

Cyclic Alternating Pattern: A New Marker of Sleep Alteration in Patients with Fibromyalgia?

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ABSTRACT. Objective. In the dynamic organization of sleep, cyclic alternating pattern (CAP) expresses a condition of instability of the level of vigilance that manifests the brain's fatigue in preserving and regulating the macrostructure of sleep. We evaluated the presence of CAP in patients with fibromyalgia (FM) compared to healthy controls.

Methods. Forty-five patients with FM (42 women) were studied and compared with 38 healthy subjects (36 women) matched for age, sex, and body mass index. Entry criteria were diagnosis of FM according to 1990 American College of Rheumatology criteria; willingness to participate in the study; and having no other diagnosis of autoimmune, neoplastic, or other possible causes of secondary diffuse musculoskeletal pain. Patients in the study underwent polysomnography recordings and a sleep questionnaire. Hypersomnolence was evaluated according to the Epworth Sleepiness Scale.

Results. FM patients had less sleep efficiency (sleep time/time in bed) than controls (79 ± 10 vs 89 ± 6 ; $p < 0.01$), a higher proportion of stage 1 non-rapid eye movement (non-REM) sleep (20 ± 5 vs 12 ± 5 ; $p < 0.001$), and twice as many arousals per hour of sleep (9.7 ± 3.3 vs 4.1 ± 1.9 ; $p < 0.01$). The CAP rate (total CAP time/non-REM sleep time) was significantly increased in FM patients compared to controls ($68 \pm 6\%$ vs $45 \pm 11\%$; $p < 0.001$). CAP rate seemed to correlate with the severity of clinical symptoms in FM patients (tender points index; $p < 0.01$) and with less efficiency of sleep ($p < 0.01$).

Conclusion. The increase of CAP rate indicates a worse quality of sleep in patients with FM. These data are strongly correlated to the severity of symptoms. (J Rheumatol 2004;31:1193-9)

Key Indexing Terms:

FIBROMYALGIA CYCLIC ALTERNATING PATTERN SLEEP POLYSOMNOGRAPHY

Fibromyalgia syndrome (FM) is a common condition causing generalized musculoskeletal pain¹. 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 years². The criteria used for diagnosis were formulated by the American College of Rheumatology (ACR) in 1990³. The reported complaint of poor sleep⁴ is so common in patients with FM that in some case series its prevalence is nearly 100%⁵⁻⁷. The observation that a neuroathenic musculoskeletal pain syndrome can be elicited in healthy volunteers undergoing deep non-rapid eye movement (non-REM) sleep deprivation⁷ seems to suggest that a cycle may be in operation, with pain-impaired sleep leading to a worsening of the disease. Moldofsky, *et al*⁸ proposed an

alpha wave intrusion on delta wave sleep, characterized by alpha wave activity (frequency 7-11 cycles per second) that is superimposed on the delta wave sleep (frequency 2 cycles/s and amplitude $> 75 \mu V$), as a marker of the sleep impairment typical of FM; however, this alteration in sleep macrostructure has not been confirmed by other studies^{9,10}, whereas an association between alpha wave intrusion in non-REM sleep and other FM symptoms has been variously confirmed¹¹ and rejected⁵ by different trials.

The hypothesis that other disorders causing sleep fragmentation, such as sleep apnea syndrome¹², might be blamed for the nonrefreshing sleep symptoms is reported in another study¹³. In patients with FM, Sergi, *et al*⁶ recently described a greater number of abrupt changes in electroencephalographic (EEG) frequency, suggestive of an awake state, and/or brief increases in electromyographic (EMG) amplitude (arousal) accompanied by the presence of periodic breathing.

Another condition that can cause sleep fragmentation is the cyclic alternating pattern (CAP)¹⁴; it corresponds to a prolonged oscillation of the arousal level between two reciprocal functional states termed phase A (greater arousal) and phase B (lesser arousal), and in the dynamic organization of sleep it expresses a condition of instability of the level of vigilance that manifests the brain's fatigue in preserving and

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regulating the macrostructure of sleep. In phase A, 3 subtypes can be distinguished in the EEG pattern: A1, A2, A3¹⁵.

CAP is observed only in stage 1, 2, 3, 4 non-REM sleep^{14,16}, in accord with the Rechtschaffen and Kales classification¹⁷. CAP cycles are generally clustered in sequences; conversely, the portion of non-REM sleep associated with relative stability of arousal and autonomic activities, non-CAP, is expressed by stationary and homogeneous EEG patterns.

