

OUTCOME OF SLEEPINESS AND FATIGUE SCORES IN OBSTRUCTIVE SLEEP APNEA SYNDROME PATIENTS WITH AND WITHOUT RESTLESS LEGS SYNDROME AFTER NASAL CPAP

Raimundo Nonato Delgado Rodrigues¹, Aída Alexandra Alvim de Abreu e Silva Rodrigues², Riccardo Pratesi³, Marília Miranda Fortes Gomes⁴, Ana Maria Nogales Vasconcelos⁵, Christine Erhardt⁶, Jean Krieger⁷

ABSTRACT - Background and Purpose: The association of obstructive sleep apnea syndrome (OSAS) and restless legs syndrome (RLS) has been reported in the literature for many years. Both conditions may be responsible for fatigue and somnolence complaints secondary to nocturnal sleep disruption. The primary concern of this study is to evaluate the outcome of fatigue and daytime sleepiness symptoms at baseline and after continuous positive air pressure (CPAP) treatment in OSAS patients with and without RLS. **Method:** A prospective and comparative study between a group of 13 patients with OSAS and a group of 17 patients with OSAS+RLS. Laboratory blood tests and polysomnography were performed at baseline. The Epworth Sleepiness Scale (ESS) and the Pichot's questionnaire of fatigue/depression (PIC) were applied before and after 3 months of CPAP treatment. Results were compared. **Results:** No significant differences were found on PSG and laboratory results at baseline. Both groups had similar ESS and PIC scores at baseline ($p=0.73$ and 0.08 , respectively). After n-CPAP, OSAS+RLS patients showed higher ESS and PIC scores ($p=0.017$ and 0.03 , respectively). **Conclusions:** Despite a favorable general response, n-CPAP seemed less effective in treating fatigue and sleepiness in the OSAS+RLS group.

KEY WORDS: OSAS, RLS, fatigue, sleepiness, ESS, Pichot.

Evolução dos índices de sonolência e fadiga em pacientes com síndrome da apnéia obstrutiva do sono portadores ou não de associação com síndrome das pernas inquietas após CPAP nasal

RESUMO - Objetivo: A associação síndrome de apnéia obstrutiva do sono / síndrome de pernas inquietas (SAOS-SPI) tem sido mencionada na literatura há muito. Ambas podem ser responsáveis por queixas de fadiga e sonolência secundárias à fragmentação do sono noturno. O objetivo deste estudo é avaliar a evolução dos sintomas de fadiga e sonolência diurna excessiva antes e após o tratamento com pressão aérea positiva contínua (CPAP) em pacientes portadores de SAOS, com e sem SPI. **Método:** Estudo prospectivo e comparativo entre um grupo de 13 pacientes com SAOS e um grupo de 17 com SAOS +SPI. Exames laboratoriais e polissonografia (PSG) foram realizados no início do estudo. A escala de sonolência de Epworth (ESE) e o questionário de fadiga/depressão de Pichot (PIC) foram aplicados antes do tratamento com CPAP e 3 meses após. Os resultados foram comparados. **Resultados:** No início do estudo não foram encontradas diferenças significativas na avaliação laboratorial e PSG. Ambos os grupos apresentavam inicialmente pontuação semelhante na avaliação da ESE e PIC ($p=0,73$ e $0,08$, respectivamente). Após CPAP, os pacientes SAOS+SPI apresentaram maiores ESE e PIC ($p=0,017$ e $0,03$, respectivamente). **Conclusão:** Apesar de resposta inicial favorável em ambos os grupos, o CPAP foi aparentemente menos eficaz na redução das queixas de fadiga e sonolência nos pacientes apnéicos com associação a SPI.

PALAVRAS-CHAVE: SAOS, síndrome das pernas inquietas, fadiga, sonolência, escala de sonolência de Epworth, Pichot.

