

Hypersomnolence in fibromyalgia syndrome

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ABSTRACT

Objective: To evaluate hypersomnolence in patients affected by fibromyalgia syndrome.

Methods: Thirty consecutive patients affected by fibromyalgia syndrome (FMS) (28 F) completed a sleep questionnaire and underwent the following evaluations: lung function tests; polysomnography; the Epworth sleepiness scale (ESS), which measures sleep complaints and daytime hypersomnolence; and the visual analogical scale (VAS) to detect subjective pain, fatigue, anxiety and depression.

Results: The FMS patients were divided into two groups based on their ESS score. Patients complaining of daytime hypersomnolence had a higher number of tender points (15 ± 2 vs. 12 ± 1 , $p < 0.01$), a higher subjective pain score (72 ± 15 vs. 52 ± 13 , $p < 0.05$), and more fatigue ($p < 0.05$). The diffusing capacity of the lung (Tlco) was more impaired and the occurrence of periodic breathing was higher. FMS patients complaining of daytime somnolence had significantly less efficient sleep than the FMS patients with no daytime somnolence ($p < 0.05$), i.e. a lower proportion of stage 3 sleep ($5 \pm 2\%$ vs. $12 \pm 3\%$; $p < 0.001$), stage 4 sleep ($1 \pm 0.5\%$ vs. $4 \pm 1\%$; $p < 0.001$), and twice as many arousals per hour of sleep ($p < 0.01$). The respiratory pattern of FMS patients with hypersomnolence showed a higher occurrence of periodic breathing ($p < 0.05$). The short length of apneas and hypopnoeas did not affect the apnea/hypopnea index (5.1 ± 3 vs. 7 ± 4 ; ns), but FMS patients with daytime hypersomnolence had a greater number of desaturations per hour of sleep (11 ± 6 vs. 6 ± 5 ; $p < 0.05$). Pulmonary volumes did not differ between the two groups. The ESS score was significantly correlated in FMS patients, and even more markedly in the FMS patients with hypersomnolence, TLco, A/I, and disease duration. The ESS score was correlated significantly with the number of tender points only in FMS patients with daytime hypersomnolence.

Conclusion: The occurrence of daytime hypersomnolence in FMS patients is linked to a greater severity of fibromyalgia symptoms and to more severe polysomnographic alterations.

Introduction

Fibromyalgia syndrome (FMS) is a common condition causing generalized muscle pain (1). This syndrome affects up to 3-4% of the general population and is one of the most common diagnoses seen in ambulatory office settings. 80 to 90% of patients are women, and the peak age is 30-50 years (2).

The criteria used for its diagnosis were stated by the American College of Rheumatology in 1990 (3). The pain is widespread, lasting for at least three months, bilateral, above and below the waist, axial, and involving at least 11 of 18 specified tender points. Other characteristics of the syndrome - often present, but not essential for the diagnosis - are chronic fatigue, migraine, irritable bowel syndrome, headache, paresthesias, Raynaud's like symptoms, depression, anxiety and non-restorative and/or disturbed sleep (4).

The reported complaint of poor sleep is so common in FMS patients that in some case series its prevalence is nearly 100% (5-7). The observation that a neurasthenic musculoskeletal pain syndrome can be elicited in normal volunteers undergoing selective deep NREM sleep deprivation (7) seems to suggest that a vicious circle may be in operation, with pain impaired sleep leading to a worsening of the disease. Moldofsky *et al.* proposed an alpha intrusion on delta sleep in 1975 (8) as a marker of the sleep impairment typical of FMS patients, but this has not been confirmed by other studies (9, 10), while an association between alpha intrusion in NREM sleep and other FMS symptoms has been variously confirmed (11) and rejected (5) by different trials.

The hypothesis that other disorders causing sleep fragmentation, such as sleep apnea syndrome (12), might be blamed for the non-refreshing sleep symptoms reported by FMS patients was not confirmed by a controlled study (13).

However, increased daytime sleepiness is one of the most important symptoms in fibromyalgia patients. The aim of this study was to compare sleep complaints, sleep architecture, number of arousals, alpha-delta activity, and respiratory function in patients with FMS and hypersomnolence versus fibromyalgia with no daytime sleepiness.

Materials and methods

Population. Thirty eligible consecutive Caucasian patients (28 females) aged 51.2 ± 8.9 years with FMS, diagnosed according to the 1990 American College of Rheumatology Classification Criteria (3), were invited to participate in this study. A 2-week wash-out period for any pharmacological treatment related to FMS was requested of all patients. A sleep questionnaire and the Epworth Sleepiness Scale (ESS) were then administered to all subjects and the FMS patients were divided in two subsets according to the presence or absence of hypersomnolence. No difference was observed in the disease duration (7.3 ± 3.1 vs. 5.9 ± 3.8), age (52.2 ± 8.9 vs. 51.4 ± 2 yrs), sex (15/1 vs. 12/1 F/M) and body mass index (BMI) (25.8 ± 3.7 vs. 25.5 ± 3.1 Kg/m²) between the patients with and without hypersomnolence (HS). Informed consent was obtained in all cases. The Hospital Medical Ethics Committee approved the study.

