doi:10.1111/j.1468-2982.2005.00897.x

Investigation into sleep disturbance of patients suffering from cluster headache

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Cephalalgia

Nobre ME, Leal AJ & Filho PMF. Investigation into sleep disturbance of patients suffering from cluster headache. Cephalalgia 2005; 25:488–492. London. ISSN 0333-1024

The new discoveries relating to cluster headache (CH) encouraged the study of the relationship of the hypothalamus to respiratory physiology and its comorbidity with sleep apnoea. The question is whether the apnoeas are more frequent during REM sleep and the desaturations could be involved as triggers of the cluster attacks. Furthermore, could the connection with the hypothalamus, already proved, be responsible for an alteration in the structure of REM sleep and a chemoreceptor dysfunction. We set out to analyse when polysomnography investigation is necessary in patients with CH. We studied 37 patients suffering from episodic CH, 31 (83.8%) men and six (16.2%) women. For the control group, we selected 35 individuals, 31 (88.6%) men and four (11.4%) women. There was a greater percentage of obstructive sleep apnoea (OSA) in patients with CH (58.3%) compared with the control group (14.3%) and with the general population (2–4%). In cases of pain during sleep, the majority is deflagrated during the REM phase, following a desaturation episode. A stratified analysis of the apnoea/hypnoea index relating to body mass index (BMI) and age showed that patients with CH have 8.4 times more chance of exhibiting OSA than normal individuals ($P < 0001$). This risk increases to 24.38 in patients with a BMI >25 kg/m^2 and increases to 13.5 in patients >40 years old. Surprisingly, the risk decreases sharply in patients with a BMI <25 kg/m^2 and who are <40 years old. Due to the fact that polysomnography is a complex, costly and sometimes difficult examination, we suggest, in concordance with the results, that it should be carried out routinely in patients with CH that exhibit a BMI of >25 kg/m^2 and/or in patients who are >40 years of age. □ *Apnoea, cluster headache, polysomnography*

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Introduction

The first descriptions of cluster headache (CH) date from the 17th century, the earliest being from 1641, when Nicolaas Tulp (1593–1674) published a series of clinical cases with the title of 'Observationes Medicae' (1). Wolff, in 1963, noticed the particular relationship between CH and sleep: 'in two-thirds of patients, the attack always or almost always begins during sleep or the pain is so intense that the patient frequently jumps out of the bed before he has completely woken up' (2).

The first polysomnography study in patients suffering from CH was carried out by Dexter and Weitzman (1970). From this assessment, various groups began to study patients with CH polysomnographically, trying to better clarify this connection (3). Following the observation of the efficiency of oxygen inhalation in the cluster attack and attacks provoked by the hypoxaemic state, there was a tendency to connect it with hypoxaemia (4–7). The influence of the hypothalamus in cardiovascular responses was demonstrated and the authors suggested sympathetic inhibition and vagal stimulation. Other studies showed that the section of sympathetic post-ganglionic fibres in the carotid body suppress the respiratory response to sympathetic stimulation (8, 9). Thus, it is believed that the altered sympathetic activity in the carotid body can modify chemoreceptor activity, being able to represent the alteration present during the cluster attack (10). Hypothalamic activation during the attacks was observed through positron emission tomography (PET), only in patients suffering attacks (11–14). Apart from the findings with PET, studies using nuclear magnetic resonance spectroscopy showed an asymmetry of the hypothalamus (13). It seems that the postero-inferior hypothalamus has a greater volume in patients with CH, during and outside attacks. The areas found in the studies with different examinations were identical (13).

Together, these findings suggest that the hypothalamus is indeed the place where the pain is produced (10, 15, 16). The concomitance of cluster headache and sleep apnoea can be explained by the multiple hypothalamic functions. However, overnight polysomnography has been the gold standard for diagnosing obstructive sleep apnoea. This examination is often not open to the patient and our study seeks to select when it would be a genuine necessity.

Methods

Thirty-seven patients from a tertiary headache outpatient service were assessed through history, neurological examination, cranial tomography scan (CT) and polysomnography. All the patients fulfilled the criteria of the International Headache Society (IHS) (1988) for the diagnosis of episodic CH. Considering the objectives, the patients with associated heart, lung and haematological diseases were excluded, since the concomitance of these pathologies could interfere with the results.