¹Neurologist, PhD, Hospital Universitário de Brasília, Brasília DF, Brazil; ²Pulmonologist, MD, Hospital Universitário de Brasília, Brasília DF, Brazil; ³Neurologist, PhD, Universidade de Brasília, Brasília DF, Brazil (UnB); ⁴Statistician, MS, Department of Statistics, UnB; ⁵Statistician, PhD, Department of Statistics, UnB; ⁶Neurologist, MD, Chef de Clinique, Hospices Civils de Strasbourg; ⁷Neurologist, PhD, Chef de Service, Service d'Exploration Fonctionnelle du Système Nerveux et de Pathologie du Sommeil, Université Louis Pasteur (ULP) Hospices Civils de Strasbourg, France. The first author of this study was sponsored by a scholarship from CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), Programa 5300101005P-7, Ministry of the Education, Brazilian Government.

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Dr. Raimundo Nonato Delgado Rodrigues - SQN 206 K 303 - 70844-010 Brasília DF - Brasil. E-mail: reno@unb.br

The association of obstructive sleep apnea syndrome (OSAS) and restless legs syndrome (RLS) has been described for many years^{1,2}. As both conditions are frequent in the general population some difficulties in differential diagnosis may arise since both greatly disrupt nocturnal sleep, causing fatigue, limb motor hyperactivity and daytime sleepiness³. In addition, some sleep laboratories may not have surface electromyographic analysis of the anterior tibialis muscle as a routine procedure during polysomnographies and therefore many nocturnal limb movements (seen in about 85% of RLS patients⁴) may easily pass unnoticed or be attributed only to respiratory effort⁵. In fact, the details of that interesting association have not been fully elucidated. For instance, the need to treat both conditions simultaneously and their individual influence on daytime sleepiness and fatigue complaints are not fully understood.

A common relationship has been suggested, however, related to a possible dysfunction of brainstem centers². Nonetheless, to our knowledge, there is no description or clear evidence of a central nervous system disturbance resultant from OSAS and RLS in a same patient. Furthermore, the frequent concomitant occurrence of metabolic syndrome in OSAS patients^{6,7} constitutes another important causative factor (i.e. relative iron overload) for limb motor abnormalities⁸.

On the other side it is interesting to notice that continuous positive air pressure (CPAP) treatment may contribute to the reduction of fatigue and sleepiness complaints in RLS patients with associated OSAS⁹.

Therefore, this study aimed at evaluating possible differences in sleepiness and fatigue response patterns, before and after CPAP treatment, between OSAS and OSAS+RLS-associated patients. In addition, we described this association in terms of its clinical, laboratory and polysomnographic features.

METHOD

Subjects – Seventeen OSAS patients, who met the diagnostic criteria for RLS (12 men and 5 women, mean age: 52±10 years, range: 29-69), were consecutively identified⁹⁻¹¹. In addition, 13 patients presenting only OSAS (10 men and 3 women, mean age: 54±4.8 years, range: 45-62) were also selected. Patients had been admitted to the Strasbourg University Sleep Disorders Unit for the initial OSAS workup and entered the study group after informed consent was obtained and the whole protocol received the approval of our Institution's Ethics Committee. All 30 patients presented periodic leg movements (PLM) as well, except one (belonging to the OSAS group).

OSAS diagnosis was determined according to the following criteria: snoring, excessive daytime sleepiness and

an apnea-hypopnea index greater than five events per hour of sleep. PLM diagnosis was made using the parameters described by Coleman¹², while RLS was clinically determined employing international criteria¹³. All patients had been diagnosed with OSAS, RLS or PLM for the first time and had never received previous treatment for any of these disorders. Patients were divided into two groups: one comprised of OSAS patients (n=13) and the second of OSAS+RLS-associated patients (n=17).

General procedure – The protocol used in this study has been object of a previous publication where further details can be found⁹. Laboratory blood tests were performed in both groups, including blood glycemia, iron metabolism (serum transferrin and ferritin), TSHUs (thyroid stimulating hormone-ultra-sensitive) and T4 dosages. Body mass index (BMI) was also determined in all subjects.

