

Sleep architecture in patients with fibromyalgia

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The main objective of this work was to evaluate the characteristics of sleep in patients diagnosed with fibromyalgia syndrome. Sleep architecture in 32 patients with fibromyalgia and 20 healthy controls was evaluated. Following the recommendations of the International Federation of Clinical Neurophysiology, polysomnographies were conducted with fibromyalgia patients and the control subjects. The fibromyalgia patients showed alterations in cyclic organization of sleep and an increased number of periodic leg movements associated with cortical arousals. No significant differences were found in respiratory and oximetry variables or in alpha-delta sleep. The results support that fibromyalgia patients present an increase of superficial sleep at the expense of deep sleep and also an increase of periodic leg movements, which could have a pathogenic effect, facilitating the onset of the illness. Lastly, we discuss the results and propose some future lines of research.

Arquitectura del sueño en pacientes con fibromialgia. El objetivo central del trabajo fue evaluar las características del sueño en pacientes con fibromialgia. Se evaluó la arquitectura del sueño en 32 pacientes con fibromialgia, utilizando como controles 20 personas sanas. Tanto a las pacientes fibromiálgicas como a los controles se les realizó una polisomnografía de acuerdo con las recomendaciones de la Federación Internacional de Neurofisiología Clínica. Las pacientes con fibromialgia mostraron alteraciones en la organización cíclica del sueño, así como mayor número de movimientos periódicos de las piernas asociados a despertares corticales. No se han obtenido diferencias significativas en las variables respiratorias ni oximétricas, tampoco en el sueño alfa-delta. Los resultados obtenidos indican que las pacientes con fibromialgia presentan incremento del sueño superficial en detrimento del sueño profundo, así como un incremento de los movimientos periódicos de las piernas, que podrían actuar de forma patogénica, favoreciendo la aparición de la enfermedad. Finalmente, se discuten los resultados y se proponen futuras líneas de investigación.

Fibromyalgia (FM) is a kind of nonarticular rheumatism (Arnold, 2010; Arnold, Hudson, Hess, Ware, Fritz, & Auchenbach, 2004; Arnold, Hudson, Keck, Auchenbach, Javaras, & Hess, 2006; Ballina, 2004) that is characterized by chronic musculo-skeletal pain associated with painful palpation certain predetermined sites (Casanueva, 2007). The pathogenic mechanisms that provoke the symptoms in these patients are currently unknown, and no objective alterations in the structures where the pain is located, in the muscles or the adjacent nervous paths have been found (Bennett, Clark, & Campbell, 1991). There is evidence supporting the participation of undefined anomalous psychophysiological processes (Dailey, Bishop, Russell, & Fletcher, 1990; Goldenberg, 2010; Uveges, Parker, & Smarr, 1990), which increases the confusion of the clinical approach to this highly prevalent disease (Pastor, Lledó, López-Roig, Pons, & Martín-Aragón, 2010).

One of the most relevant issues is the association of the fibromyalgic syndrome with diverse sleep alterations. Ever since the polysomnographic studies of Moldofsky (Moldofsky, Lue, & Smythe, 1983; Moldofsky & Scarrisbrick, 1976; Moldofsky, Scarrisbrick, England, & Smythe, 1975; Smythe & Moldofsky, 1977), many works have found evidence that sleep disorders play a determinant role in the physiopathology of FM (Carette, Oakson, Guimont, & Steriade, 1995). As noted by Yunus and Kalyan-Raman (1989), in 80% of patients with FB, nonrestorative, fragmented, and superficial sleep is observed, which is related to the intensity of pain and a feeling of exhaustion. Other kinds of sleep anomalies have also been described in patients with FM, such as the increase in the number of awakenings (Jennum, Drewers, Andreasen, & Nielse, 1993; Sarzi-Puttini et al., 2002), a reduction of the quantity of phases III and IV (Sarzi-Puttini et al., 2002), an increase in sleep latency and in the number of phase changes per hour, as well as an increase in the duration of phase I (Moldofsky, 1997).

One of the most controversial aspects is the existence of a specific polysomnographic pattern in FM. It has been postulated that this could be identified by the presence of an alpha disorder of the non-rapid eye movement (NREM) sleep (Branco, Atalia, & Paiva, 1994; Moldofsky, 1986; Moldofsky, Tullis, Lue, Quance, & Davidson, 1984). A link between FM and the obstructive sleep

apnea syndrome has also been described (Donald, Esdaile, Kimoff, & Fitzcharles, 1996; May, West, Baker, & Everett, 1993; Molony et al., 1986; Sarzi-Puttini et al., 2002); or, lastly, a high incidence of Periodic Limb Movements in patients diagnosed with this disease (MacFarlane, Shahal, Mously, & Moldofsky, 1996; Tayag-Kier et al., 2000).