We evaluated the presence of CAP in patients with FM compared to healthy controls.

MATERIALS AND METHODS

Study population. Forty-five eligible consecutive Caucasian patients (42 women) aged 52.2 ± 8.2 years, with FM diagnosed according to the 1990 ACR classification criteria, were invited to participate in this study and were compared with 38 healthy controls (36 women) matched for age, sex, and body mass index (Table 1). A 2-week washout period for any pharmacological treatment related to FM was requested of all patients. A sleep questionnaire and the Epworth Sleepiness Scale (ESS) were then administered to all subjects. Informed consent was obtained in all cases, and 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; intensity of somatic pain expressed on a 100 mm visual analog scale (VAS); and anxiety, depression, and fatigue expressed on 100 mm VAS.

Study measures. A sleep questionnaire was administered to all subjects to evaluate sleep complaints¹². Hypersomnolence was evaluated according to the ESS¹⁸. The ESS is a questionnaire measuring the general level of daytime sleepiness and is the sum of 8 item scores. It can vary 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 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 techniques¹⁷. Nasal-oral thermocouples and thoracic and abdominal belts with attached piezo-

electrodes recorded airflow and ventilatory efforts, respectively. Oxyhemoglobin 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. To avoid 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 2 physicians, blinded, in 30 s epochs, according to standard criteria¹⁷. Correlation between sleep, breathing, and body position was analyzed automatically by the computer.

The overnight EEG activity was recorded using 10 bipolar leads (Fp2-F4, F4-C4, C4-P4, P4-O2, Fp1-F3, F3-C3, C3-P3, P3-O1, FZ-CZ, and CZ-PZ) and a classical unipolar C3-A2.

Apneas were defined as 10-second pauses in respiration. Hypopnea was defined as a decrement in airflow $\geq 50\%$, 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 apnea and hypopnea per hour of sleep, and the desaturation event frequency (DEF) was defined as the number of episodes of fall $\geq 4\%$ in oxyhemoglobin saturation per hour of sleep. Periodic breathing was defined as a series of at least 3 successive cycles of waxing and waning in ventilation, with apneas or hypopnea. Arousals were scored according to the American Sleep Disorders Association (ASDA) criteria¹⁹. Alpha-delta intrusion was defined as the spontaneous occurrence of alpha waves in delta wave sleep⁸.

CAP parameters were identified according to the scoring rules established in a recent consensus report²⁰. All CAP sequences include at least 2 consecutive CAP cycles and always begin with a phase A and a phase_B. Absence of a phase A for > 60 consecutive seconds creates a prolonged stationary condition of arousal stability and is scored as non-CAP.

CAP rate referred to non-REM sleep is a percentage ratio of total CAP time to total non-REM time. We also calculated the mean duration of B phases, and number and mean duration of A1, A2, and A3 subtypes.

Through computer analysis, we were able to determine the sleep histogram of each patient to identify the sequences of the periods corresponding to the CAP and to periodic breathing.

Statistical analysis. Data were reported as mean \pm standard deviation. Statistical analysis of the anthropometric data and polysomnographic recordings was performed using unpaired Student t tests. Pearson's chi-square was used for other comparisons of means and proportions. The

Table 1. Demographic and clinical data of subjects.

	FM, n = 45	Controls, n = 38	P
Duration of disease, yrs	7.8 \pm 3.2	—	—
Age, yrs	53.2 \pm 8.9	52.4 \pm 8.2	NS
F, M	42, 3	36, 2	NS
BMI, kg/m ²	25.6 \pm 3.5	26.4 \pm 3.3	NS
ESS score	15 \pm 4	4 \pm 2	0.001
No. tender points	15 \pm 2	3 \pm 1	0.001
Pain (VAS)	73 \pm 15	15 \pm 5	0.001
Chronically poor sleep, %	90	10	0.001
Wake up unrefreshed, %	85	5	0.001
Nocturnal awakening, %	100	20	0.001
Habitual snorers, %	50	35	NS
Headache, %	85	25	0.001
Irritable bowel syndrome (L), %	54	15	0.05
Anxiety (VAS)	64 \pm 11.2	21 \pm 3.8	0.01
Depression (VAS)	75 \pm 15	13 \pm 12.4	0.001
Fatigue (VAS)	80 \pm 12	22 \pm 10	0.05

BMI: body mass index; ESS: Epworth Sleepiness Scale; VAS visual analog scale; NS: not significant.

