A Case-Control Sleep Study in Children with Polyarticular Juvenile Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To investigate the relationship between clinical manifestations and sleep abnormalities in patients with juvenile rheumatoid arthritis (JRA).

Methods. Twenty-one patients with active polyarticular JRA and 20 healthy controls were enrolled consecutively. Pain and functional impairment were assessed with standardized, validated Brazilian questionnaires. Sleep evaluation was based on parent reporting of their child's sleep habits and polysomnography; subjects underwent an adaptation night in the sleep laboratory. Sleep architecture was analyzed and spectral analysis of non-rapid eye movement (REM) sleep was carried out by electroencephalography.

Results. Patients with JRA exhibited higher indexes of periodic leg movements (PLM; $p = 0.02$), isolated leg movements (LM), and arousals, as well as increases in alpha activity in non-REM sleep (all $p < 0.01$), in spite of similar frequency of sleep complaints in comparison to controls. Among JRA patients, greater alpha activity in non-REM sleep was observed in the participants with greater joint involvement assessed by the Escola Paulista de Medicina-Pediatric Range of Motion Scale ($p = 0.03$) or joint count ($p = 0.02$). Correlation was observed between morning stiffness and PLM and/or LM ($r_S = 0.75$, $Sr = 0.74$, $p < 0.001$ for both), and between self-rating scores of pain and alpha activity in non-REM sleep ($r_S = 0.74$, $p < 0.001$).

Conclusion. Pain symptoms and disability are related to sleep fragmentation in patients with active polyarticular JRA. (First Release Mar 1, 2006; J Rheumatol 2006;33:796–802)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS SLEEP PAIN FRAGMENTATION

Nocturnal sleep disruption in children can result in daytime sleepiness, fatigue irritability, attention disorders, hyperactivity, and school absenteeism[1]. Based on parental reporting, intermittent nocturnal awakenings and daytime sleepiness are the most common sleep related complaints in patients with juvenile rheumatoid arthritis (JRA)[2,3]. Zamir, *et al*[4] found an increase in daytime sleepiness in patients with JRA by the Multiple Sleep Latency Test (MSLT) in 3 of 7 patients analyzed, and sleep fragmentation as the main finding using polysomnography (PSG). Subsequently, Labyak, *et al* detected a slight correlation between morning pain and total sleep period determined by actigraphy in a controlled study of 14 children[5]. But the severity of daytime dysfunction was not correlated with sleep fragmentation in any of these studies. Thus, we designed a case-control sleep study to determine the relationship between sleep abnormalities and the severity of pain and functional impairment in children with polyarticular JRA.

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Supported by AFIP and FAPESP/CEPID (98/14303-3).

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Accepted for publication November 23, 2005.

MATERIALS AND METHODS

Study population. From 2000 to 2002, 24 participants aged 9 to 17 years with active JRA and polyarticular course[6] were prospectively enrolled. The inclusion criteria were a minimum followup period of 6 months, presence of clinical disease manifestations (at least one inflamed joint), and increased erythrocyte sedimentation rate as laboratory evidence of inflammatory activity, despite conventional treatment for arthritis. The exclusion criteria were the presence of comorbidities (e.g., endocrine, respiratory, cardiovascular, digestive, infectious, inflammatory, neurological, or psychiatric disease) and the use of medications that influence sleep, except those necessary for treatment of arthritis. Children with specific conditions that might influence sleep, such as respiratory disturbances associated with adenotonsillar hypertrophy and microcytic-hypochromic anemia, were also excluded. The control group comprised 24 age and sex matched healthy children and adolescents with no sleep related complaints.

Clinical evaluation. All participants answered a questionnaire related to pain and to sleep features, and underwent a physical examination and 2 recordings of their nocturnal sleep. Children and/or their legal caregivers gave signed informed consent that had been approved by the research ethics board of São Paulo Federal University. Adherence to the study was voluntary.

An experienced pediatric rheumatologist assessed participants for the presence of morning stiffness, number of inflamed joints, joint impairment (i.e., degree of loss of motion), and presence of fibromyalgia tender points. The degree of joint involvement was scored with the Escola Paulista de Medicina-Pediatric Range of Motion Scale (EPM-ROM)[7], from 0 (no impairment) to 3 (maximum impairment). Functional disability was evaluated by the Childhood Health Assessment Questionnaire (CHAQ)-Brazilian version[8], ranging from 0 (normal functional ability) to 3 (total physical disability); and by American College of Rheumatology (ACR) criteria, ranging from 1 (normal functional ability) to 4 (important physical disability)[9]. Self-assessment of pain was scored on a categorical 5-point face scale ranging from "no hurt" to "hurts worst"[10], validated for the Brazilian population[11]. Fibromyalgia tender points were assessed according to the ACR criteria[12], using the Fisher dolorimeter.