Although the conclusion of most of these studies suggests the existence of electroencephalographic anomalies in the sleep of patients with FM, the association of both processes is not acknowledged by all the authors (Horne & Shackell, 1991; Hyypä & Kronholm, 1995). In addition, it is still unclear whether FM is originated by these anomalies, or whether FM and sleep alterations are both the result of another, as yet unknown, pathogenic factor.

However, the diversity of the response criteria and of the instruments used, in addition to the many variables assessed, have not allowed us to define the relation of sleep disorders and FM completely. Therefore, all the above-mentioned results should be interpreted with caution, as the review of the diverse works on the relation of fibromyalgia with sleep disorders reveals various problems, among which are included: (a) an insufficient sample size in most of the studies (Branco et al., 1994; Horne & Shackell, 1991); (b) the absence of control groups when conducting the studies (Moldofsky et al., 1975; Molony et al., 1986); and (c) the absence of standardized recording techniques (Carette et al., 1995; Mahowald & Mahowald, 2000). These methodological deficiencies can, to a great extent, explain some of the discrepancies in the results obtained to date.

According to the hypothesis that patients with FM present sleep alterations that may be involved in their pathogenesis, we should observe a specific pattern when comparing them to the control group of healthy population. Along the lines of the preceding studies, the goal of this work is to contribute data about the probable relation of sleep alterations as an essential physiopathological component of FM (Okifuji, Turk, & Sherman, 2000; Villagrán, Páez, Campo, Pérez, & Salaberri, 2000). We wish to determine whether sleep alterations, their structure, the number of cortical awakenings, alpha-delta activity, or the respiratory function present a characteristic pattern of fibromyalgia (Pöyhaiä, Da Costa, & Fitzcharles, 2001). To achieve this goal, we will assess not only fibromyalgic patients but also healthy controls without chronic pain, conducting studies of sleep according to the recommendations of the *International Federation of Clinical Neurophysiology* (Deuschl & Eisen, 1999).

Method

Participants

After the study was approved by the Ethical Committee of the Hospital Centro Médico [Medical Center Hospital], and respecting the Helsinki Declaration of the World Medical Association in its entirety, we recruited a total sample of 32 women, aged between 28 and 70 years ($Mean = 50.1$, $SD = 10.33$), selected consecutively from among those who came to the rheumatology consulting office, with symptomatology duration of over 2 years, who met the diagnostic criteria of the American College of Rheumatology (Wolfe, Smythe, & Yunus, 1990) and who agreed to participate, signing an informed consent form. Patients with associated diseases susceptible of provoking secondary FM and patients who consumed medication that could affect their sleep for at least 3 months prior to

the test were excluded. As control group, we included 20 women, aged between 28 and 64 years ($M = 44$, $SD = 10.77$) who did not present any kind of physical or psychological pathology (sleep disorders, rheumatic disease, major psychopathology, multiple organic pathology, neoplasia, psychotropic or drug dependency) that required medical intervention or medication.

The inclusion criteria, both in the FM group and the control group, were confirmed by expert professionals and ratified by the specialized neurophysiologist in charge of conducting the polysomnography. All the patients were selected through the Rheumatology Service of the Medical Center Hospital of Asturias (Spain) and from the Psychology Faculty of the University of Oviedo (Spain), and the women used as healthy controls were randomly selected from a list of volunteers, also through the Medical Center Hospital. No significant differences were observed in age, civil status, and educational level among the people from the experimental and control groups.

Sleep polysomnography

Procedure

In all cases (patients and healthy controls), the polysomnographies were conducted in similar and standardized conditions, individually, in a sleep laboratory of the Medical Center Hospital of Asturias (Spain). After two hours preparation, the recordings were initiated at 11 o'clock p.m. and concluded at 7 o'clock a.m., thus covering 8 hours of nocturnal recording in basal conditions. All the recordings were carried out with an infrared camera for nocturnal vision.

