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ПРЕДИКТОРИ ЗА ОБСТРУКТИВНА СЪННА АПНЕЯ ПРИ НЕВРОЛОГИЧНИ ЗАБОЛЯВАНИЯ

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PREDICTORS OF OBSTRUCTIVE SLEEP APNEA IN NEUROLOGICAL DISEASES

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ABSTRACT

Introduction

Obstructive sleep apnea (OSA) is high prevalence and unfortunately underdiagnosed in neurological diseases. Therefore, this study aimed to explore parameters of OSA in ischemic stroke (IS), myasthenia gravis (MG), and multiple sclerosis (MS).

Methods

We prospectively evaluate seventy-two patients with IS, MG, and MS. A full history and clinical examination were carried out. Psychometric scales as the Epworth Sleepiness Scale (ESS), the STOP-BANG, and the Berlin questionnaire (BQ) were implemented for OSA screening. A 3-channel portable recording device was used for diagnosing sleep parameters.

Results

Of the 72 neurological patients, 25 were with IS, 24 with MG, and 23 with MS. OSA was found in 80% of stroke patients, 33% of patients with myasthenia gravis and in 13% of patients with multiple sclerosis. In the stroke group, cervical circumference (OR 1.43, 95% CI 1.063-1.950, p=0.019) and the STOP-BANG questionnaire ≥ 4 (OR 3.239, 95% CI 1.099-9.543, p=0.033) are significant predictors for the presence of OSA. A higher risk in the BQ is a significant independent predictor for OSA (OR 7.222, 95% CI 1.076-48.475, p=0.042) in MG patients, whereas for those with MS, the body mass index (OR 1.297 95% CI 1.007-1.672, p=0.044), the waist circumference (OR 1.148 95% CI 1.010-1.305, p=0.035) and STOP-BANG ≥ 3 (OR 8.302 CI 1.012-68.095, p=0.049) are significant independent predictors for the presence of OSA.

Conclusions

The all-night polygraphy in combination with psychometric tools could be a reliable predictor for OSA in neurological diseases.

KEY WORDS: Obstructive sleep apnea, Predictors of OSA, Stroke, Myasthenia gravis, Multiple sclerosis

INTRODUCTION

Sleep-disordered breathing (SDB) is a major health issue which leads to increased morbidity and mortality (10). Unfortunately obstructive sleep apnea (OSA) remains underdiagnosed in more than 80% of the population (23). Neurological disorders such as ischemic stroke (IS) (12), myasthenia gravis (MG) (27), and multiple sclerosis (MS) (11) are generally of higher risk for

SDB and OSA, despite their different underlying pathophysiological mechanisms.

IS and SDB are in clear bidirectional relationship (1). Some efforts have been made to establish routine screening methods and predictive models for SDB in the acute phase of stroke (19) MG, as a neuromuscular disorder, is also of higher risk for SDB (11). Another well-known neurological condition, the MS is a demyelinating disorder of central nervous system (CNS) which leads to severe disability. However, there are no consistent data on the implementation on OSA screening in MS.

The gold standard for detecting OSA during sleep in neurologically ill patients is the full night polysomnography (PSG). However, due to its complexity and insufficient accessibility, PSG is rarely performed in neurological clinics. Portable devices have been found to successfully detect sleep apnea in the general population as well as in patients with neurological disorders (5, 15). ApneaLink Plus™ (ALP), is a portable three-channel recording tool, categorized according to AASM as Type III device (21). Previous studies with single- and 2-channel ApneaLink™ recorders, compared to polysomnography, have demonstrated good results in the diagnostics of OSA (6). Well-validated in the general population sleep questionnaires such as the Epworth sleepiness scale (ESS), the STOP-BANG, and the Berlin questionnaire (BQ), have also found widespread use in neurological patient populations with a good predictive value.

Since, to our knowledge, there is not a comparative study concerning SDB screening with portable device in hospitalized patients with distinct neurologic conditions, we formulated the main objective in this study: to compare patients' profiles in selected three neurological disorders – IS, MG and MS, with respect to parameters of OSA and to identify the usefulness of screening scales in these three neurological entities in order to predict the occurrence of SBD.