Clinical evaluation. In all subjects the following clinical variables were evaluated: examination of 18 tender points using the protocol of Wolfe *et al.* (3) (a score for number of tender points was obtained and could range from 0 to 18); intensity of somatic pain expressed on a 100 mm visual analog scale (VAS); and anxiety, depression and fatigue expressed on a 100 mm VAS [(0: absent; 100: very severe)].

Study measures. A sleep questionnaire was administered to all subjects to evaluate sleep complaints (12). Hypersomnolence was evaluated according to the ESS (14). The ESS is a questionnaire measuring the general level of daytime sleepiness and is the sum of eight item scores. It can range from 0 to 24; the "clinically" normal range of the ESS score is 2 to 10 with a normal statistical distribution and a model score of 6.

Polysomnography. Polysomnography (PSG) was performed in the sleep laboratory, a sound attenuated room with temperature control, using a computer-assisted device (Alice 3 Healthdyne, Marietta, OH, USA). The electroencephalogram, electro-oculogram, and submental electromyogram were recorded with surface electrodes using standard techniques (15). Naso-oral ther-

mocouples and thoracic and abdominal belts with built-on piezo electrodes recorded airflow and ventilatory efforts respectively. Oxyhaemoglobin saturation was recorded by finger pulse oximetry (Pulsox-7 Minolta, Osaka, Japan). The transducers and lead wires allowed normal positional changes during sleep. Bedtime and awakening time were at each subject's discretion; the polysomnography was terminated after final awakening. In order to avoid the first night effect, each subject spent 2 nights in the sleep laboratory; only data recorded during the second night were evaluated.

Sleep and breathing variables were stored on an optical disk and then manually scored by two physicians, blinded, in 30s epochs, according to standard criteria (15). The correlation between sleep, breathing and body position was analysed automatically by the computer.

Apneas were defined as 10-second pauses in respiration. Hypopnoeas were defined as a decrement in airflow 50%, associated with either an arousal at the end of the episode or a fall in arterial oxygen saturation $\geq 4\%$. The respiratory disturbance index (RDI) was defined as the average number of episodes of apnoea and hypopnoea per hour of sleep and the desaturation event frequency (DEF) was defined as the number of episodes of fall $\geq 4\%$ in oxyhaemoglobin saturation per hour of sleep. Periodic breathing (PB) was defined as a series of at least 3 successive cycles of waxing and waning in ventilation, with apneas or hypopnoea.

Arousals were scored according to the American Sleep Disorders Association criteria (16).

Alpha-delta intrusion was defined as the spontaneous occurrence of alpha waves in delta wave sleep (17). Alpha waves usually appear during wakefulness with the eyes closed or in drowsy individuals, with a frequency of 7 to 11 cycles per second. Delta waves are the slow waves of deep sleep, with a frequency of less than 2 cycles per second, and amplitude greater than 75 μ V.

Lung function tests. All subjects underwent body plethysmography (Bodystar FG 90, Fenyves and Gut, Basel, Switzerland), transfer factor assessment for

the lung with the single breath holding method (TLco), including membrane (Dm) and capillary (Vc) components (T.T Autolink Morgan, Andover, MA, USA) and blood gas analysis (BG3, Instrumentation Laboratory, Paderno Dugnano, Italy).

Statistical analysis. Data were reported as mean \pm standard deviation. Statistical analysis of the anthropometric data, polysomnographic recordings and lung function tests was performed using the unpaired Student's *t* test. Pearson's chi square was used for other comparisons of means and proportions. The Mann-Whitney U test and the Spearman Rank correlation were used where appropriate. The level of significance was $p < 0.05$. All statistical analyses were performed using the statistical package SPSS 9.0 (SPSS Inc., Chicago, IL, USA).

Results

FMS patients were divided into two groups according to their ESS score: 16 FMS patients with hypersomnolence (FMS+HS) and 14 FMS patients without hypersomnolence (FMS-HS).

Patients complaining of daytime hypersomnolence had a higher number of tender points ($p < 0.01$), a higher subjective pain score ($p < 0.05$) and a significant fatigue score ($p < 0.05$) (Table I). Lung volumes (Table II) did not differ between the two groups, but lung diffusing capacity (TLco) and the diffusing capacity of the alveolar membrane (Dm) were significantly reduced in the FMS group with hypersomnolence ($p < 0.01$ and 0.001 , respectively).

