Sleep disordered breathing concomitant with fibromyalgia syndrome

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ABSTRACT

Objective: To identify fibromyalgia syndrome in patients with sleep disordered breathing. Method: We studied 50 patients seeking treatment at a sleep disorder clinic for snoring, apnea and excessive daytime sleepiness. Sleep disordered breathing was diagnosed through the use of polysomnography. To diagnose fibromyalgia syndrome, patients were evaluated in accordance with the criteria established by the American College of Rheumatology. Results: Of the 50 patients, 32 were male. The mean (± standard deviation) age of the group was 50 ± 12 years. The mean body mass index was 29.7 ± 5.6 kg/m². The mean apnea-hypopnea index was 36 ± 29 attacks of apnea or hypopnea per hour of sleep. Of the 18 women and 32 men evaluated, 9 and 2, respectively, met the American College of Rheumatology criteria for fibromyalgia syndrome. Conclusion: Considering the fact that the prevalence of fibromyalgia syndrome in the general population is 0.5% for men and 3.4% for women, the more than ten-fold higher proportion of fibromyalgia cases seen in this sample supports the hypothesis that there is an association between sleep disordered breathing and fibromyalgia syndrome.

Keywords: Respiration disorders/complications; Fibromyalgia/complications; Sleep apnea, obstructive; Polysomnography
INTRODUCTION

According to the literature, sleep-disordered breathing (SDB) is defined as obstructive breathing episodes occurring exclusively during sleep and is related to relaxation of the pharynx and the consequent increase in upper airway resistance. The degree of pharyngeal occlusion varies, and the consequences can be more or less evident. Such consequences can include the following: primary snoring during sleep; increased upper airway resistance causing the individual to awaken; hypopnea with desaturation; and (in the case of full obstruction) apnea. In individuals with SDB, there is an increase in respiratory effort-related arousals, which fragment sleep and result in nonrestorative sleep, excessive daytime sleepiness, fatigue, decreased libido and migraines, as well as in mood disorders, such as anxiety, lack of concentration, irritability, apathy and symptoms of depression. Prominent among the forms of SDB is obstructive sleep apnea-hypopnea syndrome (OSAHS), defined as more than five episodes of apnea or hypopnea per hour of sleep, accompanied by symptoms of sleep disturbance. Worldwide, the prevalence of OSAHS varies from 1% to 10% of the adult population. The syndrome affects twice as many males as females, probably for anatomical and functional gender-related reasons, especially those related to the distribution of body fat. Among women, OSAHS occurs mostly in the postmenopausal period, suggesting a hormonal influence on the physiopathology of upper airway obstruction during sleep. Partial upper airway obstruction, even without apnea, results in awakenings and is designated upper airway resistance syndrome, which is characterized by excessive daytime sleepiness and more than five respiratory effort-related arousals per hour. This syndrome includes individuals whose apnea-hypopnea index (AHI) is lower than five events per hour, with no significant oxygen saturation drop. The prevalence of upper airway resistance syndrome is similar among males and females, and the mean age of patients is approximately 30.

Fibromyalgia syndrome (FMS) is characterized by diffuse muscular-skeletal pain, emanating from the tendons, ligaments, muscles and tender points in soft tissues. In general, it is accompanied by stiff joints, fatigue and sleep disorders. It encompasses nonspecific signs and symptoms that can occur in various diseases. The etiology of FMS is unknown. Using the criteria established by the American College of Rheumatology (ACR) for the diagnosis of FMS, its prevalence has been found to be approximately 2% in the North-American population: 0.5% for men and 3.4% for women. In a study involving patients complaining of chronic musculoskeletal pain and conducted in the Brazilian cities of Fortaleza, Porto Alegre and Rio de Janeiro, the authors found that 10.1% of those patients presented FMS.

Through polysomnography (PSG), the authors made the following observations: increased sleep latency; longer duration of stage 1 sleep; a greater number of awakenings; a drop in sleep efficiency; and a reduction in the quantity of REM sleep and of slow-wave sleep (stages 3 and 4 of non-REM sleep). In addition, sleep spindles are rare in individuals with FMS. The intrusion of the alpha rhythm in electroencephalograms, mainly in stages 3 and 4 of non-REM sleep, is of special interest. Under normal conditions, the electroencephalographic alpha rhythm, from 8 to 13 Hz, is associated with a relaxed alert state, in which the eyes are closed. Alpha intrusion, or alpha-delta sleep, is defined by the activity of alpha waves overlapping delta waves, the latter being typical of sleep stages 3 and 4. Alpha intrusion can also be found in patients with other rheumatological diseases, such as rheumatoid arthritis and chronic fatigue syndrome, as well as in those using medications that act on the central nervous system and in asymptomatic individuals. Alpha-delta activity can be tonic, phasic or periodic/complex (K-alpha type).