The recording consisted of monitoring two bipolar EEG derivations (Cz-A1 and O1-A1), a bipolar channel for the left and right electrooculogram (EOG), and two bipolar channels for the electromyogram (EMG), one for the submentonian muscle, and the other for the tibialis anterior muscle. Respiratory parameters included a channel for nasal-oral air flow and a channel for abdominal respiratory movements, a bipolar channel for electrocardiographic recording, and a channel to record snoring and body position. Respiratory activity was recorded by means of elastic bands with a piezoelectric sensor that recorded thoracic and abdominal movements and a nasal-oral air flow sensor. The level of oxygen saturation was recorded by means of a pulsometer placed on the index finger.

Instrument

To conduct the polysomnographies, we used a 32-channel *Discovery* electroencephalograph (Medelec Vickers Medical, Inc.)

Interpretation of the polysomnographic data

To analyze the polysomnographies, we followed the classification system of Rechtschaffen and Kales (1968). The diverse sleep phases were recorded manually in 30-second epochs, and the successive NREM-REM cycles were recorded taking the REM periods into account. The percentages of the sleep phases with regard to total sleep time were determined. NREM phases III and IV were considered slow-wave sleep. Sleep efficiency was defined by the percentage of time in bed used for sleeping, and sleep latency by the time it took to initiate sleep.

Arousals were defined according to the ASDA (American Sleep Disorders Association) criteria, by abrupt changes in the EEG frequencies, with activation of the submentonian EMG or of the EOG. *Alpha* activity was defined in a frequency range of 7.0 - 12.0 Hz., with a minimum peak-to-peak amplitude of 5 µv, and grouped in four scales as a function of the percentage of alpha events in the NREM phase II and deep sleep phases: 1) 0-25%, 2) 26-50%, 3) 51-75% and 4) 76-100% (MacLean, Lue, & Moldofsky, 1995). The K-alpha phenomenon (micro-arousal) is defined by a K-complex immediately followed by an explosion of abnormal alpha activity lasting less than 5 seconds (Roizenblat, Moldofsky, Benedito-Silva, & Tufik, 2001).

Apnea is defined as the cessation of airflow for 10 seconds or more (including the different types: central, obstructive, or mixed). Hypoapneas were recorded when a reduction of airflow of at least 50% of the baseline, during at least 10 seconds, was produced. The level of oxygen saturation (Sa= 2) obtained at night, which allows identification of the severity of the apnea, was also measured. Up to 85% of oxygen desaturation is considered mild, up to 75% moderate, and lower than 75% is considered severe. A rate of apneas/hypoapneas higher than 5 events/hour of sleep is considered

pathological. Likewise, we defined periodic limb movements as the onset of sequences of at least four muscular contractions lasting 0.5 to 5 seconds, with an interval between each twitch of 5 to 90 seconds (Aldrich, 1996; Thorpy, 1990). When these movements provoke fragmentation of sleep architecture, they are associated with K-complexes or with alpha activity (cortical micro-awakenings). To determine their severity, we used an index that considers the number of motor events followed by awakening reaction per hour of sleep, and if it was higher than 5, it was considered pathological.

Data analysis

To compare the results obtained in the polysomnography for the people of the two groups, we carried out multivariate analysis of variance (MANOVA), which yielded global differences. When Wilks' λ was significant (p≤05), univariate analyses of variance (ANOVA) was used to determine the variables in which the groups differed. We used η² as an effect size index. Values of η²> .15 can be considered high, and when η² > .06 , the effect size is moderate. All the statistical analyses were conducted with version 15.0 of the SSPS program for Windows.

Table 1
Analysis of variance of the scores obtained by the experimental and control group in the polysomnographic variables