A polysomnographic assessment (PSG) was conducted during a 4 night period spent at the Sleep Unit: (1) one night for habituation to the laboratory settings, (2) one for diagnostic purposes (polysomnographic night), (3) one for nasal-CPAP titration, and (4) one for employing nasal-CPAP with a fixed pressure, as determined during the previous night. The polygraphic digital systems used comprised of two Brainnet® Medatec and an Alice® 4 Respironics both provided with a pneumotachograph (Tyco-Healthcare-Puritan Bennett®) or a nasal canula coupled to a pressure transducer (Protech® Salter Labs) and an esophageal pressure sensor or a thoracic-abdominal strain gauge. Limb EMG was detected via surface electrodes placed over the right and left tibialis muscle. Biological calibration was held prior to recording and data were digitally stored and analyzed off-line. PLM were scored according to Coleman's criteria¹².

Sleep was visually scored according to Rechtschaffen and Kales criteria¹⁴. Microarousal criteria were those described by ASDA (later AASM)¹⁵.

Additional sleep parameters were included, defined as follows:

- Total sleep time (TST): time between the beginning and end of sleep (TSP) minus the time spent awake during the night;
- Sleep efficiency (SE): TST during the entire the recordings expressed as percentages;
- Percentage of stages 1 and 2 (PS 1-2): time spent in stages 1 and 2 during the TST;
- Percentage of stages 3 and 4 (PS 3-4): time spent in stages 3 and 4 during the TST;
- Percentage of REM (PREM): time spent in rapid-eye movement sleep during the TST;
- Index of arousals (IAr): total number of microarousals per hour of sleep;
- Apnea-hypopnea index (AHI): number of respiratory events occurring per hour of sleep;
- PLM index (PLMi): number of periodic leg movements occurring per hour of sleep.

Subjective daytime sleepiness and fatigue evaluation – The Epworth Sleepiness Scale (ESS) scores¹⁶ were used to

evaluate the patients' level of daytime sleepiness, while fatigue was measured employing the Pichot questionnaire (PIC)¹⁷. The later is a practical 24-item self-rating account with three homogeneous sub-scales of 8 items each which measure depressive mood, asthenia-fatigue and anxiety parameters, respectively. The asthenia-fatigue scale was used, consisting of 8 questions scored progressively from "0" (not at all) to "4" (extremely) (Table 1). Three months after initiating n-CPAP treatment, all patients returned to the Sleep Unit on an outpatient basis and had their daytime sleepiness and fatigue re-evaluated by applying the questionnaires described above.

Statistical analysis – Statistical analyses were performed using SPSS for Windows, v.13.0. Mann-Whitney tests were used to compare biometric, laboratory and polysomnographic data. Data before and after n-CPAP treatment were compared via Wilcoxon tests. Statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics – Both groups presented a wide range of OSAS severity. Mean apnea-hypopnea index was $56 \pm 35/h$ for group 1 and $44 \pm 27/h$ for group 2 ($p = 0.14$), and BMI was $34.7 \pm 9 \text{ Kg/m}^2$ for group 1 and $34 \pm 8 \text{ Kg/m}^2$ for group 2 ($p = 0.81$). All subjects had low sleep efficiencies (mean: group 1 - $69 \pm 16\%$, group 2 - $72 \pm 12\%$; $p = 0.54$) and a high microarousal index (mean: group 1 - $67 \pm 28/h$, group 2 - $44 \pm 20/h$; $p = 0.11$). Age ($p = 0.5$) and gender (23.1% and 29.4% women in group 1 and 2, respectively) did not differ significantly between the two groups.

Clinical and laboratory characteristics – The baseline biochemical profile (Table 2) of both groups was not significantly different. Polysomnographic and n-CPAP data are presented in Table 3.

Sleepiness, PLM index and fatigue – Similar baseline ESS scores were observed between the two groups ($p = 0.73$).

Following 3 months of n-CPAP treatment, ESS

Table 1. Pichot's questionnaire: items measuring the asthenia-fatigue dimension.

