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Clinical factors associated with extreme sleep apnoea [AHI > 100 events per hour] in Peruvian patients: A case-control study—A preliminary report

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ABSTRACT

Purpose: The severity of obstructive sleep apnoea (OSA) ranges from mild or moderate to severe sleep apnoea. However, there is no information available on the clinical characteristics associated with cases involving more than 100 events per hour. This is a preliminary report and our goal was to characterise the demographics and sleep characteristics of patients with Extreme OSA and compare with patients with sleep apnoea of lesser severity. We hypothesised that patients with Extreme OSA (AHI > 100) is associated with an increased comorbidities and/or risk factors.

Methods: We carried out a case-control study on male patients with OSA who were seen in a private hospital in Lima, Peru between 2006 and 2012. Cases were identified if their apnoea/hypopnea index (AHI) was higher than 100 (Extreme OSA), and four controls were selected per case: two with 15–29 AHI and two with 30–50 AHI, matched according to case diagnosis dates.

We evaluated demographic, past medical history, and oxygen saturation variables

Results: We identified 19 cases that were matched with 54 controls. In the multivariate model, only arterial hypertension, neck circumference, age, and over 10% in SatO₂Hb ≤ 90% in total sleep time (T90) were associated with Extreme OSA. Arterial hypertension had an OR = 6.31 (CI95%: 1.71–23.23) of Extreme OSA. Each 5-cm increment in neck circumference was associated with an increase of OR = 4.34 (CI95%: 1.32–14.33), while T90 > 10% had an OR = 19.68 (CI95%: 4.33–89.49). Age had a marginal relevance (OR = 0.95; CI95%: 0.92–0.99)

Conclusion: Our results suggest that arterial hypertension, neck circumference, and over 10% SatO₂Hb ≤ 90% in total sleep time were associated with a higher probability of Extreme OSA. We recommend investigators to study this population of Extreme OSA looking for an early diagnosis and the identification of prognostic factors in comparison with moderate to severe levels.

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1. Introduction

Obstructive sleep apnoea (OSA) is a common disease, with a prevalence of 3–5% symptomatic and 24–26% asymptomatic patients [1–3]. OSA is caused by episodic upper airway obstruction which occurs during sleep. Obstruction can be total (apnoea) or partial (hypopnea), and can occur several times during sleep [4]. The Apnoea–Hypopnea Index (AHI) is used to classify the severity of the illness: mild AHI 5 to <15; moderate 15 to <30; and severe 30 or more [5].

It is well known that patients with severe OSA have higher morbidity and mortality rates compared to those with mild or moderate levels [6,7]. This is relevant mainly in patients with arterial hypertension, coronary disease and stroke [8,9], ventricular dysfunction [10]. For this reason, severe cases require more immediate treatment [11,12]. However, severe OSA includes a very broad spectrum in a group of patients with an AHI ≥ 30 , and morbid-mortality outcomes could be different in patients with different degrees of severe disease.

In a preliminary study, Jurcevic et al. postulated that patients with AHI ≥ 60 had increased mortality and more severe clinical parameters [13]. The study compared them to patients with AHI <60. Thus, the cut-off point included the conventional severity category. In this scenario, it is very complicated to differentiate the added effect of the proposed new category. Our goal was to identify the clinical and polysomnographic association between moderate to severe OSA with an arbitrary category known as Extreme OSA, defined as an AHI >100. We hypothesised that patients with Extreme OSA (AHI >100) is associated with an increased comorbidities and/or risk factors in comparison with moderate to severe levels.

2. Methodology

2.1. Study design

We carried out a case-control study. The records came from a primary database study that aimed to describe all patients evaluated at a sleep laboratory operating in a private hospital (Clínica Anglo Americana) in Lima, Peru.

2.2. Population

We included all cases with an Apnoea–Hypopnea Index (AHI) >100 events per hour. We named them Extreme Obstructive Sleep Apnoea (X-OSA case group), and compared with patients who met the criteria for moderate to severe sleep apnoea (control group). We randomly selected four controls per case: two with 15–29 AHI (moderate control group) and two with 30–50 AHI (severe control group). Cases and controls were matched according to the polysomnographic study date of each case. All cases and controls patients had less than 5% of central respiratory events. The period considered for controls was up to three months prior to the index case. We excluded females and controls with sleep disease comorbidity.

2.3. Polysomnography

All patients were diagnosed with OSA undergo polysomnography. For acquisition, we used the Easy II, Easy III from Cadwell Inc., and Neuro BE Light devices. The arrangements were: F2-M1, C2-M1, O2-M1, E1-M2, E2-M2, chin electromyography, airflow with thermistor and nasal cannula pressure, snoring microphone in the pre tracheal area, thoracic and abdominal effort, pulse oxymetry, ECG with DII derivation, body position sensor and electromyography of both anterior tibia muscles. The PSG acquisition was a supervised level I study in accordance with the American Sleep Disorders Association (ASDA) classification [14]. The scoring criteria for staging system was done according to the AASM Manual [15]. Arousal criteria was defining according to ASDA criteria [16], and we used the Sleep Spanish Group criteria for qualification of the respiratory events [17].