To evaluate the quality of sleep, we used an inventory comprising 26 questions with a scale ranging from 0 (never) to 4 (always), covering disorders of initiating and maintaining sleep, sleep breathing disorders, disorders of arousal, sleep-wake transition disorders, disorders of excessive somnolence, and sleep hyperhidrosis[13]. The questions were answered by the mother or caregiver in the presence of the child.

Polysomnography. All volunteers participated in a 2-night sleep protocol, the first night used for adaptation to laboratory conditions and the second night to obtain sleep data for analysis. Participants were instructed to stop any medication 48 hours preceding the sleep recordings, and to take only paracetamol for pain during this 4-day period. For both sleep recordings, participants were asked to go to bed at their usual time and all-night PSG was recorded for at least 7.5 hours with a computerized, 16 channel system (Harmonie 2.4; Stellate Systems, Montreal, Quebec, Canada). The following data were collected: electroencephalogram (EEG; C3-A2, C4-A1, O1-A2, O2A1) at sampling rates of 200 Hz per channel; electroculogram (right and left); electromyogram (EMG; chin and anterior tibial); electrocardiogram (modified V2 lead); respiration with nasal cannula and oral thermistor, neck microphone, abdominal and thoracic belts, and pulse oximetry (Ohmeda^{TM}). An experienced researcher, blinded to the clinical condition of participants, performed sleep scoring using standardized criteria[14].

Total time of recording (TTR), sleep period time (SPT = TTR – sleep latency), total sleep time (TST = SPT – wake stages after sleep onset), and percentage of time in non-rapid eye movement (REM) sleep stage and REM sleep were determined. Stages 3 and 4 of non-REM sleep were scored as slow-wave sleep (SWS). Leg movements (LM) derived from EMG recorded in both anterior tibialis muscles were scored by an increase in the amplitude of the leg EMG of at least 25%, lasting 0.5 to 5 seconds. Periodic leg movements (PLM) were considered present with scoring of a sequence of 4 or more leg movements with an intermovement interval of 5 to 90 seconds[15]. Arousals were scored when shift in frequency of sleep EEG (mostly in the theta range 4–8 Hz) lasting 3 to 15 seconds occurred[16].

Spectral analysis of non-REM sleep was performed on the C4-A1 EEG channel in the first, most stable sleep cycles, comprising all sleep stages. Along with signal averaging, 4-second Hanning window with 3.75% overlapping was used to fully capture incoming signals. The Welch-Bartlett technique was applied to increase stability of spectral analysis[17]. Single or double epochs of movement or artifact were automatically removed using 3 and 5-point median filters. The relative power spectra density was calculated by integrating the spectral density power in the following bands: delta-1 (0.5–2.0 Hz), delta-2 (2.0–4.0 Hz), theta (4.0–8.0 Hz), alpha (8.0–12.0 Hz), sigma-1 (12.0–14.0 Hz), sigma-2 (14.0–16.0 Hz), and beta (16.0–30.0 Hz).

Statistical analysis. The normality of the distribution was tested by Kolmogorov-Smirnov test. Descriptive data are presented as mean ± standard deviation for parametric data and median (interquartile range, 25th and 75th percentile) for nonparametric data. Comparisons between patients and control children, and of subgroups of children with JRA with different degrees of impairment, were performed using Student t test for parametric data and by Mann-Whitney U test for nonparametric data. Comparisons among sleep stages for sleep phase phenomena were by Kruskal-Wallis ANOVA, followed by the multiple comparison test based on Kruskal-Wallis scores, when indicated. Fisher's exact test was used for comparison of qualitative data, and Spearman's correlation coefficient r_S to correlate clinical and PSG variables. The degree of correlation was considered moderate for r_S from 0.41 to 0.60, and substantial from 0.61 to 0.80. All analyses were performed using Statistica/W (StatSoft; Tulsa, OK, USA). The level of significance was established as $p < 0.05$ for parametric and $p < 0.01$ for nonparametric analysis and correlations.