MATERIALS AND METHODS

Patient sample, clinical and anthropometric assessments

Between February 2017 and March 2018, 73 consecutive patients were examined at the University Hospital for Active Treatment in Neurology and Psychiatry „St. Naum", Sofia. All patients were recruited prospectively within 4 days after hospitalization. An informed consent was signed by each participant in the study. Basic anthropometric measurements such as height and weight were obtained, and the body mass index (BMI) was then calculated. We examined neurologically each participant in the study, with focus on some specific characteristics of the explored diseases: in stroke – disease severity, as assessed by the NIHSS, in myasthenia gravis – disease duration, clinical classification by Osserman, and concomitant treatment, and in MS – disease course and duration, and disability, using the Expanded Disability Status Scale (EDSS), as well as MRI data.

The following exclusion criteria were implemented: 1. Alteration of consciousness that would impede the participant to follow the study protocol; 2. Baseline saturation lower or equal to 90%; 3. Respiratory recordings with less than 4 hours recording time or with low quality; 4. Previous history of chronic sleep disorders.

Questionnaires

We used the three most widespread screening questionnaires for OSA. Sleepiness was assessed using the Epworth sleepiness scale (13), where patients with scores equal or greater than 10 were considered sleepy. The STOP-BANG questionnaire (7) and the Berlin questionnaire (BQ) (17) were implemented for OSA detection. For the study purposes, we used STOP-BANG values as scale variables. BQ scores were dichotomized to high or low risk for OSA.

Recording device

ApneaLink™ Plus (ALP) is a 3-channel portable testing device which records pulse, oxygen saturation and nasal airflow categorized as Type III device feasible for SDB screening. It has high correlation coefficients for central (0.939) and obstructive (0.852) apnea indices compared with in-laboratory polysomnography. Overnight sleep data was analyzed manually by a registered sleep technologist. We defined apneas as a 90% signal reduction for a period of ≥ 10 seconds. Hypopneas were defined as a 30% signal reduction, with a ≥ 10 seconds duration with associated ≥4% oxygen desaturation. The apnea-hypopnea index (AHI) was calculated from the total number of apneas and/or hypopneas per hour, divided by the total recording time. OSA was defined as an AHI ≥ 5.

Statistical analysis

All subjects were described using descriptive statistics and frequency analysis. Means and standard deviations (SDs) were calculated for normally distributed continuous variables and compared with unpaired t-tests. Chi-square test was used for the comparison of categorical frequencies. Parametric and non-parametric tests were implemented for the independent sample group comparison. Independent predictors of OSA were determined using a bivariate logistic regression. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each potential predictor. Receiver operating characteristic (ROC) curve were computed for each OSA screening tool for AHI ≥ 5. A p-value of ≤ 0.05 was set as statistically significant. All statistical analysis were performed with the Statistical Package for the Social Sciences, version 23 (IBM Corp., Armonk, NY).

RESULTS

In this prospective cross-sectional study, we recruited 72 patients, 25 with IS, 24 with MG, and 23 with MS. OSA was found in 80% of stroke patients, 33% of patients with myasthenia gravis and in 13% of patients with multiple sclerosis. The level of sleepiness, measured by ESS, did not differ significantly among the groups. The other subjective screening for OSA showed some variations. In absolute values, IS patients had a higher STOP-BANG score, compared to both MG and MS participants ($p < 0.0001$). A high risk for OSA in BQ was calculated in 68% of IS, 33.3% of MG, and in 13% of MS patients ($p < 0.0001$).

Stroke and OSA

Of all stroke patients OSA was diagnosed in 20 (80%) participants. No age and gender difference were observed between patients with and without OSA. A statistically significant difference was found with respect to cervical circumference (p=0.024) and waist circumference (p=0.026) (table 1.). When comparing cardiovascular concomitant diseases, no difference was found between the two groups. There was also no statistically significant difference in stroke severity as assessed by the NIHSS.

Binary logistical analysis found that cervical circumference (OR 1.43, 95% CI 1.063-1.950, p=0.019) and STOP-BANG ≥ 4 (OR 3.239, 95% CI 1.099-9.543, p=0.033) were significant predictors for the presence of OSA in patients with ischemic stroke. Waist circumference would most likely also be a significant factor in a larger sample of patients (OR 1.101, 95% CI 0.998-1.215, p=0.055).