Alpha-delta activity in patients with FMS has been related to restless sleep and pain (diffuse or at tender points). It has been shown that, when deprived of the deep phases of sleep, healthy young volunteers present complaints similar to those seen in patients with FMS. Except for diffuse musculoskeletal pain and pain at tender points, the symptoms reported by patients with SDB are similar to those of patients with FMS. Patients with OSAHS can also present FMS. There was an interesting case report in which FMS symptoms improved after continuous positive airway pressure was used to treat SDB.

Another reported
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fourteen cases of FMS symptom improvement in patients with SDB after three weeks of continuous positive airway pressure. These findings suggest that SDB plays a role in the development of FMS.

Few studies have investigated the association between SDB and FMS, which remains controversial. The present study was conducted in order to identify FMS in individuals with SDB.

METHODS

A prospective, observational study was conducted involving patients who sought treatment at the Sleep Clinic in Porto Alegre, Brazil for snoring, apnea and excessive daytime sleepiness. A total of 50 patients volunteered to be submitted to PSG in the sleep lab. Inclusion criteria were being at least eighteen years of age, presenting SDB in the PSG results and agreeing to participate in the study. Individuals presenting a predominance of central sleep apnea were excluded.

The study was conducted according to the guidelines for research involving human beings established in National Health Council Resolution no. 196/96, and the project was approved by the Ethics in Research Committee of the Federation for the Establishment of Higher Education University Center in Novo Hamburgo, Brazil.

When the patients arrived in the sleep lab for the PSG, they were informed of the purpose of the study and of which procedures would be carried out. Those who agreed to participate in the study then gave written informed consent. Subsequently, personal data were collected, histories were taken regarding diffuse pain, defined by location and duration, based on the ACR criteria, and an interview focusing on specific symptoms was conducted.

The physical examination consisted of using a clinical scale to obtain weight and height measurements for each patient, together with the calculation of body mass indices. The anthropometrical variables analyzed were gender, age and body mass index.

For ethical reasons (to minimizing the discomfort of volunteers who might deny having experienced diffuse pain within the last three months), algometry was avoided at this point. This was due to the fact that the criteria for detection of FMS, as determined by the ACR, could not be met in this phase of the study. In cases of diffuse pain lasting more than three months, an assessment for the diagnosis of FMS was conducted. The PSG was then carried out. If the analysis of the PSG did not reveal SDB, the patient was excluded from the study on the following day.

Pain was considered diffuse when all of the following parameters were present: pain on the left side of the body; pain on the right side of the body; pain above the waistline; pain below the waistline; and pain in the axial skeleton (cervical, anterior thoracic, dorsal or lumbar spine). Under this definition, pain in shoulders or buttocks is considered pain for each side involved. Back pain is considered pain below the waistline.

The examination of patients with diffuse pain lasting more than three months consisted of using a mechanical algometer (FDK; Wagner Instruments, Greenwich, CT, USA) to apply pressure of up to 4 kgf/cm² in eighteen standard anatomical areas, designated tender points. In order for the sensitive area to be considered positive, the individual would have to state that the pressure was painful or express the sensation of pain. To meet the criteria set by the ACR for the diagnosis of FMS, patients must report diffuse pain lasting more than three months and test positive for pain in at least eleven of the eighteen tender points.

The PSG was carried out in accordance with standard methods, including the use of electroencephalograms (C3-A2 and C4-A1), electrooculograms (left and right eyes), electromyograms (chin and anterior tibia) and electrocardiograms. All of the equipment employed was manufactured by Emsa Equipamentos Medicos Ltda. (Rio de Janeiro, Brazil). Airflow was measured using a nasal cannula connected to a pressure transducer, and the oxygen saturation in arterial blood was measured by a pulse oximeter (Ohmeda, Boulder, CO, USA).

