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DAYTIME SLEEPINESS AND POLYSOMNOGRAPHIC VARIABLES IN SLEEP APNOEA PATIENTS [1, 2, 3, 4]

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[4]Running title: Daytime sleepiness and polysomnography.

ABSTRACT

Objective: Excessive daytime sleepiness (EDS) is not invariably present in patients with obstructive sleep apnea (OSAS). This study investigates polysomnographic determinants of EDS in patients with OSAS.

Methods: EDS was assessed using the Epworth Sleepiness Scale and the Multiple Sleep Latency Test (MSLT). Patients had EDS whenever the ESS was > 10 and the MSLT < 5 min. Absence of EDS was defined when ESS was < 10 and the MSLT > 10 min.

Results: We studied 23 male patients with EDS (mean [±SD] Epworth 17±3 and MSLT 4±1 min) and 17 without EDS (Epworth 5±2 and MSLT 16±3 min). Both groups had similar apnea-hypopnea index (62±18 vs 60±20 h-1). Patients with EDS exhibited shorter sleep latency (11±16 vs 18±18 min., p=0.05) and a greater sleep efficiency (90±7 vs. 82±13%, p<0.05) than those without it. Patients with EDS showed lower oxygenation (lowest SaO2 69±12 vs 79±8%, p<0.01; mean SaO2 87±6 vs 90±5%, p<0.05). Sleep stage distribution and arousal index were not different between groups.

Conclusions: Patients with OSAS and EDS are characterized by shorter sleep latency, increased sleep efficiency and worse nocturnal oxygenation than those without EDS. Nocturnal hypoxemia can be a major determinant of EDS in patients with OSAS.

INTRODUCTION

The obstructive sleep apnoea syndrome (OSAS) is characterized by repeated episodes of upper airway obstruction during sleep, nocturnal hypoxemia and sleep fragmentation[1]. Excessive daytime sleepiness (EDS) is frequent but not universally present in patients with OSAS. When present, EDS imposes a substantial burden on quality of life, morbidity, and mortality in patients with OSAS[2] because it is a know risk factor for motor vehicle[3;4] and work-related accidents, and it can result in significant psychological and cognitive deficits[5;6].

The mechanisms explaining why some patients with OSAS complain of EDS whereas others don't are unclear. Some authors have related it to the abnormal sleep structure of these patients (as assessed by the number of arousals during sleep)[2;7;8], but this has not been confirmed by others[9]. Likewise, those studies that investigated a potential relationship between EDS and several indices of nocturnal oxygenation also yielded controversial findings[10;11].

The present study aims at investigating potential mechanisms of EDS in patients with OSAS. Contrary to previous ones, however, we did not tried to establish relationships between all these variables in patients with different degrees of EDS. Rather, we decided to compare several polysomnographic variables in two groups of patients with either absolute absence or clear presence of EDS. We reasoned that, by excluding patients with intermediate levels of EDS, this strategy may help to unravel nocturnal determinants of EDS in OSAS.

METHODS

Subjects

We initially included in the study 65 consecutive male patients who attended the Sleep Unit of our institution and were found to have, by full polysomonography, an apnea-hypopnea index (AHI) > 20 h^{-1} . In these subjects the presence of EDS was diagnosed by considering the results of both the Epworth Sleepiness Scale (EES) and the multiple sleep latency test (MSLT) (see methodological details below). EDS was considered present whenever the EES was greater than 10 *and* the MSLT lower than 5 minutes. Conversely, absence of EDS was diagnosed in those patients with an EES lower than 10 *and* a MSLT greater than 10 minutes. Of the 65 patients initially included, we had to exclude 25 due to discrepancies between the ESS and the MSLT results. Of the remaining 40 patients, 23 were considered to have EDS and 17 not to had it. None of the participants suffered from any chronic disease, chronic obstructive pulmonary disease (COPD), liver cirrhosis, thyroid dysfunction, rheumatoid arthritis, chronic renal failure and/or was taking any type of medication.

The study was approved by the Institutional Ethics Committee, and all participants signed their informed consent after being fully informed of the study goals and procedures.

Polysomnographic evaluation

The diagnosis of OSAS was established by overnight polysomnography (E-Series Compumedics, Abbotsford, Australia). Variables included oronasal flow by nasal cannula, thoracoabdominal movements, electrocardiography, submental and pretibial electromyography, electrooculography, electroencephalography (C3-A2, C4-A1) and

pulse oximetry. Apnea was defined by the absence of airflow for > 10 seconds. Hypopneas were defined as any airflow reduction greater than 50% that lasted longer than 10 seconds and resulted in either arousal or oxyhemoglobin desaturation. We defined a oxyhemoglobin desaturation event as a decrease in SaO2 > 4%. The apnea-hypopnea index (AHI) was defined as the sum of the number of apnea and hypopnea per hour of sleep. Sleep stages were scored using the Rechtschsffen and Kale criteria[12]. Sleep latency was defined as the period of time between lights off and the first 30 seconds of stage 1 (sleep onset). Sleep efficiency was defined as the night sleep duration expressed as percentage of total sleep time in bed. Arousals were defined as recommended by the American Sleep Disorders Association Task Force criteria[13]. According to these criteria, arousals were classified as breathing-related arousals (occurring within 3 seconds following an apnea, hypopnea or snore) and other type of arousals (spontaneous arousal, periodic limb movements-associated arousals and technical arousals). The total number of arousals was calculated by the sum of every type of arousal.