Two protocols were used for polysomnographic recordings: all-night and split-night studies. Although differences have been identified in the selection of patients for a type of polysomnographic recording, no variations have been reported in oximeter measurements and AHI results [18,19]. In accordance with these papers, both acquisitions were combined.

2.4. Variables

The clinical and polysomnographic variables included for the analysis were: age (years), weight (kg), height (m), body mass index (BMI: kg/m^2), neck circumference (cm), Mallampati classification, blood pressure, and the score on the Epworth sleepiness scale adapted to Peruvian adults [20]. Oxygen saturation parameters included nadir saturation, and total sleep time in oxygen saturation $\leq 90\%$ (T90).

We defined obesity as a BMI ≥ 30 . Hypertension diagnosis was considered if patients were under treatment with at least one antihypertensive medication including: angiotensin receptor blocker, ACE inhibitor, beta blocker, alpha adrenergic blocker, calcium channel blocker and diuretic or systolic blood pressure >140 mmHg or diastolic blood pressure >90. Measurements were done according to the Seventh Report [21]. A score on the Epworth sleepiness scale (ESS) >10 points was defined as excessive sleepiness and we used a Peruvian validation [22]. Finally, T90 was categorised into two groups: greater than 10% and $\leq 10\%$ [23].

2.5. Statistical analysis

We compared the clinical and polysomnographic data of two control groups (moderate and severe) using t-test for quantitative variables and chi-squared for categorical. The data collected from the case group (Extreme-OSA group) were the control groups with ANOVA test. We considered a $p < 0.05$ value as significant. Next, we performed a conditional logistic regression model to estimate crude Odds Ratios (crude OR) with a 95% confidence interval (CI). All analyses were performed with STATA 12.1 (STATA Corp, College Station, Texas, USA).

2.6. Ethical considerations

We used a coded database and the study did not have any risk for patients. All patients signed two informed consent

form; one before filling out the EES questionnaire and the other one before performing the polysomnography acquisition. The Clínica Anglo Americana Bioethical Committee of and the Biomedical Research Ethics Committee (Comité de Ética en Investigación Biomédica) of the Hospital National Dos de Mayo (No. 034-2012-CEIB-AI-OACDI-HNDM, 19 May 2012, Lima, Peru) approved the secondary study.

3. Results

In our database, we identified 655 cases of OSA and 22 (0.4%) patients with an AHI ≥ 100 during a six-year period. Four case patients were excluded: one for short sleep period time; one for Goldenhart syndrome diagnosis; one because of comorbid severe periodic limb movements; and one female patient. Nineteen case patients that met the inclusion criteria were matched with 38 moderate OSA controls and 38 severe OSA controls.

The average age was 48.9 ± 13.7 years. Forty-eight (51%) had arterial hypertension under treatment. Seven (7%) patients had normal weight, 39 (41%) were overweight, and 10 (11%) suffered from morbid obesity. Forty-three (46%) patients exhibited sleepiness. Only the greater than 10% in T90 variable was more frequent in the severe OSA control group (24%) vs. moderate OSA control group (5%), this difference was significant ($p < 0.01$); there were no other differences between control groups.

The case group had significant differences with the control group in age, weight, BMI, neck circumference, ESS score, saturation time $\leq 90\%$, and nadir saturation. These variables had a higher average value in the Extreme-OSA group. Furthermore, the average age was lower in the Extreme-OSA group as compared to the control group. Arterial hypertension, sleepiness, and obesity were higher in the Extreme-OSA group (Table 1).

In the bivariate analysis, T90 $> 10\%$ was the variable with the closest association with Extreme-OSA (crude OR: 19.68,

$p < 0.001$), followed by obesity (crude OR: 9.29, $p = 0.005$), arterial hypertension (crude OR: 6.31, $p = 0.006$), and, to a lesser degree, sleepiness, neck circumference, BMI, and weight. Age and nadir saturation during sleep had an inverse association with the probability of having Extreme-OSA in the crude regression models (Table 2).

4. Discussion

Our results for the bivariate analysis are consistent with the associations found in the study conducted by Jurcevic et al. [13], who included the category of AHI ≥ 60 . In the adjusted analysis, we found that the group with Extreme-OSA has an increased and consistent association with arterial hypertension, more time with saturation $\leq 90\%$, and higher neck circumference. We also found differences in the magnitude of these associations depending on whether the Extreme OSA cases were compared with moderate or severe OSA controls, suggesting that the differences are more notable when compared with patients with moderate OSA.