Spearman rank correlation was used where appropriate. The level of significance was $p < 0.05$. All statistical analyses were performed using SPSS 9.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Table 1 shows the anthropometric data of patients with FM and the control group, and the most common complaints of FM patients: nocturnal awakening (100%), chronically poor sleep (90%), morning headache and sensation of waking unrefreshed (85%) ($p < 0.001$ vs controls). Moreover patients with FM had a higher number of tender points ($p < 0.001$), higher ESS score ($p < 0.001$), significant subjective pain ($p < 0.001$), anxiety ($p < 0.01$), depression ($p < 0.001$), and fatigue ($p < 0.05$) scores compared to controls.

The sleep values (Table 2) showed that patients with FM had lower sleep efficiency (sleep time/time in bed) than controls ($p < 0.01$) and twice as many arousals per hour of sleep ($p < 0.01$). The percentage of stage 1 non-REM sleep was markedly increased in FM patients, causing a reduction of slow wave sleep ($p < 0.001$); the stage 2 NREM and the REM phase sleep were not increased. Alpha intrusion during delta sleep, not correlated with the appearance of CAP, was identified in 14 patients (31%) and in 2 control subjects (5%) ($p < 0.001$).

The DEF per hour of sleep was higher in FM patients ($p < 0.01$) than in controls. There was no difference in RDI or $\text{SaO}_2\%$ average and nadir during sleep between the FM and control subjects. Periodic breathing was observed in 40 patients (89%), but in only 2 controls (5%), in both of whom it was limited to sleep onset. The usual length of apneic or hypopneic episodes during periodic breathing was < 10 s; therefore the RDI and average percentage oxygen saturation (SaO_2) during sleep did not differ between the 2 groups. Nevertheless, periodic breathing was present for a mean 17% of the night in FM patients, mainly occurring during light stages of non-REM sleep.

The CAP values are reported in Table 3. The CAP rate was significantly increased in FM patients compared to controls ($68 \pm 6\%$ vs $45 \pm 11\%$; $p < 0.001$); the mean duration of the CAP cycle and the duration of phase A and phase B were also increased (45 ± 3 vs 28 ± 2 , $p < 0.001$; 20 ± 4 vs 10 ± 1 , $p < 0.001$; 25 ± 3 vs 18 ± 3 , $p < 0.001$). In the FM patients the CAP scoring revealed a greater amount subtype A1 and subtype A2 + A3 of A phase compared to the control group (158 ± 12 vs 75 ± 13 , $p < 0.001$, and 115 ± 20 vs 63 ± 18 , $p < 0.001$, respectively).

The CAP rate seems to correlate negatively with sleep efficiency ($p < 0.001$) and positively with the severity of clinical symptoms in FM patients (tender point index; $p < 0.001$), the duration of FM in years ($p < 0.05$), the ESS score ($p < 0.01$), and the periodic breathing as a percentage of sleep time ($p < 0.01$) (Table 4). A positive linear correlation was found between arousals index and subtype A2 + A3 of the CAP ($r = 0.80$, $p < 0.001$) and between periodic breathing and number of tender points ($r = 0.66$, $p < 0.01$).

DISCUSSION

Fibromyalgia syndrome is characterized by a high prevalence of disturbed sleep^{1,3-6}. However, the severity of these symptoms is not supported by any finding of dramatic alterations in the macrostructure of sleep: stage 1 sleep was increased in FM patients, but only slow-wave sleep was reduced (Table 2). Although Moldofsky, *et al*⁷ showed that slow-wave sleep deprivation can exacerbate pain and fatigue during the daytime, this can hardly explain hypersomnolence. Indeed, in a group of FM patients with hypersomnolence Sarzi-Puttini, *et al*²¹ observed a greater sleep fragmentation, a higher number of tender points, and longer disease duration. The amount of both stage 2 and REM phases was not different from control subjects, thus excluding REM deprivation as a possible cause of excessive anxiety or psychological disorders that could lead to an

Table 2. Sleep values in 45 FM patients and 38 healthy controls.