Assessment of excessive daytime sleepiness (EDS)

Subjective sleepiness was assessed using the validated Spanish version[14] of the Epworth Sleepiness Scale (ESS)[15], a simple self-administered questionnaire, with eight-item and four point scales that evaluate daytime somnolence among patients suffering from sleep-awake disorders. Objective sleepiness was evaluated by MSLT according to international guidelines[16]. In brief, the MSLT consists of a series of five twenty-minutes naps at 2-hour intervals. Patients are asked to try to sleep in a dark room with a recorded montage similar to that used during polysomnography the preceding night. The mean of the individual latencies to achieve sleep during the naps was considered to represent

MSLT. A mean latency sleep shorter than 5 min. is considered as EDS and longer than 10 min. is taken as evidence of no EDS.

Statistical analysis

Results are shown as mean ± SD. Comparisons between both groups of patients were performed with independent t-tests or Mann-Whitney tests for normally or not-normally distributed data respectively. Correlations were performed using linear regression, followed by calculation of Pearson correlation coefficient. Statistical significance was defined as $p < 0.05$.

RESULTS

Table 1 shows the main demographic characteristics of the subjects studied. Age and BMI were similar in both groups. Based on the AHI value, patients suffered from severe OSAS.

Table 2 presents the main findings of our study. Patients with EDS had lower sleep latency and a greater sleep efficiency. Furthermore, the nocturnal oxygenation indices were significantly worse in the EDS group. In contrast, there were no differences in the arousal indices or in the overall distribution of sleep stages. A significant correlation was found between MSLT and mean nocturnal SaO_2 ($r = 0.36$, $p<0.05$), minimal nocturnal SaO_2 ($r = 0.47$, $p<0.005$) or sleep efficiency ($r = -0.43$, $p<0.005$). Similarly the ESS showed a significant linear correlation with the previous variables ($r = -0.38$, $p<0.05$; $r = -0.5$, $p<0.005$ and $r = 0.33$, $p<0.05$ respectively).

DISCUSSION

In order to investigate potential nocturnal determinants of excessive daytime sleepiness (EDS) in patients with OSAS, we compared several polysomnographic variables in two groups of patients with severe OSAS who were carefully selected by the presence or absence of EDS (defined by the combined use of both subjective (EES) and objective measures (MSLT)) but who were otherwise undistinguishable in terms of several potentially relevant confounding factors, such as age, gender or body mass index. The main finding of our study was that patients with EDS present shorter sleep latency, higher sleep efficiency and worse nocturnal oxygenation than patients without EDS. Yet, there were no significant differences between groups in their apnea-hypopnea index and, arousal index and /or sleep macroarchitecture.

The pathogenesis of EDS in patients with OSAS is unclear. In the late 1980´s, Guilleminault[9] et al did not find significant associations between EDS and sleep fragmentation or nocturnal oxygenation in a large series of patients with OSAS. At about the same time, Bedard and collaborators[11] suggested that EDS was related to nocturnal hypoxemia, while Colt and colleagues[10] showed a stronger relationship between sleep fragmentation and EDS in a randomised controlled trial. Since then, several authors have indicated that EDS is primarily attributable to sleep disruption[17], while others have suggested that EDS may be related to other factors, namely alterations in oxygenation[8], or alternatively that indices of nocturnal hypoxemia and sleep fragmentation contribute independently to an increased risk for the presence of hypersomnolence in patients with OSAS[18;19]. These discrepancies between polygraphic variables and the presence of daytime somnolence prompted other investigators to

develop alternative measures that may eventually improve our understanding of the mechanisms of EDS in these patients. For example, Gonçalves at al[2] investigated the potential role of arousals during sleep and showed a significant correlation between the number of sleep disorder breathing (SDB)-related arousal of more than 3 seconds and several subjective complains of sleepiness (ESS) and quality of life. A recent study[8] also found that although hypoxemia was an important factor for the presence of daytime sleepiness, the microarousal index appeared to be the most important determining factor associated with EDS. Gozal and colleagues developed a new index of sleep disruption based on the dynamic changes in spontaneous and respiratory-related arousals, which they termed "sleep pressure score" [20], and found a strong association between this score and measures of daytime neurocognitive and behavioural functioning[21]. In addition, Chervin et al[22] developed a novel EEG signal analysis method whereby respiratory cycle-related EEG changes were found useful in the prediction of excessive daytime sleepiness among patients with OSAS. **Additional data on EDS and neural injury have been derived from animal models of intermittent hypoxia[23;24], and have led to the conceptual framework proposing the interactions between disease severity and duration in the context of environmentally and genetically-define susceptibility. We are of course unable at this stage to account for the disease duration or for the specific individual or environmental elements that may have played a role in the discrepant EDS of our study groups, and this issue will have to await future studies.**

