 6 □
المجموعة الثانية: تعد إيجابية في حال وجود رد ين إيجابيين أو أكثر على الأسئلة 7 ← 9 □
المجموعة الثالثة: تعد إيجابية في حال وجود رد واحد إيجابي أو أكثر بالإضافة إلى / أو BMI >30 □

النتائج النهائية: مجموعتين إيجابيتين أو أكثر يشيروا إلى إحتمالية عالية لحدوث وعكات تنفسية أثناء النوم.

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