	FM, n = 45	Controls, n = 38	p
Sleep time, min	291 ± 46	390 ± 41	0.001
Sleep efficiency, %	79 ± 10	89 ± 6	0.01
Stage 1	20 ± 5	12 ± 5	0.001
Stage 2	36 ± 10	33 ± 8	NS
Stage 3	5 ± 2	12 ± 3	0.01
Stage 4	1 ± 1	6 ± 3	0.001
REM sleep time, %	17 ± 9	18 ± 8	NS
SaO_2 average during sleep, %	94.4 ± 1.9	95 ± 2	NS
SaO_2 nadir during sleep, %	84.4 ± 4	89 ± 3	NS
DEF, events/h	9.1 ± 6	3.2 ± 2.8	0.01
PB sleep time, %	15 ± 8	1 ± 2	0.0001
Arousal index, n/h	9.7 ± 3.3	4.1 ± 1.9	0.01
α intrusion, n	14	2	0.001

DEF: desaturation event frequency, REM: rapid eye movement, SaO_2 : oxygen saturation, PB: periodic breathing, NS: not significant.

Table 3. Cyclic alternating pattern (CAP) values in 45 FM patients and 38 healthy controls.

	FM, n = 45	Controls, n = 38	p
CAP rate	68 ± 6	45 ± 11	0.001
CAP cycle duration, s	45 ± 3	28 ± 2	0.001
Phase A duration, s	20 ± 4	10 ± 1	0.001
Phase B duration, s	25 ± 3	18 ± 3	0.001
Subtype A1, n	158 ± 12	75 ± 13	0.001
Subtype A2 + A3, n	115 ± 20	63 ± 18	0.001

Phase A and phase B are components of the CAP cycle. Variation during CAP involves different degrees of muscle tone, heart rate, and respiratory activity, which increase during phase A and decrease during phase B. Phase A subtype A1: slow high voltage EEG patterns generally associated with mild or trivial polygraphic variations. Phase A subtype A2: rapid low amplitude EEG patterns preceded by or mixed with slow high voltage waves, linked with a moderate increase of muscle tone and/or cardiorespiratory rate. Phase A subtype A3: phase with fast low voltage EEG patterns alone exceeding 2/3 of the phase A length, and coupled with remarkable enhancement of muscle tone and/or cardiorespiratory rate.

Table 4. Spearman rank correlation between the CAP score and sleep, functional data, symptoms, and duration in patients with FM.

CAP Score versus	r	p
ESS score	0.57	0.01
Sleep efficiency	-0.86	0.001
No. tender points	0.85	0.001
Duration of FM, yrs	0.51	0.05
Periodic breathing	0.71	0.01

overestimation of symptoms. The number of arousals was about twice that in controls, but still lower than 10 episodes per hour, a figure that 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)^{22,23}.

The analysis of arousals was performed according to ASDA criteria¹⁹.

Moldofsky, *et al*⁸ identified alpha-delta sleep in FM patients and implicated sleep in the pathophysiology of FM. In addition to alpha intrusion, polysomnography clearly showed that, compared with controls, FM patients have less slow-wave sleep, less REM sleep, and less total sleep time. They also have a greater number of arousals and awakenings. These are all nonspecific findings of disturbed sleep. Spectral analysis of EEG of alpha and delta power supports this hypothesis, as shown by Branco, *et al*⁹ and Drewes, *et al*^{24,25}; these researchers, using cluster analysis to obtain additional information from the sleep EEG, observed a characteristic EEG pattern in patients with FM, compared with matched controls, that was independent from the stage of sleep. The alpha wave intrusion during delta sleep, as a possible factor of disrupting sleep, occurred sporadically in our patients (14/45 patients, 31%); thus a significant role in the pathogenesis of hypersomnolence cannot be alleged on

the basis of these data. Moldofsky, *et al*²⁶ described a possible relation between alpha intrusion and periodic limb movements during sleep in FM patients that could worsen the disruption of sleep architecture. Recently, Rains, *et al*²⁷, using the multiple sleep latency test (MSLT) for evaluating the physiologic level of daytime sleepiness, observed that excessive daytime sleepiness is not a common characteristic of patients with FM. On the other hand, we observed²¹ that FM patients have excessive daytime sleepiness (ESS score 15 ± 4); the different severity of the excessive daytime sleepiness measured by the MLST or by a scale like the ESS could suggest a discrepancy between the subjective sensation and the objectivity of diurnal hypersomnolence.