Myasthenia gravis and OSA

Of the 24 patients with myasthenia gravis 5 were classified as Osserman grade I (pure ocular), 9 as Osserman IIa (mild generalized), 8 as Osserman IIb (moderate generalized), and two

Table 1. Subject characteristics for ischemic stroke patients

BMI=Body mass index; AH= arterial hypertension; ESS= Epworth Sleepiness Scale; BQ= Berlin questionnaire; AHI=Apnea-hypopnea index

	Ischemic stroke			
	All	*AHI < 5*	*AHI ≥ 5*	*p-value*
Age, mean ± SD	66.3 ± 9.6	67.4 ± 4.99	66.0 ± 2.12	0.777
Male sex, N (%)	19 (76)	3 (60)	16 (80)	0.221
BMI, mean ± SD	29.3 ± 6	25.02 ± 1.65	30.43 ± 1.37	0.075
Neck circ., mean ± SD	**42.8 ± 4.3**	**39 ± 1.61**	**43.75 ± 0.89**	**0.024**
Waist circ., mean ± SD	**107.9 ± 13.4**	**96.2 ± 6.55**	**110.8 ± 2.63**	**0.026**
AH, N (%)	21 (84)	3 (60)	18 (90)	0.437
Diabetes, N (%)	8 (32)	1 (20)	7 (35)	0.475
Dyslipidemia, N (%)	4 (16)	1 (20)	3 (15)	0.975
Atrial fibrillation, N (%)	6 (24)	1 (20)	5 (25)	0.733
ESS, mean ± SD	5.5 ± 3.2	6.60 ± 1.29	5.20 ± 0.72	0.388
STOP-BANG, mean ± SD	4.8 ± 1.3	4.0 ± 0.45	5.05 ± 0.30	0.120
BQ, N High risk (%)	17 (68)	3 (60)	14 (70)	0,4
NIHSS	2.6 ± 1.1	2.8 ± 0.58	2.6 ± 0.25	0.728

Table 2. Subject characteristics for myasthenia gravis patients

BMI=Body mass index; AH= Arterial hypertension; ESS= Epworth Sleepiness Scale; BQ= Berlin questionnaire; AHI=Apnea-hypopnea index; AChEI= Acetylcholinesterase inhibitors

	Myastenia gravis			
	All	*AHI < 5*	*AHI ≥ 5*	*p-value*
Age, mean ± SD	47.9 ± 12.4	45.38 ± 3.18	52.88 ± 3.76	0.166
Male sex, N (%)	9 (37.5)	6 (38)	3 (38)	1.000
BMI, mean ± SD	24.6 ± 6.3	23.54 ± 0.91	26.56 ± 3.46	0.423
Neck circ., mean ± SD	37.3 ± 3	37.0 ± 0.68	37.75 ± 1.42	0.594
Waist circ., mean ± SD	90.4 ± 14.6	88.44 ± 2.12	94.25 ± 8.06	0.506
AH, N (%)	11 (46)	5 (31)	6 (75)	0.093
Diabetes, N (%)	–	–	–	–
Dyslipidemia, N (%)	1 (4)	–	1 (13)	0.653
Atrial fibrillation, N (%)	–	–	–	–
ESS, mean ± SD	5.6 ± 3.3	4.88 ± 0.66	7.13 ± 1.46	0.117
STOP-BANG, mean ± SD	2.1 ± 1.4	1.94 ± 0.34	2.5 ± 0.5	0.351
BQ, N High risk (%)	8 (33)	3 (19)	5 (63)	0.093
Duration of MG, y	6 ± 6.8	6.06 ± 1.89	5.75 ± 1.86	0.918
AChEI, N (%)	21 (88)	14 (88)	7 (88)	1.000
Corticosteroids, N (%)	8 (33)	5 (31)	3 (38)	0.834
Azathiporine, N (%)	3 (13)	1 (6)	2 (25)	0.490

Table 3. Subject characteristics for multiple sclerosis patients
BMI=Body mass index; AH= Arterial hypertension; ESS= Epworth Sleepiness Scale; BQ= Berlin questionnaire; AHI=Apnea-hypopnea index