Thirty-five subjects were selected for the control group, with equivalence in average age, body mass index (BMI) and predominance of sex, without complaints of chronic headache or any complaint of health problem.

The assessment was from March 1998 to March 2004. The following items were studied: sex, age when attended, BMI, Epworth Sleepiness Scale (ESS) and presence of obstructive sleep apnoea (OSA). Nocturnal polysomnography included electroencephalographic (EEG) leads (C3-A2, C4-A1, O1-A2, and O2-A1 of the 10–20 international electrode placement system), two electrooculographic (EOG) leads (right and left), chin and bilateral anterior tibialis surface electromyograms (EMGs), two electrocardiographic (ECG) leads, nasal and oral airflow, thoracic and abdominal excursion, and finger oximetry. Sleep-stage scoring was performed on 30-s periods according to standard criteria. Apnoea is defined as the cessation of airflow in 10 s. Hypopnoea is defined as a recognizable, transient reduction, but not a complete cessation of breathing in 10 s (50% decrease in the amplitude of a validated measure of breathing or a <50% amplitude reduction that is associated with either an oxygen desaturation of 3% or an arousal must be evident). Obstructive apnoeas and hypopnoeas are typically distinguished from central events by the detection of respiratory efforts during the event. In general, if there are more than five episodes per hour apnoea is significant, and if there are more than 15, the condition is serious.

Statistical analysis was based on the χ^2 test and stratified analysis.

Results

The apnoea/hypnoea (A/H) index was greater in patients with CH. Both the analyses of the averages, and the percentage analysis above five, were statistically significant. The diagnosis of OSA was made in 21 patients (58.3%) and in five of the control group (14.3%) (χ^2 test: $P < 0.001$) (Table 1).

The stratified analysis examining the A/H index in relation to BMI and age showed that a patient with CH has 8.8 times more chance of exhibiting OSA than a normal individual ($P < 0.001$). This risk increases to 26 in patients with BMI >25 kg/m^2 and increases to 14.25 in patients >40 years old. Surprisingly, the risk diminishes sharply in patients with BMI <25 kg/m^2 and <40 years old (Table 2).

Discussion

OSA is characterized by repeated episodes of obstruction of the upper airway during sleep, generally accompanied by a reduction in oxyhaemoglobin (17, 18). The clinical picture is generally related to day sleepiness and snoring. A population study observed a prevalence of snoring in 27.2% (male

Table 1 Distribution of the study groups according to categories of the apnoea/hypnoea (A/H) index

A/H index	Cases	%	Controls	%
0–4	15	40.5	30	85.7
≥5	22	59.5	5	14.3
Total	37	100.0	35	100.0

χ^2 test: $P < 0.001$.

Table 2 Stratified analysis of the distribution of the study groups according to categories of the apnoea/hypnoea (A/H) index

Stratification variable	A/H index	Cases	%	Controls	%	OR	CI 95%	*P*
Body mass index								
<25 kg/m^2	0–4.9		53.8	17	81.0			
	≥5		46.2	4	19.0			
	Total	3	100.0	21	100.0	3.64	0.62	0.130
≥25 kg/m^2	0–4.9		33.3	13	92.9			
	≥5	6	66.7	1	7.1			
	Total	4	100.0	14	100.0	26.00	2.59	<0.001
Age								
<40 years old	0–4.9		70.0	18	85.7			
	≥5		30.0	3	14.3			
	Total	0	100.0	21	100.0	2.57	0.31	0.358
≥40 years old	0–4.9		29.6	12	85.7			
	≥5	9	70.4	2	14.3			
	Total	7	100.0	14	100.0	14.25	2.17	<0.001
Total	0–4.9	5	40.5	30	85.7			
	≥5	2	59.5	5	14.3			
	Total	7	100.0	35	100.0	8.80	2.48	<0.001

36.5%, female 18.9%) and apnoea in 8.5% (31% of all snorers) (19). Morning headache is a frequent symptom, described by 36% of patients with OSA (20). The pain is generally moderate and short-lasting. It seems that the frequency and intensity are related to the seriousness of the apnoea (21). The most widely accepted epidemiological statistics come from the Wisconsin Sleep Cohort Study, in which 602 individuals were assessed, between 30 and 60 years old, showing attacks in 2–4% of the adults (2% women and 4% men). The validity of the studies is assessed in accordance with the studied population and the parameters for inclusion in the study. The most recent epidemiological study assessed 76 individuals and the prevalence of OSA was 0% of women and 7% of men. Race, age and BMI can be important risk factors, and should be assessed in a statistical study (22–25). Another study carried out in Switzerland with 583 individuals, from 30 to 64 years old, cited a prevalence of 1.3–4% in men and 2% in women (26).