The presence of another sleep-related respiratory disorder, namely OSAS, was not detected in our population of non-obese patients with FM, although more than half were snorers; these results are in agreement with those from 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. As shown by Sergi, *et al*⁶, the occurrence of periodic breathing in the 17 ± 9% of sleep time in this study could play an important role in the poor sleep complaints of the FM patients. It is well known that periodic breathing may be linked to an unstable functioning of the control system of ventilation, elicited by the transition from wakefulness to sleep, which can occur even in healthy subjects for a limited amount of time. Pain can reduce sleep efficiency, causing more frequent arousals and increasing the chances for periodic breathing to occur⁶.

In 1993, Staedt, *et al*²⁸ showed by cluster arousal analysis that these patients had a significant alteration of the microstructure of sleep in comparison with controls; in 1996 MacFarlane, *et al*²⁹ described in a group of FM patients another variety of periodic arousal disturbance termed periodic K α , which is a variety of CAP. The increase of sympathetic activity and the presence of periodic limb movements

during sleep in FM patients^{26,30,31} are 2 indirect signs of CAP increase in these patients; indeed, as shown by Ferini-Strambi, *et al*³², during CAP the sympatho-vagal balance is shifted toward the sympathetic prevalence, and CAP seems to be closely involved in the pathophysiological mechanisms of nocturnal myoclonus³³. We found a significant increase of the CAP rate, which appears independently by the appearance of α wave intrusion but closely correlated to the number and to the mean duration of CAP cycles in FM patients compared to controls. This suggests that the painful symptomatology plays an important role in the increase of CAP in the FM patients, as shown by the significant positive correlation between CAP rate and the number of tender points and duration of FM ($p < 0.001$, $p < 0.05$, respectively).

The lack of correlation between CAP and the appearance of α intrusion could be because α intrusion appears only during slow-wave sleep (δ), whereas CAP is present in all phases of non-REM sleep.

Moreover, the control mechanisms of vigilance, respiration, muscle tone, and other autonomic processes are mutually influenced by interdependent anatomical and functional constraints, as shown by experimental and clinical data. A statistical measure of these dynamic linkages has been designated as phasing³⁴. In cats, the values of phasing are greater during sleep, and sustained synchronization of the averaged activities are associated with transitional states³⁵. The length of CAP may be the synchronized effect of the different subsystems in pursuit of a common dynamic equilibrium³⁶, rather than the result of a single pacemaker. Indeed, this dominating rhythm seems to exert an overwhelming role in the interplay between respiration and arousal in non-REM sleep.

The occurrence of episodes of periodic breathing during CAP (Figure 1) suggests that this phasic fluctuation process is much more critical for breathing activity than the near-to-equilibrium stable states of non-CAP³⁷. In our patients, the periods of decrescendo of tidal volume during periodic breathing were consistently correlated with phase B (Figure 2). The inhibitory effects of this component of CAP are likely to operate beyond the range of flexibility of the subsystems involved in the respiratory cycle. A more prominent depression on the charge of the breathing centers during decrescendo of tidal volume may be hypothesized. Further, the phasic inhibition of neurovegetative functions and muscle tone in phase B during light levels of sleep results more effectively in triggering the period of decrescendo of tidal volume than the tonic inhibition of the same functions normally operating in the states of deep sleep. However, the occurrence of periodic breathing may in turn modify the phenomenology of CAP and thus close the circular interaction between the nervous centers and the peripheral structures³⁸. This interplay between respiratory function and vigilance resulted in (1) a longer average CAP cycle length compared to the controls; (2) a longer duration of the CAP cycles associated with periodic breathing; and (3) an enhancement of the arousal level instability with a consequent increase of the CAP rate, as reflected by the excessive daytime sleepiness.

The positive linear correlation between the number of tender points and the CAP rate and periodic breathing ($p < 0.001$ and $p < 0.01$, respectively) suggests the strong influence of pain in these 2 variables in patients with FM.

The positive linear correlation between CAP subtypes A2 + A3 and the arousal index confirmed that the subtype A2 and A3 of CAP corresponds strikingly with ASDA arousal,