RESULTS

Among the children enrolled, 21 patients with JRA and 20 controls completed all parts of the study. The participants' demographic and clinical data are shown in Table 1. Although more frequently reported by JRA patients, the frequency of sleep complaints, such as difficulty falling asleep or waking in the morning, motor activity during sleep, or presence of parasomnias, was not different between JRA patients and controls (Table 2).

PSG variables are shown in Table 3. There was a lower sleep efficiency ($p = 0.046$) and a significant increase in indexes of arousals ($p = 0.00001$), PLM ($p = 0.02$), LM ($p = 0.004$), and LM related to arousals ($p = 0.00002$) as well as alpha/delta activity during non-REM sleep ($p = 0.0005$) in the JRA group compared to the control group. EEG arousals and alpha-delta activity were increased in JRA patients compared to controls (Table 4), not only in sleep stages 1 and 2 but particularly in SWS (Figure 1).

JRA patients with a CHAQ functional disability score > 1 also exhibited a higher frequency of arousals (77.8% vs

Table 1. Characteristics of the patients with JRA and controls. Data are mean ± SD or number (%).

	Controls, n = 20	JRA, n = 21	p*
Age, yrs	13 ± 2	13 ± 2	NS
Female:male	10:10	12:9	NS
JRA onset (%)			NA
Systemic		9 (43)	
Polyarticular		12 (57)	
ACR functional impairment (%)			NA
I and II		16 (76)	
III and IV		5 (24)	
CHAQ		1.0 ± 0.7	NA
EPM-ROM		1.2 ± 0.7	NA
Inflamed joints, n		3.4 ± 2.0	NA
Impaired joints, n		10.7 ± 0.3	NA
Morning stiffness, n (%)		10 (48)	NA
Morning stiffness, min		61 ± 10	
Pain scale	0	1.4 ± 1.1	NA
Tender point count	3.0 ± 1.7	4.3 ± 2.6	NS
Treatment			
NSAID, n (%)		19 (90)	NA
Steroids, n (%)		7 (33)	NA
Methotrexate, n (%)		16 (76)	NA
Other immunosuppressor, n (%)		7 (33)	NA

NSAID: nonsteroidal antiinflammatory drugs; CHAQ: Childhood Health Assessment Questionnaire, functional evaluation scale; EPM-ROM: Escola Paulista de Medicina-Pediatric Range of Motion Scale, joint mobility scale; NS: nonsignificant; NA: not applicable.

Table 2. The Sleep Disturbance Scale for Children[13].

	Controls, n = 20	JRA, n = 21	p
DIMS	9.0 ± 2.4	9.8 ± 3.2	0.37
SBD	3.0 ± 0	3.0 ± 0	1.00
DA	12.0 ± 2.4	12.8 ± 3.2	0.37
SWTD	6.8 ± 1.5	7.5 ± 1.3	0.13
DOES	6.2 ± 1.4	6.4 ± 1.0	0.64
SHY	2.0 ± 0	2.0 ± 0	1.00
Total score	39.0 ± 6.1	41.5 ± 6.8	0.23

DIMS: Disorders of initiating and maintaining sleep; SBD: sleep breathing disorders; DA: disorders of arousal; SWTD: sleep-wake transition disorders; DOES: disorders of excessive somnolence; SHY: sleep hyperhidrosis.

Table 3. Polysomnography data.

	Controls, n = 20	JRA, n = 21	p
TTR (min)	496.3 ± 37.0	519.6 ± 49.6	NS
Range	434.8–544.0	387.0–595.5	
SPT (min)	484.7 ± 34.5	493.7 ± 59.3	NS
Range	424.8–529.0	356.0–583.0	
TST (min)	472.1 ± 35.3	439.6 ± 64.9	NS
Range	398.5–527.0	277.0–522.0	
Sleep efficiency (%)	91.5 ± 4.7	86.1 ± 10.7	0.04
Range	80.0–98.0	49.0–98.0	
Sleep Latency (min)	10.0 (6.3)	15.0 (12.8)	NS
Range	2.0–61.5	0.0–136.5	
REM Latency (min)	144.7 ± 38.0	139.1 ± 59.6	NS
Range	64.5–206.5	31.5–345.0	
Stage 1 (%)	6.6 ± 2.8	8.2 ± 5.0	NS
Range	1.0–10.8	2.9–19.6	
Stage 2 (%)	49.3 ± 10.2	44.9 ± 8.2	NS
Range	25.6 –72.4	25.6–55.5	
SWS (%)	23.3 ± 8.0	25.7 ± 8.2	NS
Range	12.6–44.7	11.3–44.7	
REM (%)	20.3 ± 5.6	21.6 ± 5.5	NS
Range	9.1–28.1	9.8–35.1	
Arousals/h	3.3 ± 1.9	10.7 ± 6.3	0.00001
Range	1.1–8.5	1.5–24.2	
PLM/h	1.1 (1.0)	2.3 (7.1)	0.02
Range	0–4.5	0–34.1	
LM/h	1.5 (1.0)	3.7 (8.2)	0.004
Range	0.2–5.5	0.6–36.1	
LM arousals/h	0.1 (0.06)	0.8 (4.0)	0.00002
Range	0.01–0.4	0.03–11.0	
Alpha-delta	0.08 (0.09)	0.6 (0.3)	0.0005
Range	(0–0.2)	(0.02–1.0)	
AHI (events/h)	0.3± 0.2	0.3 ± 0.2	NS
Range	0–0.8	0–0.8	