Variables	Fibromyalgia M (SD)	Healthy controls M (SD)	F	p	η²
<i>Sleep architecture</i>					
Time in bed (minutes)	408.49 (27.73)	420.59 (20.74)	2.811	.100	.053
Sleep interval (minutes)	377.67 (40.19)	387.96 (27.34)	1.014	.319	.020
Total sleep time (minutes)	327.20 (55.63)	357.31 (41.50)	4.336	.042	.080
Index of sleep efficiency	.853 (.114)	.907 (.073)	3.529	.066	.066
Time of wakefulness after sleep onset (minutes)	18.93 (10.45)	8.85 (8.15)	13.460	.001	.212
Number of awakenings	70.31 (47.89)	19.60 (13.06)	21.288	.000	.299
Phase I (%)	7.12 (4.52)	11.82 (18.11)	1.980	.166	.038
Phase II (%)	57.00 (9.48)	48.55 (16.25)	5.628	.022	.101
Phase III (%)	8.92 (4.24)	8.62 (5.30)	.350	.557	.007
Phase IV (%)	9.53 (5.48)	13.15 (4.06)	6.435	.014	.114
REM phase (%)	16.552 (6.68)	16.366 (5.23)	.011	.916	.000
REM latency (minutes)	129.48 (84.50)	110.45 (61.13)	.763	.378	.015
Sleep latency (minutes)	16.96 (16.77)	26.50 (36.62)	1.639	.206	.031
<i>Sleep events</i>					
Apneas	3.637 (10.12)	.0500 (.223)	2.491	.121	.047
Apnea index	.3875 (1.53)	.000 (.000)	1.260	.267	.025
Hypoapneas	1.100 (3.84)	.000 (.000)	2.178	.146	.042
Hypoapnea index	.0962 (.4004)	.000 (.000)	.926	.340	.018
Apnea + Hypoapnea Index	.7094 (2.27)	.000 (.000)	1.929	.171	.037
Desaturations > 90%	2.312 (12.72)	.000 (.000)	.656	.422	.013
Alpha-delta sleep 0-25%	1.561 (3.96)	.1500 (.670)	2.469	.122	.047
Alpha-delta sleep 26-50%	1.146 (3.45)	.0500 (.223)	1.922	.164	.038
Alpha-delta sleep 51-75%	.6047 (2.83)	.000 (.000)	.902	.347	.018
Alpha-delta sleep 76-100%	.2546 (1.41)	.000 (.000)	.644	.426	.013
Limb movements	17.781 (19.81)	7.050 (6.35)	5.477	.023	.099
Limb movements+awakenings	41.838 (46.58)	4.400 (3.76)	12.772	.001	.203
Index of limb movements	11.115 (10.80)	2.378 (2.55)	12.554	.001	.199
K+awakenings	17.05 (13.27)	8.660 (5.08)	7.283	.009	.127
p≤0,05 Wilks value= 3.535; p= .001					

Results

The summary in Table 1 shows group differences (Wilks' value: $F= 3.723$, $p= .001$) in the scores obtained in the polysomnography. When analyzing sleep architecture, the neurophysiological study showed that the patients with FM presented a decrease in *total sleep time* ($F= 4.336$, $p= .042$) in comparison to the healthy controls. Fibromyalgic patients also presented an increase in the *time of wakefulness after sleep onset* ($F= 13.460$, $p= .001$) and in the *number of awakenings* ($F= 21.288$, $p= .000$) as compared with healthy controls.

When comparing the percentages of the diverse NREM sleep phases, we observed alterations in the cyclic organization of sleep: the percentage of phase II time was higher in the FM group than in the control group ($F= 5.628$, $p= .022$), whereas in phase IV, the opposite pattern was observed, that is, the percentage of phase II time was lower in the FB patients than in the control group ($F= 6.435$, $p= .014$).

Upon analysis of the diverse sleep events, no significant differences were obtained either in the respiratory variables, the oxymetric variables, or in alpha-delta sleep. In contrast, we observed differences between the FM patients and the control group in myoclonic movements. Spontaneous limb movements occurred at intervals during sleep and especially during NREM sleep (Moldofsky et al., 1984). We observed that the FM group presented a higher number of periodic limb movements ($F= 5.477$, $p= .023$) and of periodic limb movements associated with cortical awakenings ($F= 12.772$, $p= .023$). The FM group also presented a higher rate of limb movements ($F= 12.554$, $p= .001$) and of K-complex + *awakenings*, characteristic of superficial sleep phases ($F= 7.267$, $p= .010$).

Discussion and conclusions

After decades of research, we have not yet identified the pathogenic mechanisms that provoke pain in fibromyalgia. There is evidence of the existence of anomalous psychophysiological processes in the origin of fibromyalgia (Dailey et al., 1990; Uveges et al., 1990). In this sense, alterations at multiple levels, both in the afferent transmission of the signal and in the efferent responses produced as mechanisms to modulate pain, have been observed. Multiple neurotransmitters and regions have been implicated to date in the anomalous processing of pain in patients with FB, in an attempt to establish the physiopathological mechanisms that could explain the hyperpathia produced in practically all these patients (Ablin, Buskila, & Clauw, 2009; Williams & Clauw, 2009).

