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SLEEP RELATED BREATHING DISORDERS IN PATIENTS WITH ISCHEMIC STROKE AND TRANSIENT ISCHEMIC ATTACKS: RESPIRATORY AND CLINICAL CORRELATIONS

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Fifty five patients with ischemic stroke and 15 patients with transient ischemic attacks (TIA) were screened for sleep related breathing disorders (SRBD). Apnea-hypopnea index (AHI) and desaturation index (DI) were analyzed. The clinical status was assessed with National Institute of Health Stroke Scale (NIHSS). The patients with stroke were stratified into groups: without (AHI≤5), with mild (5<AHI≤10), and with moderate or severe SRBD (AHI>10). SRBD were present in 36 patients with stroke and in 10 patients with TIA. There were significant differences in the clinical status on admission, as quantified with NIHSS, between stroke patients with mild and moderate or severe SRBD. AHI positively correlated with NIHSS on admission in stroke patients ($r=0.54$, $P<0.01$). The final NIHSS score was significantly greater in patients with moderate or severe SRBD than in those with mild SRBD: 3.4 ±1.9 and 1.8 ±1.2, respectively. Our data suggest that the severity of SRBD is related to the clinical status on admission and it influence the clinical outcome after ischemic stroke.

Key words: *apnea-hypopnea index, ischemic stroke, sleep related breathing disorder, transient ischemic attack*

INTRODUCTION

Sleep related breathing disorders (SRBD) are defined as cessation or reduction of air flow in the airways associated with a concurrent decrease of blood oxygenation saturation. Most often SRBD are due obstruction along the upper airway, the underlying cause of the obstructive sleep apnea syndrome (OSAS).

Another example of SRBD are central sleep apneas, where apnea is secondary to the lack of inspiratory muscle contraction. Mixed apneas are a combination of the two types. A frequent occurrence in clinical practice are overlapping syndromes. The prevalence of OSAS is at least 2% in women and 4% in men in the general population. In selected populations, *e.g.*, in men aged 30-60 years, the prevalence of OSAS exceeds 10% or even 20% according to some authors (1-4).

The ischemic stroke is the third leading cause of death worldwide (5). SRBD are strongly associated with increased risk for stroke and transient ischemic attack (TIA) (2-4, 6), independently of other cardiovascular risk factors (7).

The development of new diagnostic methods, especially polysomnography and portable screening devices measuring breathing parameters during sleep, led to significant progress in the field of sleep medicine and sleep related breathing disorders (8, 9). The diagnostic criteria for SRBD, as described in the Report of the American Academy of Sleep Medicine Task Force (10), made it possible to use comparable parameters of sleep related breathing pathology. In numerous studies it has been shown that SRBD are independent risk factors for hypertension, ischemic heart disease, myocardial infarction, and pulmonary hypertension (11, 12).

Special attention has been drawn toward the cardiovascular diseases related to sleep apneas. This is supported with pathophysiological mechanisms evoked during sleep apneas which lead to the hypoperfusion and procoagulation of blood in some vascular beds. These changes also affect the brain vasculature. The aim of the study was to estimate the incidence of SRBD in patients with ischemic stroke or transient ischemic attack and to correlate the clinical and respiratory parameters in these patients. Our recent results (13) have shown that SRBD is a common pathology in the Polish population of patients with ischemic stroke and TIA.

MATERIAL AND METHODS

Patients

The study was approved by a local Ethics Committee and was conducted according to the Declaration of Helsinki for Human Research. Patients were recruited from those admitted to the First Department of Neurology of the Institute of Psychiatry and Neurology in Warsaw, Poland with the diagnosis of the first-ever ischemic stroke or TIA. Patients with TIA were included into the study only if they presented hemispheric symptoms. Patients with significant reduction of consciousness (Glasgow Coma Scale, GCS<10), symptoms of severe neurological deficit (NIHSS score >20), aphasic patients, or patients with a history of significant heart failure (NYHA >3) or dementia were judged unfit for this study. All included patients gave written informed consent.

Seventy patients (mean age 66.2 ±10.7; 60 males, 10 females, 55 patients with stroke and 15 patients with TIA) without previously diagnosed SRBD were screened for SRBD within the first 7 days of the ischemic event.

The diagnosis of a stroke or TIA was determined by trained neurologists on the basis of clinical symptoms and a CT brain scan performed within the first 6 hours after admission and was based on the criteria described by the American Academy of Neurology.