Mean ± standard deviation for parametric data and median (interquartile range) for nonparametric data. NS: nonsignificant. TTR: total time of recording, SPT: sleep period time (TTR – sleep latency), TST: total sleep time (SPT – wake stages after sleep onset), PLM: periodic leg movements, LM: isolated leg movements, AHI: apnea hypopnea index. * Student t test or Mann-Whitney U test.

Table 4. Distribution of alpha/delta activity and arousal index according to sleep stage. Data are median (interquartile range), range.

	Controls, n = 20	JRA, n = 21
Stages 1 and 2		
Alpha/delta	0.1 (0.05)[#]	0.3 (0.15)[#]
Range	0–0.2	0.02–0.6
Arousals/h	4.4 (2.62)[#]	24.3 (10.4)*[#]
Range	1.3–11.5	1.2–60.0
LM/h	9.0 (6.3)[#]	23.7 (40.8)*[†]
Range	1.6–31.8	4.1–224.6
SWS		
Alpha/delta	0 (0.05)	0.2 (0.1)*
Range	0–0.1	0–0.3
Arousals/h	2.6 (0.9)	12.4 (5.8)*[#]
Range	1.1–8.6	0.6–57.0
LM/h	1.6 (1.2)[#]	4.3 (7.5)
Range	0.3–5.8	0.7–41.2
REM		
Alpha/delta	0 (0.005)	0.02 (0.01)
Range	0–0.02	0–0.03
Arousals/h	4.4 (2.6)	24.3 (10.5)*
Range	1.3–11.5	1.2–60.0
LM/h	0.4 (0.3)	0.9 (1.7)
Range	0.1–1.3	0.2–9.2

SWS: slow wave sleep, LM/h: leg movements/hour of total sleep time. Kruskal-Wallis ANOVA test followed by multiple-comparison tests between individual groups, $p < 0.01$. Arousals: $H(5, 123) = 65.74$; alpha/delta: $H(5, 123) = 57.83$; and LM/h: $H(5, 123) = 79.10$. * Greater than in controls; [†] greater than in other sleep stages; [#] greater than in rapid eye movement sleep.

16.7%; p = 0.009) and increase of and decrease of sleep efficiency (80.8 ± 13.9 vs 90.3 ± 5.3; p = 0.04). Patients with high functional impairment and with morning stiffness had higher PLM and/or LM indexes than other participants (Table 5). Patients with higher amount of joint involvement by EPM-ROM and with pain symptoms had increased alpha/delta activity ($p < 0.01$).

Table 6 shows significant correlation between clinical variables and PSG observations: there was a substantial correlation ($p < 0.01$) between duration of morning stiffness and PLM ($r_S = 0.75$) and LM ($r_S = 0.78$) scores, as well as between pain symptoms and the alpha/delta rate ($r_S = 0.74$). Correlation between hemoglobin level and PLM or LM index could not be established.

Fisher's exact test showed no significant difference in any of the sleep variables in relation to presence/absence or amount of medication usage (Table 1).