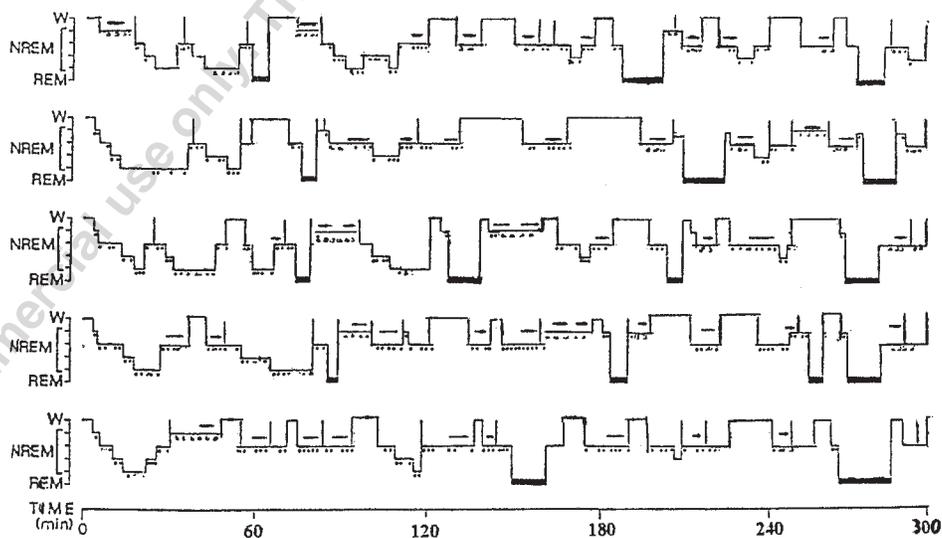


Figure 1. Sleep histograms of 5 patients with FM. The black dots correspond to sequences of the cyclic alternating pattern; black lines correspond to the periodic breathing sequences. REM: rapid eye movement, NREM: non-rapid eye movement, W: wake.

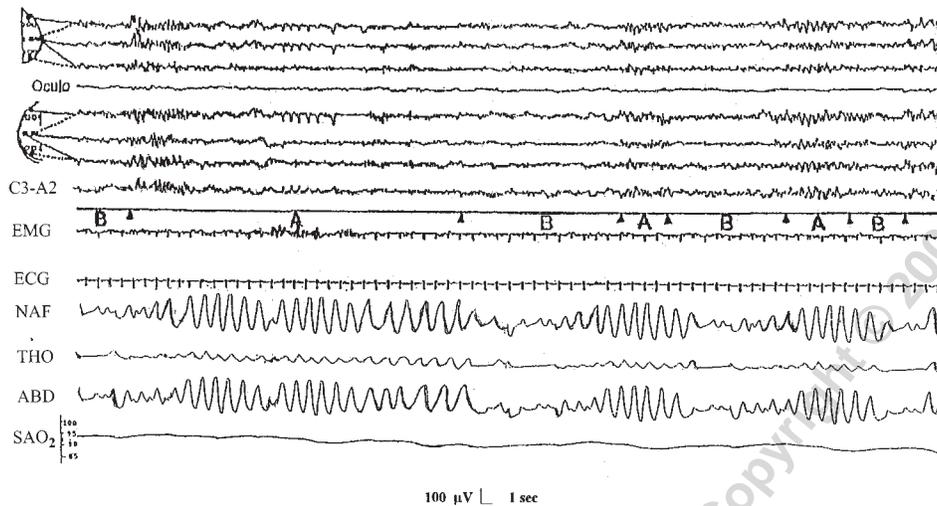


Figure 2. Periodic breathing and the cyclic alternating pattern (CAP) in a patient with FM; A and B correspond to phase A and phase B of CAP cycles. Electroencephalogram activity was recorded as described in Materials and Methods. Oculo: electro-oculogram, EMG: submental electromyogram, ECG: electrocardiogram, NAF: naso-oral airflow, THO: thoracic effort, ABD: respiratory abdominal effort, SAO₂: percentage oxygen saturation.

as reported by Parrino, *et al*³⁹. This correlation can be explained by the fact that the EEG criteria for identification of subtype A3 and partially of subtype A2 (Table 3) show extensive similarities with the criteria proposed for ASDA arousal¹⁹.

Our data confirm that the nonrestorative sleep of patients with FM is not related to a marked disruption of sleep architecture; FM patients may be more easily arousable and have less slow-wave sleep because of the exacerbation of pain. It is, however, closely related to serious alteration of the microstructure of sleep, as shown by the 29% increase of the CAP rate in the FM patients in comparison to controls. The abnormal presence of CAP and periodic breathing that are generated by chronic pain may be because chronic pain reduces sleep efficiency, causing more light sleep, more CAP, and more arousals, and increasing the occurrence of periodic breathing. Our study indicates that systematic attention to the microstructural dynamics of sleep may provide integrative information to reveal the underlying pathophysiological mechanisms of sleep in fibromyalgia.

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