PSG recordings (Table III) showed that FMS+HS patients had lower sleep efficiency ($p < 0.01$), and nearly twice as many arousals per hour of sleep (A/I) ($p < 0.01$).

The percentages of stage 1 and 2 sleep were similar in the 2 groups, although stages 3 and 4 were markedly reduced in the FMS+HS group ($p < 0.001$). Sporadic alpha intrusion during delta sleep was identified in 10/30 patients (33%) with no difference between the two FMS groups. The number/hour of DEF during sleep were higher in FMS+HS patients ($p < 0.05$). There was no difference in the RDI, average and nadir SaO₂ during sleep between the two

Table I. Clinical data of the patients admitted to this study in accordance to hypersomnolence.

	Hypersomnolence		p
	Yes	No	
N° of patients	16	14	ns
Epworth Sleepiness Scale score	15 ± 4	4 ± 2	0.001
N° of tender points	15 ± 2	12 ± 1	0.01
Pain (VAS)	72 ± 15	52 ± 13	0.05
Chronically poor sleep (%)	90	82	ns
Wake-up unrefreshed (%)	85	78	ns
Nocturnal awakening (%)	100	85	ns
Habitual snorers (%)	60	46	ns
Headache (%)	85	70	ns
Irritable bowel syndrome (%)	54	45	ns
Anxiety (VAS)	64 ± 11.2	54 ± 9.8	ns
Depression (VAS)	75 ± 15	63 ± 12.4	ns
Fatigue (VAS)	80 ± 12	62 ± 10	0.05

Table II. Pulmonary function data in 30 patients affected by fibromyalgia syndrome (FMS) according to presence or absence of hypersomnolence.

	Hypersomnolence		p
	Yes	No	
N° of patients	16	14	
Forced Vital Capacity (FVC) (L)	3.0 ± 0.8	3.2 ± 0.7	ns
Forced Expiratory Volume in 1 sec (FEV1) (L)	2.4 ± 0.7	2.5 ± 0.8	ns
Residual Volume (RV) (L)	1.6 ± 0.8	1.7 ± 0.6	ns
Total Lung Capacity (TLC) (L)	4.6 ± 1.2	4.7 ± 1.0	ns
Diffusing capacity of lung (TLco) (mmol/min/kPa)	5.3 ± 1	6.4 ± 1	0.01
Diffusing capacity of alveolar membrane (Dm) (mmol/min/kPa)	9.3 ± 0.8	11.4 ± 0.7	0.001
Volume of blood in alveolar capillaries (Vc) (L)	0.51 ± 0.05	0.53 ± 0.07	ns
Arterial blood O ₂ partial pressure (PaO ₂) (kPa)	11.8 ± 0.6	12.5 ± 0.5	0.01
Arterial blood CO ₂ partial pressure (PaCO ₂) (kPa)	4.6 ± 0.3	5.2 ± 0.4	0.01
Haemoglobin (Hb) (g/dl)	13.5 ± 1.0	13.6 ± 0.9	ns

Table III. Polysomnographic data in 30 fibromyalgia syndrome (FS) according to hypersomnolence.

	Hypersomnolence		p
	Yes	No	
No. of patients	16	14	
Sleep time (min.)	291 ± 46	334 ± 45	0.05
Stage 1 (% sleep time)	20 ± 5	22 ± 7	ns
Stage 2 (% sleep time)	36 ± 10	33 ± 8	ns
Stage 3 (% sleep time)	5 ± 2	12 ± 3	0.001
Stage 4 (% sleep time)	1 ± 0.5	4 ± 1	0.001
Rapid Eye Movement (% sleep time)	17 ± 9	18 ± 8	ns
Sleep efficiency (%)	79 ± 10	89 ± 6	0.01
Oxygen saturation (SaO ₂ %) average during sleep	94.4 ± 1.9	95 ± 2	ns
SaO ₂ % nadir during sleep	84.4 ± 4	86 ± 3	ns
Desaturation Event Frequency (events/hr)	11 ± 6	6 ± 5	0.05
Respiratory Disturbance Index (events/hr)	5 ± 3	7 ± 4	ns
Periodic Breathing (% sleep time)	18 ± 7	11 ± 7	0.05
Arousal index (N°/hr)	10 ± 3	6 ± 2	0.01

FMS groups (Table III).

Periodic breathing was observed in 26/30 patients (86%); the usual length of apnoeic or hypopnoea episodes during

PB was less than 10 sec; therefore the RDI and average SaO₂ during sleep did not differ between the two groups. Nevertheless, PB was present for a

mean 18% of the night in FMS+HS patients in comparison with 11% in FMS-HS (p < 0.05)

The ESS score was significantly correlated in FMS patients, and even more markedly in FMS+HS patients, with Tlco,A/I and the disease duration. The correlation between the ESS score and PB of the total sleep time (%) was similar in the two groups. The ESS score was correlated significantly with the number of tender points only in the FMS+HS patients (Table IV).