DISCUSSION

Our study was designed to evaluate the possible association between clinical manifestations and sleep disturbances in patients with JRA. We used a different approach than previous studies and selected school-age children with polyarticular and active disease, as these individuals have prominent pain and functional disability. A higher prevalence of sleep frag-

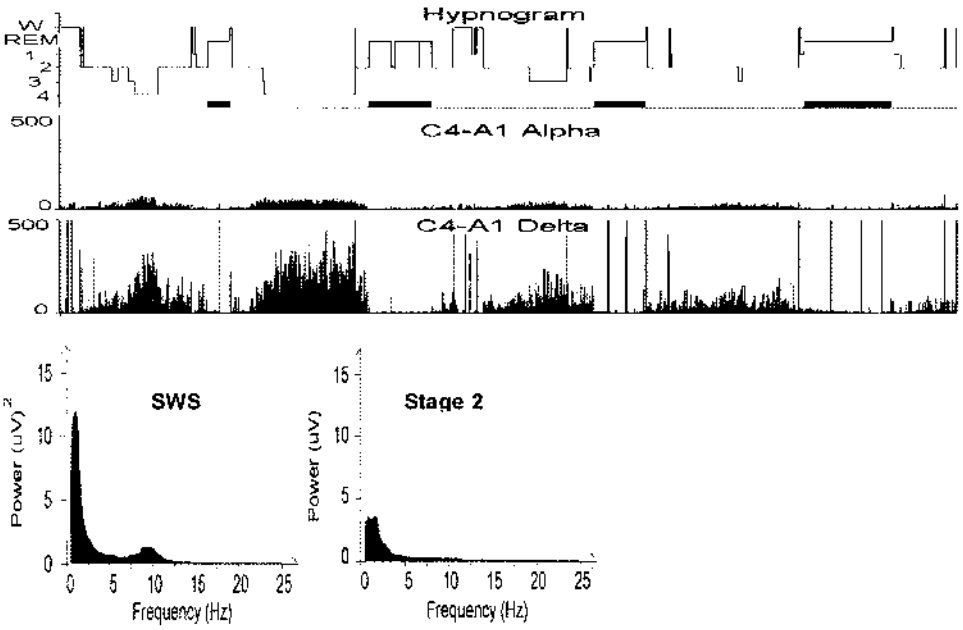

Figure 1. Spectral profile of alpha-delta sleep in a patient with JRA.

Table 5. Phasic events of sleep according to clinical indicators of JRA. Data are median (interquartile range).

Clinical Indicator	PLM/h	LM/h	Alpha/delta
Impaired joints, N			
≤ 4, n = 7	0.8 (0.6)	1.4 (0.3)	0.2 (0.3)
> 4, n = 14	13.3 (10.6)	14.8 (11.0)	0.5 (0.3)
p	0.02	0.001	0.02
Morning stiffness			
No, n = 11	0.8 (0.7)	1.8 (1.0)	0.2 (0.3)
Yes, n = 10	17.3 (0.5)	20.3 (8.0)	0.6 (0.3)
p	0.001	0.0001	NS
EPM-ROM			
≤ 1, n = 7	1.2 (0.5)	1.4 (1.1)	0.1 (0.3)
> 1, n = 14	13.3 (10.7)	14.6 (11.0)	0.6 (0.3)
p	NS	0.01	0.03
CHAQ			
≤ 1, n = 12	1.4 (3.5)	1.9 (3.8)	59.5 (34.8)
> 1, n = 9	13.5 (10.6)	18.2 (17.6)	86.0 (72.5)
p	Ns	0.03	NS
Pain*			
No, n = 9	0.0 (0.5)	1.8 (7.5)	0.1 (0.04)
Yes, n = 12	7.4 (7.8)	8.2 (8.8)	0.7 (0.05)
p	NS	NS	0.0001

PLM: periodic leg movements, LM: isolated leg movements. * For pain evaluation, "no" represents score 0 (zero) and "yes" represents scores 1 to 4. Mann-Whitney U test. NS: nonsignificant; EPM-ROM: Escola Paulista de Medicina-Pediatric Range of Motion Scale; CHAQ: Childhood Health Assessment Questionnaire.

mentation was verified in the JRA sample, as well as a relationship of these abnormalities with functional impairment, pain, and morning stiffness.