Clinical assessment

Neurological deficit was assessed according to the National Institute of Health Stroke Scale (NIHSS) (14) on the day of admission and on the day of discharge from the hospital. NIHSS quantifies neurological deficit and estimates the state of consciousness, oculomotor disturbances, facial nerve paresis, limb motor and sensory deficits, and ataxia and aphasic signs. Additionally, functional disability using the Rankin scale (15) was assessed on the day of admission and on the day of discharge.

Risk factors for cardiovascular events such as BMI, smoking, hypertension, diabetes mellitus, atrial fibrillation, and hypercholesterolemia were assessed in the patients. The following laboratory parameters were analyzed: total concentration of cholesterol, LDL and triglycerides (TG) concentration, plasma fibrinogen concentration and the platelet count.

Sleep related breathing disorders evaluation

All patients included to the study underwent an eight-hour nocturnal (between 10 p.m. and 6 a.m.) screening for SRBD with a portable 8 channel recorder (Embletta, Medcare, Iceland). The examination took place within 7 days after the onset of stroke or TIA symptoms. The recorded variables were: nasal flow, abdomen and thorax effort, pulse oximetry, body position, and snoring. Breathing parameters were automatically analyzed with Somnologica Software (Medcare, Iceland) and were always visually checked by the researcher.

The apnea-hypopnea index (AHI) and desaturation index (DI) were estimated according to the American Academy of Sleep Medicine Task Force guidelines and definitions. The patients with stroke were stratified according to AHI into three groups: without SRBD (AHI≤5), with mild SRBD (AHI >5 and ≤10), and with moderate or severe SRBD (AHI>10).

Results are shown as means ±SD. Statistical comparisons were done with one-way ANOVA analysis followed by Tukey`s test in case of the normal distributions of data. When data appeared to deviate from the normal distribution a non-parametric Kruskall-Wallis test followed by Dunn`s *post hoc* test were used. Correlations were calculated using Spearman Rank correlation. A $P<0.05$ indicates statistical significance of differences; the NS acronym refers to non-significant changes.

RESULTS

The mean age of the patients with stroke (67.1 ±11.1) did not differ statistically from that of the patients with TIA (62.7 ±11.0). Nor were there appreciable differences among the subgroups of stroke patients without SRBD, with mild SRBD, and moderate or severe SRBD: 62.8 ±10.6, 66.6 ±11.8, and 70.0 ±10.2, respectively (P=0.26; *Fig. 1*). Likewise, BMI was not statistically different in the patients with stroke and TIA (28.8 ±4.0 and 28.7 ±5.0, respectively), nor among the subgroups of stroke patients: without SRBD - 28.1 ±4.9, mild SRBD - 26.8 ±4.1, and moderate or severe SRBD - 30.0 ±5.3; P=0.17) (*Fig. 1*). Cardiovascular risk factors for stroke were similarly distributed in all groups. In the patients with TIA and with stroke without SRBD, with mild SRBD and with moderate and severe SRBD hypertension was present in 72.9%, 68.4%, 69.2%,