In our recent study, carried out between 1997 and 1999, 16 patients were assessed (14 male and two female, aged from 26 to 55 years) by night polysomnography. All the patients fulfilled IHS criteria (1988) for the diagnosis of episodic CH. Twenty-nine individuals were selected for the control group (26 male and three female, aged 19–59 years), with equivalence in ages, BMI and predominance of sex, without complaints of headache or any referred alteration of physical status. The results of this study confirm the perspective finding of a higher percentage of OSA in patients with episodic CH (27). Although not an uncommon pathology, OSA is generally more prevalent those who are older and of greater BMI. Among the patients studied, the average age was 30.9 years, not conforming to the age group of major prevalence of OSA. We found 31.3% prevalence of OSA. Only two attacks occurred during the polysomnography examination, in two patients with OSA. Both occurred during REM sleep, following an episode of desaturation. Of five patients with OSA, two were treated with continuous positive airway pressure (CPAP) and showed an immediate improvement in their painful condition. There is a concordance with literature data, which suggests that oxygen desaturation could be a trigger factor or even related to pathophysiology (28). The data confirm previous studies suggesting a relationship of REM sleep and OSA only for the episodic form, favouring the hypothesis of different physiopathological mechanisms for the two forms.

Chervin et al. studied 25 patients with CH (22 men and three women), evaluating the A/H index, desaturation <90%, final concentration of CO_2 and oesophageal pressure. Twenty patients (80%) presented sleep-disordered breathing (A/H index >5), a term which the authors used to include OSA and upper airway resistance syndrome, in accordance with the measure of oesophageal pressure. Of these, 11 patients exhibited an A/H index >10. Ten patients exhibited saturation below 90% during the examination. The study also compared patients who were suffering from attacks ($n = 8$) with patients who were outside the cluster period ($n = 17$). The authors observed that there were no significant differences between the two periods; however, there was an increase in the final concentration of CO_2 in attacks (29).

The possible explanations for the association of CH and OSA are related to the convergence of risk factors for the two conditions, such as accentuated intoxication caused by tobacco and frequent use of alcohol. A study with 36 patients with CH showed that even though 83% presented night pain, only 40% of the patients exhibited symptoms related to apnoea, such as daily sleepiness and snoring. The study concluded that CH could not be explained by these symptoms (30).

The BMI was not referred to in any study of CH, even in polysomnography assessments. In our assessment, we found a difference between the BMI averages of patients suffering from CH and control individuals. The studies showed that in patients with OSA, BMI is above the ideal in 75% of cases; however, no study separated the groups according to the BMI. The BMI average in cases of CH was 25.8 kg/m^2, therefore in the lower limit of the preobese group (BMI = 25–29.9 kg/m^2) and the BMI average of the control group was 24 kg/m^2, in the upper limit of normal weight (BMI = 18.5–24.9 kg/m^2).

The A/H index was greater in patients with CH. A diagnosis of OSA was made in 21 patients (58.3%) and in five control individuals (14.3%) ($P < 0.001$).

Some studies apply the ESS when there is no possibility of a polysomnography study. It would be an indirect assessment of the presence of OSA (31, 32). The punctuation average obtained through the Epworth scale was 6.9 for the patient group and 5.3 for the control group. The averages of the two groups remained below the necessary score for probability of OSA. With these data, there would be no predisposition to OSA in any of the groups, which was not observed following polysomnography. Therefore, the ESS was not shown to be efficient in the isolated assessment for OSA diagnosis.

The stratified analysis examining the A/H index in relation to the BMI and age showed that a patient with CH has 8.4 times more chance of exhibiting OSA than a normal individual ($P < 0.001$). This risk increases to 24.38 in patients with BMI >25 kg/m^2 and increases to 13.5 in patients >40 years old. Surprisingly, the risk diminishes sharply in patients with BMI <25 kg/m^2 and <40 years old. As the polysomnography investigation is complex, costly, and sometimes difficult to carry out, we suggest, in concordance with the results, that it should be applied routinely in patients with CH with a BMI of >25 kg/m^2 and/or in patients >40 years of age.

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