- 1) I feel short of stamina
- 2) Everything I do requires a huge effort
- 3) I have a feeling of weakness in certain parts of my body
- 4) My arms or legs are heavy
- 5) I feel tired for no reason
- 6) I feel like lying down and resting
- 7) I have difficulty to concentrate
- 8) I feel discouraged, my arms and legs are sore and heavy

scores decreased significantly. In OSAS patients, the mean score of 10.5 ± 4.6 observed prior to n-CPAP treatment was reduced to 4.7 ± 4.9 after treatment ($p = 0.004$). Similarly, the mean score of 10.6 ± 4.8 in OSAS+RLS patients decreased to 7.4 ± 3.5 ($p = 0.014$). In addition, final ESS scores after n-CPAP differed significantly between groups ($p = 0.017$). This finding may suggest that n-CPAP treatment was less efficient at improving daytime sleepiness in OSAS+RLS patients.

Furthermore, periodic movements of OSAS subjects ranged from 0-164 (mean PLM index: $15.7 \pm 27.2/h$), while in the OSAS+RLS group the PLM range was that of 3-127 (mean PLM index: $5.1 \pm 3.4/h$; $p = 0.51$).

Via Pichot's questionnaire we observed that fatigue scores were similar in both groups before treatment (Table 4). Scores decreased significantly, however, after n-CPAP treatment within both groups, particularly in the OSAS+RLS group (Table 4). Nonetheless, OSAS+RLS patients' final scores were still higher than those of the remaining subjects (OSAS group).

DISCUSSION

OSAS+RLS associations are observed in only 2.0-8.3% of OSAS patients¹⁸⁻²⁰. Such small prevalence may be due, however, to the fact that RLS is in itself a

Table 2. Baseline biochemical profile of OSAS and OSAS+RLS patients.

Biochemical parameter	Normal values	Group 1 (OSAS)	Group 2 (OSAS+RLS)	p
TSH (mU/l)	0.15-4.5	1.7 ± 0.8	1.5 ± 0.5	0.23
T4 (ng/l)	11.6-26	16.3 ± 2.5	15.4 ± 2.69	0.23
Glucose (mmol/l)	4.1-5.9	6.5 ± 3.1	6.2 ± 1.1	0.36
Transferrin (g/l)	1.68-2.7 (women) 1.70-2.8 (men)	2.5 ± 0.4	2.3 ± 0.67	0.11
Ferritin (ug/l)	14-186 (women) 32-284 (men)	156.9 ± 130.4	274.5 ± 245.8	0.17

TSH, thyroid stimulating hormone; T4, thyroxin hormone.

Table 3. Polysomnographic and n-CPAP data of OSAS and OSAS+RLS patients.

	Group 1 (OSAS)	Group 2 (OSAS+RLS)	p
TST (hours)	4.2±1.5	4.8±0.7	0.29
SE (%)	69±0.16	72±0.12	0.54
PSI-2 (%)	71.34±16.92	70.34±22.38	0.57
PS3-4 (%)	13.74±11.75	14.65±9.78	0.81
PREM (%)	14.91±8.43	9.12±6.96	0.11
IAR (number/h)	67.38±28.1	44.54±19.97	0.11
IAH (number /h)	56.11±35.25	44.26±27.5	0.41
n-CPAP (cmH ₂ O)	9.69±2.92	9±2.93	0.5

TST, total sleep time; SE, sleep efficiency; PSI-2, percentage of stages 1 and 2; PS3-4, percentage of stages 3 e 4; PREM, percentage of REM; IAR, index of arousals; IAH, apnea-hypopnea index; n-CPAP, positive pressure level.

Table 4. Fatigue scores observed before and after n-CPAP treatment.

Fatigue score	Group 1 (OSAS)	Group 2 (OSAS+RLS)	p (between groups)
PIC (before CPAP)	11.7±6.6	16.6±7.3	0.08
PIC (after CPAP)	5.1±6.1	10.1±6.4	0.03
p (within-group)	0.008	0.001	

PIC, Pichot's questionnaire.

highly under-diagnosed condition²¹. In this context, the present study aimed at determining if the occurrence of RLS was associated to a clinically distinct OSAS profile or to a specific response of daytime sleepiness and fatigue complaints to n-CPAP therapy in two groups of patients with and without the association OSAS+RLS.