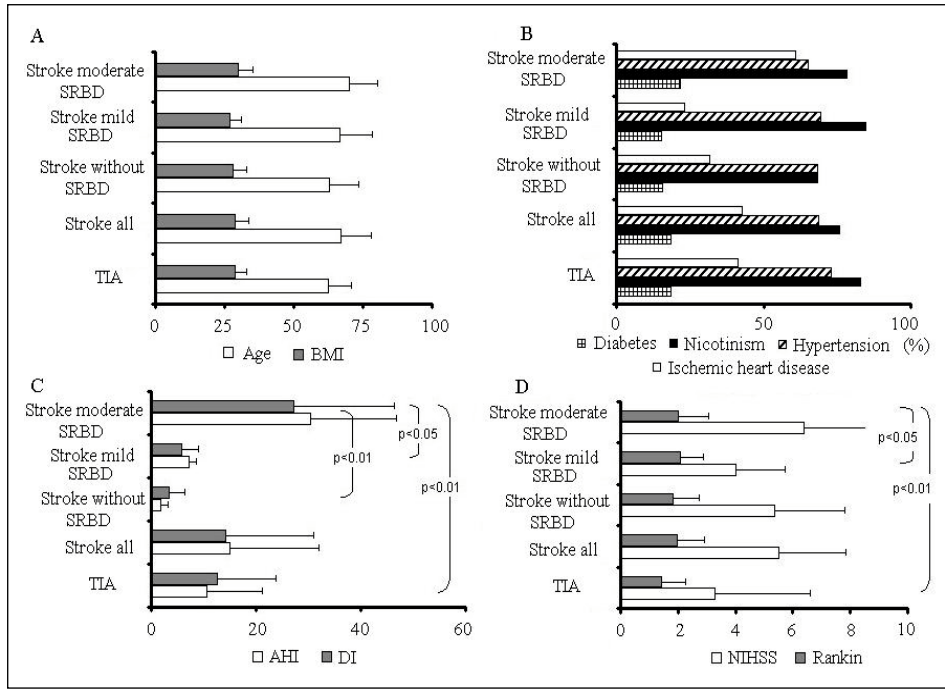

Fig. 1. Demographic data, risk factors, respiratory, and clinical parameters. On the vertical axis there are patients groups, on the horizontal axis the analyzed parameters. A - Age and body mass index in patient subgroups; B - Cardiovascular risk factors in patient subgroups; C - Apnea-hypopnea and desaturation indexes in patient subgroups; D - Clinical neurological deficit (NIHSS scale) and functional disability status on admission (Rankin scale).

and 65.2%, respectively (NS); diabetes in 18.6%, 15.8%, 15.4%, and 21.7%, respectively (NS); and nicotinism in 82.9%, 68.4%, 84.6%, and 78.3%, respectively (NS) (*Fig. 1*). There was a significantly greater incidence of ischemic heart disease in the patients with stroke and moderate or severe SRBD, compared with the patients with stroke and mild SRBD (60.9 and 23.1% respectively, $P<0.05$). There were no differences among the other groups in the incidence of heart ischemic disease. The mean plasma fibrinogen level was significantly higher in the patients with stroke and moderate or severe SRBD, compared with the patients with TIA (4.37 ±0.99 and 3.3 ±0.83; $P<0.01$). The mean platelet count and other biochemical parameters were not significantly different between the patients with stroke and TIA.

AHI>5 was present in 36 (65.4%) patients with stroke and in 10 (66.6 %) patients with TIA (NS). The mean AHI in patients with stroke and TIA was 14.0 ±15.9 and 10.5 ±10.6, respectively; the difference did not assume statistical significance. The percentage of hypopneic and apneic events was not statistically different between the stroke and TIA patients. In stroke patients, apneas

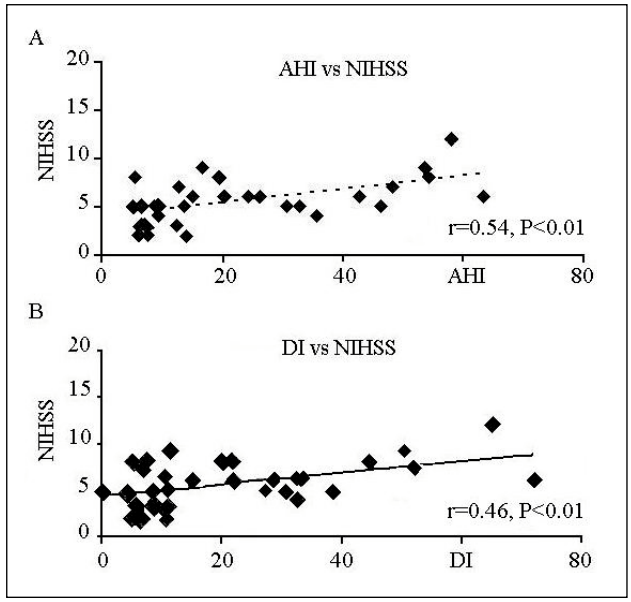

Fig. 2. Correlation between the clinical status, quantified by NIHSS scale, and respiratory parameters on admission: A - Apnea/hypopnea index (AHI) and B - Desaturation index (DI).

predominated and constituted 51.2 ±23.6% of all SRBD events, whereas in TIA patients hypopneas reached 56.0 ±28.1% of all SRBD events. Obstructive apneas were most frequent apneic episodes in both stroke and TIA patients; 77.6 ±12.6% and 80.5 ±13.6%, respectively. Central apneas amounted to 13.2 ±9.6% and 10.5 ±8.6%, and mixed apneas to 9.0 ±5.3% and 8.9 ±6.7% of all apneic episodes in stroke and TIA patients, respectively; all these differences between the two groups of patients being insignificant.