	Multuple sclerosis			
	All	*AHI < 5*	*AHI ≥ 5*	*p-value*
Age	40.1 ± 7.5	40.3 ± 1.76	39.0 ± 3.22	0.787
Male sex	6 (26.1)	4 (20)	2 (67)	0.071
BMI	**23.4 ± 5.1**	**22.4 ± 0.90**	**29.9 ± 4.34**	**0.013**
Neck circ.	36.1 ± 4.1	35.5 ± 0.69	40.0 ± 4.58	0.428
Waist circ.	**85.8 ± 12.4**	**83.1 ± 2.08**	**103.7 ± 10.33**	**0.004**
AH (%)	–	–	–	–
Diabetes (%)	–	–	–	–
Dyslipidemia (%)	–	–	–	–
Atrial fibrillation	–	–	–	–
ESS, mean ± SD	5.9 ± 4.5	5.45 ± 1.01	8.67 ± 2.19	0.256
STOP-BANG, mean ± SD	**1.2 ± 0.9**	**1.0 ± 0.16**	**2.3 ± 0.67**	**0.011**
BQ, N High risk (%)	3 (13)	2 (10)	1 (33)	0.387
Duration of MS, y	7.0 ± 7.7	10.1 ± 1.76	5.67 ± 3.48	0.364
EDSS, mean ± SD	3.5 ± 1.8	4.25 ± 0.40	2.67 ± 0.44	0.150
Brainstem lesion, N (%)	12 (52)	11 (30)	1 (33)	0.957

patients as Osserman IV (severe late). OSA was diagnosed in 8 (33%) participants. When comparing patients with and without OSA, no statistically significant difference was found with respect to the basic anthropometric parameters. There was no significant difference in the concomitant cardiovascular diseases either. Disease duration and clinical course of MG evaluated according to the Osserman classification, as well as the intake of disease-specific therapy did not demonstrate any significant differences (table 2).

In the binary logistical regression, the BQ score was a significant independent predictor for the presence of OSA in patients with MG (OR 7.222, 95% CI 1.076-48.475, p=0.042). The presence of arterial hypertension probably also would be accepted as a predictor in a larger sample, as it clearly shows a tendency towards such (OR 6.600, 95% CI 0.970-44.926, p=0.054).

Multiple sclerosis and OSA

Of 23 patients with MS 83% had a relapsing-remitting, and 17% a secondary-progressive disease course. OSA was found in 3 (13%) patients. In the comparison between the MS patients with and without OSA, we found a statistically significant difference with respect to the BMI (p=0.013) and waist circumference (p=0.004). No concomitant cardiovascular diseases were identified in the MS group. No difference was found in terms of the duration, clinical course, or disability of the disease, as assessed by EDSS. As to the presence of brainstem lesion, no significant difference was found when comparing MS patients with present and absent OSA (table 3).

Binary logistical analysis identified BMI (OR 1.297 95% CI 1.007-1.672, p=0.044), waist circumference (OR 1.148 95% CI 1.010-1.305, p=0.035), and STOP-BANG c ≥ 3 (OR 8.302 CI 1.012-68.095, p=0.049) as significant independent predictors for the presence of OSA in patients with MS.

DISCUSSION

In this study we explored the presence of OSA in three different neurological disorders. Of the 75 patients, sleep apnea was found in 31 (43%) which is above that incidence in the general population. Since exclusively clinical evaluation for SDB in neurological patients apparently leads to its underdiagnose (16), we implemented a combination of subjective and objective signs and symptoms, which may be related to OSA in calculate a predictive model of the disorder. This approach has been successfully used also in other studies (5).

Similar to previous studies (14), we found AHI ≥ 5/h in 80% of IS patients. The male sex and age were not significant predictors for the presence of OSA in this patient group, which corresponds to the literature data (19). BMI showed no statistical differentiation between the two groups, although there is a clear trend that would assign it to risk factors. The cervical and waist circumference turned out to be significantly higher in patients with apnea, unlike those with stroke and without apnea. These anthropometric indicators are risk factors for apnea in the general population, and this may be a sign that the OSA predates rather than be a consequence of stroke. The results of cardiovascular concomitant diseases showed no significant significance for the presence of apnea, which corresponds to other studies (14). Others have identified the role of atrial fibrillation (AF) as a risk factor for OSA, which differs from our results. The most likely reason for the lack of statistical significance is that the number of patients studied is small, since AF occurs in 5 people with OSA and in 1 without OSA and also tends to play a role as a predictive risk factor. The results of our study confirm that the severity of the stroke is not a significant factor for the presence of OSA, a conclusion drawn also in previous studies

(5, 19). Our study confirmed the previous opinion that excessive daytime sleepiness, assessed by the ESS scale, was not a characteristic feature of OSA in the neurological disorders we studied (19). In accordance with other studies, the BQ showed to be a weak predictor for OSA in the stroke group (5, 19). Despite the average specificity and sensitivity values for the STOP-BANG questionnaire, this tool can successfully distinguish stroke patients with and without OSA. Although Boulos et al. have shown that the modified version, without the cervical circumference assessment, shows good sensitivity, judging by the fact that the cervical circumference is a significant predictor for OSA in our population, we recommend that the questionnaire be used in its original version (5). In our study the combination of cervical circumference and the STOP-BANG questionnaire ≥ 4 only are significant predictors for the presence of OSA in patient with IS and could be used as a screening combination in the clinical practice.