Sleep was staged using the criteria established by Rechtschaffen and Kales. Apnea was defined as a reduction in airflow to 10% or less of the baseline value for 10 seconds or more. Hypopnea was defined as a reduction in airflow of 50% or more, combined with awakening and a drop in arterial oxygen.
saturation of 3% or more. Episodes of airflow limitation were identified by a flattening of the airway curve, measured by the pressure transducer, which normalized after an awakening of at least three seconds. Accuracy in measuring airflow limitation is similar that of measuring intrathoracic pressure. Airway limitation is measured by esophageal catheter in order to detect respiratory effort-related arousals typical of the upper airway resistance syndrome. The AHI was calculated by dividing the total number of apnea-hypopnea episodes by the number of hours slept. If the AHI was lower than 5 episodes/hour, and the patient complained of daytime sleepiness, a diagnosis of upper airway resistance syndrome was made. An AHI between 5 and 15 episodes/hour was considered characteristic of mild SDB, an AHI between 16 and 30 episodes/hour, of moderate SDB, and an AHI above 30 episodes/hour, of pronounced SDB.\(^{(23)}\)

The following PSG variables were included in the statistical analysis: sleep efficiency; body movements; awakenings of more than five minutes; sleep spindle frequencies; alpha-delta scale; REM sleep latency; REM density; percentage of stage 1 sleep; percentage of stage 2 and 3 sleep; percentage of REM stage sleep; number of apnea-hypopnea episodes during REM sleep; total number of apnea-hypopnea episodes during the night; AHI during REM sleep; and minimum arterial oxygen saturation during the night.

Two independent observers measured the alpha activity during delta sleep according to a subjective scale of 0 to 5 points, based on the density and duration of the alpha activity, in which 0 is equal to no alpha wave during the delta activity, and 5 is equal to 100% alpha wave intrusion into the delta activity. A score of 3 or more points was considered abnormal. In the abnormal cases, we used fast Fourier transformation (via the frequency analysis module of the Poliwin 4 computer program) to determine the density of alpha-delta sleep.

The data were analyzed using the Statistical Package for Social Sciences software in order to obtain the descriptive statistics of frequency, mean, standard deviation, and confidence interval. Nonparametric data were compared using Fisher’s exact test, and parametric data were compared using Student’s t-test. In order to identify variables that would be predictive of FMS, Pearson’s correlation coefficient was used, together with logistic regression. Findings for which the probability of an alpha error was lower than 5% were considered statistically significant.

## RESULTS

The anthropometrical and PSG data for the 50 patients studied are shown in Table 1.

Of the 32 men and 18 women evaluated, 29 and 14, respectively, were diagnosed with OSAHS. The criteria for a diagnosis of upper airway resistance syndrome were met by 3 men and 4 women. The OSAHS was considered mild in 6 cases, moderate in 14 cases and severe in 23 cases.

Of the 50 patients, 9 women and 2 men were diagnosed with FMS based on complaints of diffuse pain for more than three months, as well as on presenting more than 11 tender points that tested positive for pain in the algometry (mean, 17 ± 1 points; range, 14 to 18 points). The predominance of the diagnosis in women over that of the diagnosis in men was significant (chi-square = 11.8; p = 0.001). In comparing only women with FMS to those without, we found no significant differences in the anthropomorphic data or in FMS severity.

Cases of FMS occurred in patients with all degrees of SDB: 2 cases among the 7 patients with upper airway resistance syndrome; 3 cases among the 6 patients with mild OSAHS; 3 cases among the 25 patients with moderate SDB; and 1 case among the 10 patients with severe SDB.

### TABLE 1

<table>
<thead>
<tr>
<th>Fibromyalgia syndrome</th>
<th>Yes</th>
<th>No</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>48 ± 15</td>
<td>50 ± 11</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4 ± 3.8</td>
<td>30.7 ± 5.7</td>
<td>0.023</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>87 ± 8</td>
<td>82 ± 12</td>
<td>n.s.</td>
</tr>
<tr>
<td>Body movements</td>
<td>200 ± 165</td>
<td>261 ± 163</td>
<td>n.s.</td>
</tr>
<tr>
<td>Awakenings lasting more than 5 minutes</td>
<td>3 ± 2</td>
<td>3 ± 2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Alpha-delta sleep</td>
<td>2 ± 1</td>
<td>2 ± 1</td>
<td>0.009</td>
</tr>
<tr>
<td>Stage 1 sleep (%)</td>
<td>6 ± 4</td>
<td>8 ± 3</td>
<td>0.051</td>
</tr>
<tr>
<td>Stages 3 and 4 sleep (%)</td>
<td>16 ± 7</td>
<td>11 ± 8</td>
<td>n.s.</td>
</tr>
<tr>
<td>REM Sleep (%)</td>
<td>17 ± 5</td>
<td>15 ± 7</td>
<td>n.s.</td>
</tr>
<tr>
<td>AHI (episodes/hour)</td>
<td>23 ± 27</td>
<td>39 ± 29</td>
<td>n.s.</td>
</tr>
<tr>
<td>Minimum SaO₂ (%)</td>
<td>84 ± 7</td>
<td>74 ± 16</td>
<td>0.006</td>
</tr>
</tbody>
</table>