The mean AHI was 1.8 ±1.4, 7.1 ±1.4, and 30.4 ±16.4 in patients with stroke without SRBD, with mild SRBD, and with moderate or severe SRBD, respectively. There were significant differences (non-parametric Kruskall-Walis test, followed by *post-hoc* Dunn`s test) between the patients with moderate or severe SRBD and the other two subgroups ($P<0.05$). Likewise, significance differences were noted in the DI. Patients with moderate or severe SRBD had a mean DI significantly higher than those with either mild SRBD or with no SRBD - 27.2 ±19 *vs.* 5.8 ±3.2 and 3.3 ±3.1, respectively ($P<0.01$). There were significant differences between the stroke patients with mild and moderate or severe SRBD in the clinical status on admission quantified by the NIHSS scale, but not in the disability quantified with the Rankin scale. The patients with moderate or severe SRBD had a significantly higher score in NIHSS than those with mild SRBD (6.4 ±2.1 and 4.0 ±1.7, respectively; $P<0.05$). AHI positively correlated with NIHSS score on admission in the group of patients with stroke ($r=0.54$, $P<0.01$) (*Fig. 2*). Moreover, DI positively correlated with NIHSS score on admission in the same group ($r=0.46$, $P<0.001$). Clinical improvement in stroke patients, presented as

NIHSS recovery index, was similar regardless of the presence of moderate and sever SRBD, mild SRBD, or their lack; amounting to 3.0 ±2.3, 2.2 ±1.2, and 3.2 ±1.9, respectively (NS). However, the final NIHSS score was significantly greater in the patients with moderate or severe SRBD than that in the patients with mild SRBD; 3.4 ±1.9 and 1.8 ±1.2, respectively ($P<0.01$).

DISCUSSION

The aim of the study was to evaluate the incidence of sleep related breathing disorders in patients with stroke and transient ischemic attack in the Polish population and to correlate the severity of stroke and clinical improvement with respiratory parameters. The first studies of SRBD a risk of stroke were conducted in early 1980s. Palomaki et al (16) showed that snoring is a risk factor for stroke. Subsequent studies (17) quantified the risk for stroke in snoring subjects as 3.37. A large cohort study shows the relative risk of stroke of 1.88 in regularly snoring women (18).

Dyken et al (9) and Mohsenin and Valor (8) showed that 70-80% patients with ischemic stroke have sleep apneas. Another study performed with 128 subjects reported the incidence of sleep apneas as 63 % in patients with ischemic stroke and 12.5% in a control group (18). It has also been shown that the incidence of sleep apnea increases in patients with transient ischemic attack (19). These results suggest that SRBD may be a cause rather than effect of ischemic events. Similar results were obtained by Parra et al (20) in a study on a group of 161 patients with ischemic stroke and transient ischemic attacks. The incidence of SRBD was 74.5% in stroke patients and 61.5% in TIA patients. Other studies show a comparable percentage of SRBD, varying from 44% to 72%, in ischemic stroke patients (21-24). The results of the present study are consistent with the above mentioned reports. In our population, SRBD were present in 65% of stroke and 66% of TIA patients, which suggests that these two nosological entities are closely associated with SRBD. Other cardiovascular risk factors, BMI, and age were similar in patients with or without stroke or TIA, so that they seemed to make no difference. Our data also showed that particularly moderate and severe SRBD were associated with more a severe neurological deficit, as quantified by NIHSS, but not with the patient's disability, as quantified by the Rankin scale. Moreover, AHI positively correlated with NIHSS, which is another argument to argue that SRBD are closely associated with ischemic stroke and influence the clinical outcome of stroke. The results also gave a consistent impression that the level of desaturation may be a reliable parameter which correlates well with the neurological status.

Sleep related breathing disorders occur in 30-90% of patients in the acute phase of ischemic stroke. Obstructive sleep apneas predominate (6, 20, 23) in this phase, whereas central apneas are associated with altered state of consciousness,

brain edema, and a brain stem localization of ischemia. During recovery after stroke, the incidence of central apneas diminishes. However, they are still a prognostic factor of poor outcome (20, 23). In our patients, the incidence of central apneas was relatively small, approximating 10%, which was due probably to the inclusion criteria used in this study which left out patients with severe neurological deficits and altered state of consciousness. Obstructive sleep apneas remain at a similar level during recovery after stroke (20, 23). It has been demonstrated in numerous studies that the quantity of SRBD negatively correlates with clinical recovery after stroke. An increased amount of obstructive sleep apneas (particularly taking over 30 seconds) correlates with increased morbidity in stroke patients (23). Our present results also support the view of a poorer outcome in stroke patients with more advanced SRBD.

Interestingly, our results showed that in stroke patients with moderate or severe SRBD, the plasma fibrinogen level was significantly higher than in TIA patients. An elevated plasma fibrinogen in ischemic stroke patients and SRBD has been reported by other authors and is consistent with the possible pathomechanism of procoagulant blood changes in patients with sleep apneas (21).

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