Discussion

Sleep architecture and hypersomnolence

Fibromyalgia syndrome is a disease with a higher female prevalence, causing poor sleep in 60-90% of subjects (1, 3-6). In our case series of 30 consecutive FMS patients symptoms such as nocturnal awakening, poor sleep quality, fatigue, morning headache and waking up unrefreshed were very common and did not significantly differ in the two FMS groups in relation to daytime sleepiness. However, no dramatic alterations in PSG were seen, a fact which does not support the severity of these symptoms. Although Moldofsky *et al.* (7) showed that slow wave sleep deprivation can exacerbate pain and asthenia during the daytime, this can hardly explain hypersomnolence. The amount of both stage 2 and REM phases was not different between patients with and without daytime hypersomnolence, thus excluding REM deprivation as a possible cause of excessive anxiety or psychological disorders which could lead to an overestimation of symptoms. The number of arousals was about twice as high in HS patients, but not greater than 10 episodes/hour, a figure which is rarely associated with hypersomnolence and far lower than that reported in other diseases causing poor sleep quality and hypersomnolence (*i.e.* obstructive sleep apnea syndrome [OSAS]). The analysis of arousals was performed according to ASDA criteria (16), which include both EEG arousals and movement arousals lasting more than 3 seconds. The alpha-delta intrusion, reported in a previous study as a possible factor disrupting sleep (10), occurred sporadically in our patients;

Table IV. Spearman rank correlation between the ESS score and sleep, functional data, symptoms and duration of FMS in years in FMS patients with and without day hypersomnolence.

ESS score versus	Hypersomnolence			
	Yes		No	
	r	p value	r	p value
Periodic Breathing (% sleep time)	0.73	0.01	0.74	0.01
TLco (mmol/min/kPa)	-0.81	0.0001	-0.75	0.01
Arousal Index (N°/hr)	0.75	0.001	0.74	0.01
N° of tender points	0.76	0.0001	0.37	NS
Durations of FMS (yrs)	0.75	0.0001	0.7	0.01

therefore, a significant role in the pathogenesis of hypersomnolence cannot be alleged on the basis of our data. The presence of another sleep-related respiratory disorder, namely OSAS, was not detected in our population of non-obese FMS patients, although more than half were snorers - a result in accordance with Molony *et al.* (12). Also the possibility of an upper airway resistance syndrome seems to be excluded by a number of arousals lower than 10 per hour.

It is thus possible that the usual criteria applied to other patients (i.e. OSAS) cannot be used in FMS patients. The high female prevalence could play a role as well, since females tend to over-report symptoms of sleep disturbance (18).

Periodic breathing and diffusion abnormalities

The occurrence of PB for a mean 18% of sleep time in FMS+HS patients could play an important role in the 'poor sleep' complaints of these patients. In a previous paper we reported this respiratory pattern during sleep in FMS patients (6). It is well known that periodic breathing may be linked to an unstable functioning of the body's ventilation control system, elicited by the transition from wakefulness to sleep, which can occur even in normal subjects for a limited amount of time. When sleep becomes more consolidated PB usually disappears (19). Pain can reduce sleep efficiency, causing more frequent arousals and increasing the chances for periodic breathing to appear. However, the occurrence of PB in our patients (26 out of 30) was too high to be explained only on this basis.

The absence of neurological diseases or cardiac failure excluded the two most common causes of PB. The fact that TLco is reduced in FMS patients, and even further reduced in those with hypersomnolence, may throw some light on the pathogenesis of PB. Again we have not found previous reports of this finding in FMS patients, probably because this index was not routinely measured, since pulmonary function and blood gases are usually normal, as was the case in our patients. When TLco is reduced, a normal PaO₂ is maintained only by hyperventilation, which causes a PaCO₂ decrease.

We have no explanation for the lower TLco in FMS patients: pulmonary function tests were normal, Hb levels were similar to normal subjects, all patients were non-smokers, and when the measurement was normalized by "CO back-tension" (COHb) the data did not change. The overlap between relative hypocapnia, hyperventilation and ventilatory instability at sleep onset and during the lighter stages of sleep (possibly enhanced by pain-related sleep disruption) could perhaps explain the occurrence of periodic breathing in FMS subjects. The similarities with high altitude periodic breathing - short apneas/hypopneas, 'poor sleep' complaints, increased percentage of phase I sleep (19) - further support the hypothesis of a hypoxic-hypocapnic mechanism.

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