In the present study, we dichotomised patients with OSAS to those with clear-cut EDS and those without EDS, in order to enhance potential polysomnographic differences among these 2 groups. Interestingly, these two groups were nonetheless similar in terms

of age, BMI, and disease severity, as assessed by the AHI . This novel approach revealed that patients with EDS sleep more efficiently, and had a shorter sleep latency and a tendency to sleep longer. We believe that these differences are probably a consequence (not a cause) of EDS. Further, these observations suggest that patients with EDS are sleepy throughout the 24-hour cycle.

EDS subjects had longer apnea duration compared to those with no EDS suggesting that there is a delay in the arousal in EDS patients. The latter could be due to either intrinsic difference in their arousal thresholds or may represent increased sleep pressure leading to an increased threshold for arousability. Since the severity of respiratory disturbance was similar, the AHI clearly does not provide insights into the EDS mechanisms. Alternatively, increased hypoxemia leading to more severe neural damage of wake-promoting structures may underlie the EDS[25]. We also observed that patients with EDS had worse noctural oxygenation indices than those without EDS, despite the fact that neither the AHI, the arousal indices or the overall sleep architecture were significantly different between groups (Table 2). These observations support, therefore, a significant role of nocturnal oxygen desaturation in the pathogenesis of EDS, as previously suggested by other authors[8;10;11]. While the biological mechanisms linking nocturnal oxygen desaturation and daytime hypersomnolence in man are unknown, recent studies in mice by Zhan and colleagues[26;27] suggest that intermittent hypoxemia during sleep triggers neural damage to brain regions that promote and control wakefulness through a convergence of oxidative and inflammatory events that ultimately lead to neuronal cell loss and the manifestation of sleepiness[23]. The investigation of these pathways in humans and their potential use in the palliation of EDS in patients OSAS seems warranted.

In conclusion, OSAS patients with excessive daytime sleepiness present shorter sleep latency, improved sleep efficiency and worse nocturnal oxygenation when compared to OSAS patients of similar characteristics without EDS. Given that the remaining nocturnal variables investigated, including the apnea-hypopnea index, the arousal index and sleep architecture do not discriminate between patients with and without EDS, we postulate that nocturnal hypoxemia plays a major role in the pathogenesis of daytime sleepiness in patients with sleep apnea syndrome.

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Table 1. Demographic characteristics of OSAS patients with and without excessive daytime sleepiness (EDS).

	EDS n = 23	No EDS n = 17	p value
Age (years)	49±6	50±9	ns
BMI ($Kg.m^{-2}$)	33 ±5	31 ± 6	ns
Awake SaO_2	96±1	96±1	ns
Epworth Scale	17 ± 3	5 ± 2	<0.0001
MSLT (min)	4 ± 1	16 ± 3	<0.0001

BMI: Body mass index

MSLT: multiple sleep latency test

Table 2: Polysomnographic findings in OSAS patients with and without excessive daytime sleepiness (EDS).

	EDS n = 23	No EDS n = 17	p value
TST (min)	401 ± 41	379 ± 63	ns
Sleep latency (min)	11 ± 16	18 ± 18	0.05
Sleep efficiency (%)	90 ± 7	82 ± 13	0.04
Awake (min)	37 ± 29	66 ± 56	0.03
Arousal index	65±20	60±24	ns
Respiratory arousals	58 ± 20	57 ±22	ns
AHI (hr^{-1})	62 ± 18	60 ± 20	ns
Apnea duration (sec)	29 ± 8	22 ± 7	0.008
PLMI (hr^{-1})	3 ± 1	2 ± 1	ns
Phase 1 + 2 (%)	81±12	78±11	ns
Phase 3 + 4 (%)	6±8	8±5	ns
REM (%)	13 ± 6	14 ±8	ns
Min Sat (%)	69 ± 12	79 ± 8	0.002
Mean Sat (%)	87 ± 6	90 ± 5	0.01

TST: total sleep time; REM: rapid eye movement sleep; Min Sat: minimal nocturnal arterial oxygen saturation; Mean Sat: mean nocturnal arterial oxygen saturation; AHI: Apnea hypopnea index; PLMI: periodic leg movement index