BMI: body mass index; AHI: apnea-hypopnea index; SaO₂: arterial oxygen saturation
among the 14 patients with moderate OSAHS; and three cases among the 23 patients with severe OSAHS. The difference was not significant (chi-square = 3.99; p = 0.26).

In 5 of the 11 patients with FMS and in 4 of the other 39 patients, electroencephalogram results detected unusually high alpha activity during slow-wave sleep. The risk for those in the FMS group to present high alpha-delta levels was seven times greater than that for the non-FMS group (odds ratio = 6.9; 95% confidence interval: 1.4-33.3; chi-square = 6.68; p = 0.02).

Four of the anthropometrical and polysomnographic variables correlated with FMS: gender (correlation coefficient = 0.507; p = 0.000), body mass index (correlation coefficient = -0.321; p = 0.23), alpha-delta sleep (correlation coefficient = 0.297; p = 0.04) and sleep spindles (correlation coefficient = 0.292; p = 0.04). In the logistic regression to predict FMS, the significant factors were gender (p = 0.001 for being female), body mass index (p = 0.029) and delta-alpha sleep (p = 0.01).

**DISCUSSION**

According to the historical control of the study conducted by Wolfe et al., which was the first epidemiological study to adopt the ACR criteria, the prevalence of FMS in the general population is 0.5% for men. However, in our study sample, we observed a prevalence of approximately 7% (p < 0.000001). Whereas the Wolfe et al. value was 3.4% for women in the general population, our sample presented an FMS prevalence of 50% among the women (p < 0.000001). In generalizing these results to other populations, one should take into account the selection bias resulting from the recruitment of patients seeking treatment at a sleep clinic, the lack of a control group and the small number of cases. Nevertheless, the detection of FMS in a proportion ten times greater than in the general population makes a strong argument in favor of the hypothesis that there is an association between SDB and FMS.

Previous studies, although also involving small study samples, have demonstrated a relationship between SDB and FMS. In 1986, Molony et al. studied eleven patients with OSAHS and reported that three met the criteria proposed for the diagnosis of FMS, concluding that frequent OSAHS awakenings could be a cause of FMS. In 1993, another group of authors detected OSAHS in 11 out of 25 men with FMS. Still others, in 2004, found SDB in 27 of 28 women with FMS. However, in various other studies involving larger study samples, no association between FMS and SDB has been observed.

Our finding that alpha activity increased during delta sleep in 5 of the 11 cases of FMS is consistent with that of other authors, who observed alpha-delta sleep in 20 out of 40 women with FMS. However, alpha activity on sleep electroencephalograms might simply mean that there are awakenings related to the increased upper airway resistance. Therefore, the painful symptoms reported by these patients may be related to the reduced quantity of delta sleep, secondary to sleep fragmentation, unlike what occurs in "primary" FMS.

The findings of the present study are consistent with the hypothesis that there is an association between SDB and FMS. The association is clear, although it does not imply a cause-and-effect relationship. The physiopathology of the upper airway collapse is multifactorial. One factor is the role played by serotonergic neurotransmission. Other anatomical, myopathic and neuropathic factors are equally involved. In fact, there is evidence to suggest that FMS and SDB are caused by disorders of neurotransmitters, notably serotonin. The depopulation of serotonergic dorsal raphe neurons may be a consequence of the long-term progression of OSAHS. In a study reviewing the pharmacology of sleep apnea, upper airway relaxation, which leads to airway collapse and apnea, was attributed to a lack of serotonin. Although still incipient, those findings are consistent with those of the present study.

In the present study, the prevalence of FMS was seven times higher among women than among men, which is practically identical to that observed in another study. The lower AHIs seen among the eleven patients with FMS can be ascribed to the fact that this group consisted of nine women, who generally present less severe OSAHS.

The purpose of this study was not to define the epidemiology or the etiology of FMS, but to promote the advancement of knowledge regarding the controversial idea that this illness is associated with SDB. Our results suggest that there is a high prevalence of FMS in patients with SDB.
REFERENCES


J Bras Pneumol. 2006;32(4):333-8