30% of patients with MG showed an AHI ≥ 5. The prevalence of OSA among patients with MG varies in different studies from 21% to 75% (9). Although limited polygraphy is thought not to be suitable for evaluation of patients with MG, the device was able to distinguish patients with OSA. Our study did not find statistically significant age difference between patients with apnea and without it, but there was a tendency for apneics to be older. Several studies have found that male sex is a risk factor for developing apnea in MG, but we have not found such dependence, probably because of the fact that the men were significantly less in our study and were equally divided into the two patient groups (18). No significant difference was found regarding other anthropometric indicators. Most likely, this is because other atypical factors for the general population affect apnea in MG. Although our patients had no indirect signs of hypoventilation (the lowest and median oxygen saturation had no statistical difference compared to the other two groups of neurological patients who did not have a characteristic night hypoventilation), we did not search properly for hypoventilation during sleep. The main percentage of patients with MG and OSA in our study were with arterial hypertension, which may be due to increased sympathetic tone due to apneas and hypopneas and become an important marker for the presence of apnea in patients with MG. This also has been shown by the binary logistic analysis, which brings arterial hypertension closer to a significance as independent risk factor for the presence of apnea. The duration of the disease showed no link with the presence of apnea, which has been confirmed in other studies (18, 22). The binary logistic analysis found that a high risk result in BQ was an independent predictor for the presence of OSA in MG with sensitivity (63%) and specificity (81%) values. The duration of the disease showed no difference for patients with the presence or absence of OSA. Yeh et al. have found that azathioprine is a strong risk factor for the presence of OSA, but our results did not confirm this conclusion (22).

Studies show prevalence of OSA among MS in the range between 0 and 58% (2). Most likely, this difference is due to the different methodology and patient contingent. In our study, OSA was found only in 13% of the patients. The share of MS patients with positive OSA screening (i.e. AHI >= 5/h) was equal to studies with polysomnography-diagnosed OSA (20), but lower than in other questionnaire-based studies where the OSA prevalence reaches almost 40% (4). No statistically significant difference was found between patients with and without OSA in terms of age and gender. The results were most likely due to the small group of patients involved. A significant difference was found between the two groups of patients in terms of BMI and waist circumference, which confirmed previous studies results (2). In our study we found no statistically significant relationship between subjective daytime sleepiness, as assessed by ESS, and OSA. Several studies found a correlation between ESS and response to the STOP-BANG questionnaire, corresponding to a high risk for the presence of OSA, but without performing a night recording (2, 4). We found a link between the OSA and a positive response to the STOP-BANG questionnaire, but there are no studies in the literature that validated its use in patients with MS. Our study did not confirm the link between the presence of sleep apnea and brainstem lesion, unlike previous studies (3). Probably this is due to the small number of patients studied, the relatively mild course of MS with a small number of progressive forms, and the shorter duration of the disease.

This study has certain limitations. Despite our findings, the examined patient groups cannot be representative for the entire clinical range in each of the explored pathologies. The exclusion of patients with more complicated disease course, mainly due to their inability to follow the study procedures, leads to a certain selection bias. In order to implement a simple screening tool, we chose a device that has certain diagnostic limitations, which some authors find concerning.

CONCLUSIONS

Our results clearly show the necessity for individualized approach to evaluate the need for night respiratory screening in different neurological disorders. The combination of anthropometric and demographic assessment with respiratory polygraphy and sleep scales allow a better prediction of OSA in neurological practice. Further studies with greater sample are needed to cover this interesting topic.

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СЕМЕЙСТВО С КАЛПАИН 3 СВЪРЗАНА ПОЯС-КРАЙНИК МУСКУЛНА ДИСТРОФИЯ С АТИПИЧНО ПРОТИЧАНЕ, ДЪЛЖАЩА СЕ НА НОВА МУТАЦИЯ

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FAMILY WITH CALPAIN 3 ASSOCIATED LIMB-GIRDLE MUSCULAR DYSTROPHY WITH AN ATYPICAL PHENOTYPE DUE TO A NOVEL MUTATION

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