Most patients with FB present sleep alterations (Carette et al., 1995; Jacobsen, Petersen, & Danneskioldsamsoe, 1993; Moldofsky et al., 1975; Sergi et al., 1999), although whether there is a specific pattern or whether it is a case of alterations related to coexisting processes, such as anxiety disorder or depression, has not been established.

Traditionally, the Alpha-NREM Sleep Disorder has been associated with a longer duration of pain and with superficial sleep. The so-called alpha-delta sleep interferes with the normal function of sleep, turning it into nonrestorative sleep and favoring daytime fatigue and muscular-skeletal pain more than the presence of behavioral changes or shortened sleep do. However, the abnormal alpha rhythm could reflect a state of alertness during nocturnal sleep that would determine the subjective feeling of nonrestorative sleep.

In comparison to the findings of previous studies (Roinzenblatt, Moldofsky, Benedito-Silva, & Tufik, 2001), the results obtained in the present study do not allow us to establish an association between alpha-delta abnormalities and FB, in comparison to the control group. Thus, although patients with FB present poor sleep quality, with more transactional sleep and high fragmentation, they do not differ from the control participants in the alpha-delta rhythm (Shaver et al., 1997), despite the significant reduction in slow-wave sleep.

The comparison of the results obtained with patients with FB confirms that the alpha-delta alterations of their sleep are not easy to explain; the existence of possible methodological differences in the selection of the patients or in sleep recording could contribute to these divergent results (Branco et al., 1994). These discrepancies could be due to the fact that alpha-delta sleep might be considered a sleep alteration that would involve partial alertness, typical of sleep apnea or of the syndrome of periodic limb movements while sleeping and, therefore, it would not be an intrinsic characteristic of FB (Branco et al., 1994; Shaver et al., 1997).

Periodic limb movements, a specific sleep disorder that is responsible for difficulties to initiate and maintain sleep and for excessive daytime somnolence, is also one of the intrinsic alterations that determine the fragmented sleep of patients with FB. These stereotyped movements of the legs are followed by partial arousals or awakenings that interrupt the continuity of sleep. In patients with FM, it has been postulated that this type of alterations is not necessarily associated with abnormal alpha-delta activity (Moldofsky, 1986; Moldofsky, Tullis, Lue, Quance, & Davidson, 1984). However, in accordance with the hypothesis proposed in the present study, we verified that the FB patients present a higher number of periodic limb movements, and their association with K-complexes, characteristic of superficial NREM sleep. These periodic movements (Coleman, Pollack, & Weitzman, 1980) could be the reflection of an unspecific disorder that provokes cortical awakenings and would respond to a chronic alteration of the circadian functioning of sleep-wakefulness occurring in patients with FB. Moreover, these motor events could be responsible for the frequent micro-awakenings found and, therefore, affect sleep continuity and provoke fragmentation of its architecture, increasing superficial sleep (NREM phase II) at the cost of deep sleep (NREM phase IV) in patients with FB (Horne & Shackell, 1991), determining a decrease in the total sleep time with a high number of awakenings.

The present study has some limitations that should be commented on. Firstly, it used a small sample, which does not allow us to reach definite conclusions, although the differences between the groups examined are sufficiently significant. The control group was selected with rigor, discarding patients with diseases that could provoke chronic pain or sleep alterations. This could introduce biases because, given the high prevalence of chronic pain or of primary or secondary sleep alterations in this age range in the female population, we may have selected an exceptionally «healthy» cohort that does not represent the truly normal population. In future studies, additional comparison groups should be included, with other causes of chronic pain and insomnia, in an attempt to define specific patterns of alteration in FB. Moreover, in view of the influence that the body mass index can have on the results of polysomnography, in the future, this measurement should be included, and excess of a certain defined threshold should be used as an exclusion criterion.

Summing up, the results obtained partially support the hypothesis that alterations in the cyclic organization of sleep (with decrease of total sleep time and increase of superficial sleep in detriment of deep sleep) in patients with FM could play an essential physiopathological role and could be a pathogenic factor for the development of this disease. However, neither respiratory anomalies (without oxygen desaturations) nor anomalies in alpha-delta sleep were detected, despite a higher percentage of superficial sleep. The increase of periodic limb movements (associated with cortical awakenings) in patients with FM could be involved in the feeling of nonrestorative sleep, and thus predict the development

of diffuse chronic pain. With a view to the future, it would be very interesting to use larger samples of patients and samples of people with other diseases that present chronic pain, which would allow us to determine whether FM presents a specific sleep pattern and thus, improve the therapeutic approach to FM.

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