The association between arterial hypertension and Extreme OSA is very high when compared to patients with severe OSA, and increases even more when compared to patients with moderate OSA, consistent with the findings of the study conducted by Nieto et al. [24], which established that the probability of arterial hypertension increased depending on the severity of the OSA. This suggests that the principal clinical characteristic of patients with Extreme OSA is that of having a greater probability of arterial hypertension, which is in keeping with other studies that found a close association between OSA and resistant hypertension [25], which increased analogously depending on the severity of the OSA.

While obesity maintained an intense association in the bivariate analysis (OR: 9.29), this association was lost in the multivariate analysis, where it was adjusted by neck circumference, which maintained a significant association. This is

Table 1 – Demographic characteristics of cases (AHI > 100) and controls.

	Moderate OSA control N=38	Severe OSA control group N=38	Extreme-OSA case group N=19	p
Age	50.2 \pm 12.8	51.4 \pm 13.8	41.4 \pm 13.3	0.023
Weight	88.0 \pm 19.5	93.0 \pm 14.8	118.2 \pm 22.2	<0.001
Height	173.6 \pm 6.6	173.3 \pm 6.4	174.1 \pm 5.3	0.911
BMI	29.1 \pm 5.3	30.9 \pm 4.5	38.9 \pm 6.9	<0.001
Neck circumference	42.1 \pm 2.9	42.5 \pm 3.3	47.4 \pm 4.7	<0.001
Epworth scale	10.2 \pm 5.8	9.1 \pm 5.0	13.8 \pm 5.9	0.012
AHI	21.5 \pm 4.3	41.3 \pm 4.3	110.0 \pm 9.1	<0.001
Saturation in W Stage	97 \pm 1.2	96 \pm 1.7	95 \pm 1.5	
Circulation time	12 \pm 2.1	13 \pm 1.4	14 \pm 1.2	
Saturation time $\leq 90\%$ of TST (T90)	4.8 \pm 15.9	8.0 \pm 11.8	33.3 \pm 26.4	<0.001
Nadir saturation	83.5 \pm 6.9	81.8 \pm 7.7	73.6 \pm 11.0	<0.001
T90 $\geq 10\%$ ^a	5.26%	23.68%	73.68%	<0.001
Sleepiness ^a	45.95%	35.14%	68.42%	0.061
HBP ^a	31.58%	52.63%	84.21%	<0.001
Obesity ^a	31.58%	52.63%	89.47%	<0.001
Mallampati level IV ^a	68.42%	68.42%	84.21%	0.223

BMI: body mass index; TST: total sleep time; HBP: high blood pressure.

^a Chi-squared.

Table 2 – Association between extreme-OSA and demographic characteristics.

	Crude OR	CI95%	p	Adjusted OR ^a	CI95%	p
HBP	6.31	1.71–23.23	0.006	4.11	1.19–14.1	0.025
Sleepiness	3.39	1.07–10.84	0.039	2.89	0.58–14.47	0.195
Nadir saturation	0.89	0.83–0.96	0.003	0.93	0.86–1.01	0.107
Neck circumference	1.36	1.19–1.53	<0.001	1.16	0.91–1.48	0.219
T90 > 10%	19.68	4.33–89.49	<0.001	1.04	0.98–1.09	0.247
Obesity	9.29	1.99–43.37	0.005	1.62	0.14–18.33	0.699
Weight	1.06	1.02–1.10	0.007	0.99	0.93–1.07	0.887
BMI	1.19	1.06–1.35	0.004	–		
Age	0.95	0.92–0.99	0.022	–		

HBP: high blood pressure; BMI: body mass index.

^a Adjusted OR for BMI and age.

consistent with the results obtained by Preis et al. [26] in the Framingham study, where they identified neck circumference as a variable with an important correlation to obesity, as well as being associated with cardiovascular risk factors. This finding is relevant to the pathogenesis of OSA, since a high correlation has been identified between an increase in neck circumference and AHI value [27]. There is only one reference in the literature where this population of Extreme sleep apnoea is distinguished from the other subgroups of severe sleep apnoea [28], on this paper, the only patients who has significant REM rebound were the patients who has AHI > 100 on the baseline portion of sleep study. In our population this occurrence was not observed.

The primary limitation of the study was related to the low number of cases identified by polysomnography in our laboratory and for this reason, the confidence intervals were wide. However, to avoid losing statistical power, we increased the number of controls to four. Additionally, we were unable to evaluate all the clinical characteristics of patients with OSA. The other limitation is the confounding variables related to OSA consequences like age, and neck circumference, and time spend with SatO2Hb below 90% for hypertension. The multi-variable analysis was not possible due to the small sample size. The limitations described requires specific studies. Our results suggest that there is a subgroup of higher severity among patients with severe OSA that deserves more study.

Patients with Extreme OSA could be associated with a higher probability of HTA, more time with saturation \leq 90%, and a higher neck circumference when compared to patients with moderate OSA, severe OSA, or both. We recommend to study this population of Extreme OSA for the identification of prognostic variables.

Conflicts of interest

The authors indicate no financial conflicts of interest.

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