Our results indicated that OSAS and OSAS+RLS patients had similar baseline biochemical and biometric profiles. In fact, the concomitant occurrence of obesity, hyperglycemia or insulin resistance and high ferritin levels in OSAS patients may suggest an association to a metabolic syndrome or syndrome "X"⁶. Some authors have even suggested that the definition of metabolic syndrome should be broadened to include OSAS²². In addition, serum ferritin levels are considered to be one of the main determinants of blood glucose and a good marker of insulin resistance²³.

Importantly, polysomnographic data indicated that sleep quality tended to be low for all patients. In addition, sleepiness evaluation, respiratory disturbance index, PLM index and therapeutic positive pressure levels determined during the titration night were also similar in both groups. Thus, no major baseline clinical or polysomnographic differences were ob-

served in the OSAS patients, regardless of a possible association with RLS.

Similarly, subjective baseline daytime sleepiness, evaluated by the ESS, did not differ among both groups. Furthermore, significant improvements in the ESS scores were observed in both groups following n-CPAP treatment for 3 months, consonant with previous findings²⁴. Such improvement is thought to occur in response to a reduction in sleep fragmentation, which stabilizes sleep structure, re-establishes correct oxyhemoglobin blood levels and decreases respiratory effort leading to a more refreshing night sleep²⁵. However, OSAS+RLS patients presented higher ESS scores, relative to OSAS subjects, regardless of the general improvement in sleepiness. Such result may suggest that these patients respond less favorably to n-CPAP therapy. To our knowledge, this is the first study to report that.

Similar baseline fatigue symptoms were found in both groups, although OSAS+RLS subjects presented higher absolute scores on the Pichot's questionnaire (16.6±7.3), compared to OSAS patients (11.7±6.6). In general, all patients responded well to n-CPAP therapy, with an important decrease in fatigue scores. When evaluated after the third month of treatment, OSAS+RLS patients still demonstrated higher fatigue scores.

Fatigue, like somnolence, is frequently viewed as a consequence of non-restorative sleep²⁶, responding favorably to n-CPAP treatment in OSAS^{27,28}. The exact etiological generator of fatigue is still not clear, although many possible sources have been suggested, notably the brainstem, hypothalamus, autonomic nervous system and the neuroendocrine system²⁹. Abnormal P300 latencies are considered a good tool for assessing fatigue symptoms²⁹.

In addition, our findings seem to suggest that correction of respiratory disturbance alone may not be sufficient to entirely overcome complaints of fatigue and daytime sleepiness in OSAS+RLS patients. Pathological changes in central pathways (at subcortical levels?), seen in RLS, could eventually have increased sleep disruption, adding to fatigue and somnolence and decreasing responsiveness to n-CPAP. It would be interesting in the future and within a larger group of patients, to study the influence of relative REM sleep deprivation in this context. At this point it would also be interesting to speculate on the need to treat OSAS+RLS patients for respiratory and motor symptoms separately, if the latter are to be considered a cause for the persistence of fatigue symptoms.

Additional studies are necessary to fully elucidate these aspects, including a larger number of patients, a longer follow-up period, and taking into account other factors such as n-CPAP compliance. In our study the compliance was evaluated (and reinforced) through personal or phone contact, which may not give a sufficient degree of certitude. A second polysomnographic evaluation would also be necessary following the onset of n-CPAP treatment in order to re-evaluate the macrostructure of sleep and compare sleepiness more objectively.

In summary, the present study demonstrated that the concomitant occurrence of RLS and OSAS does not seem to be associated to a significantly distinct basal clinical or laboratory OSAS profile. Following n-CPAP treatment, a positive response in terms of a decrease in fatigue and sleepiness scores was observed in both groups. Nevertheless, OSAS and OSAS+RLS patients responded differently to the n-CPAP therapy, with higher residual fatigue and sleepiness scores persisting in the OSAS+RLS group. Such finding may be due to possible central dysfunctions observed in RLS. Thus, there seems to be a need to treat OSAS+RLS patients for both respiratory and motor symptoms.

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