In contrast to previous publications[2,3,5], we were unable to document a significant difference in daytime sleepiness between the JRA and control groups. Although Zamir, *et al*[4] detected increases in daytime sleepiness in 3 of 7 JRA patients tested by MSLT, they also found no differences in the frequency of sleep complaints or in reports of daytime sleepiness between the total group of 16 JRA patients and 9 controls recruited in their study. Considering the relatively small sample sizes and sociocultural factors[18,19] that may play a role in these negative results, it becomes evident the instruments used to assess daytime sleepiness in this and other studies lack specificity, and more objective measures to assess daytime sleepiness in the pediatric population are needed. With the particular expressions of daytime sleepiness in children and adolescents[1] in mind, we did not use the MSLT because, apart from its objectivity in measuring sleepiness, this test provides only a cross-sectional observation of alertness/sleepiness. To evaluate daily complaints of sleepiness and tiredness, we chose instead the Sleep Disturbance Scale for Children[13], even though Factor 5 of this instrument, related to daytime somnolence, does not deal with common manifestations of sleep disruption in children such as irritability, distractibility, impulsive behavior, and impaired school performance[1].

Table 6. Significant correlations between clinical and polysomnography data.

	Spearman Coefficient (r_s)	p
Alpha/delta and pain score	0.74	0.0001
PLM/h and morning stiffness, min	0.75	0.00009
LM/h and morning stiffness, min	0.78	0.00003

PLM: periodic leg movements, LM: isolated leg movements.

In spite of the lack of differences in sleep quality and sleep restoration observed between groups, sleep fragmentation in children with JRA was indicated by lower sleep efficiency, higher arousal index, and PLM and LM associated or not with arousals. In this group, EEG spectral analysis indicated an increase in desynchronization by the appearance of alpha and low-voltage fast rhythms in non-REM sleep, particularly in SWS. Considering that secretion of growth hormone occurs predominantly during SWS[20], fragmentation of SWS in JRA patients may contribute to impaired growth hormone secretion, as suggested by Born, *et al*[21].

There is a considerable prevalence of sleep disorders in individuals with chronic pain conditions, particularly in musculoskeletal diseases[22-30]. The association between pain and sleep abnormalities is complex, as sleep disorders can increase pain, as shown by the decrease in pain thresholds in healthy individuals undergoing selective SWS deprivation[31,32]. In our study, no correlation could be established between morning pain and total sleep time, as reported by Labyak, *et al*[5]. There was no significant difference between JRA patients and controls in the distribution of sleep stages or in the detection of abnormal respiratory events.

Positive correlation has been found between alpha/delta activity in non-REM sleep and pain symptoms, even after excluding fibromyalgia[25,26]. The failure to find a correlation between alpha-delta sleep pattern and the arousal index might be because the criteria for detection and scoring of arousals[33] are still controversial[34,35]. In clinical studies, definition of what constitutes arousal is critical, particularly in children[16,36].

Consistent with our previous studies[26,37], the occurrence of alpha-delta phase events during sleep may represent a decrease in the arousal threshold and reflect a primary arousal processing in response to an endogenous painful stimulus. Sforza, *et al*[35] give evidence in favor of this hypothesis, showing that EEG synchronization occurs as a primary response to stimulation, preceding EEG desynchronization and autonomic activation and the onset of a physiological or pathological cortical arousal.

The same has been described for PLM: cardiovascular activation associated with subtle modifications in EEG frequency not detectable by visual inspection may precede the motor event and the arousal identification[38]. In our study the distribution of arousal and LM or PLM events was aleatory, with no correlation among the events. Studies have shown that the frequency of arousal is the important aspect in the recovery functions of sleep in patients with PLM, in whom arousal density is the best predictor of daytime somnolence[39].

Considering the relationship between low iron storage concentrations and PLM in children[40], one limitation of our study is that we did not examine participants' iron levels. It is well known that in JRA the anemia of chronic disease may often be indistinguishable from anemia due to iron deficiency, because of mechanisms that impair flow of iron from reticuloendothelial cells to the bone marrow, shorten red cell lifespan, and reduce erythropoietin responsiveness, and an accelerated plasma iron clearance[41]. Additional factors in the genesis of anemia are impaired iron uptake by erythroblasts and local production of cytokines such as tumor necrosis factor and interleukin 6 in bone marrow[42,43]. Serum transferrin receptor (sTfR) concentration is the measure of choice to distinguish iron-deficiency anemia from anemia of chronic disease in situations in which inflammation influences the interpretation of serum ferritin and transferrin levels[44]. Since an association between sTfR and hemoglobin level has been described[45] and we found no correlation between hemoglobin and PLM or LM indexes, we can infer that leg movements might not be attributed to low iron stores, but this possibility cannot be ruled out totally.

Other limitations of this study are the small sample size and the difficulty in withdrawing patients' pain medication for a period longer than 4 days. The absence of significant differences in sleep measures among JRA patients, independent of the medication used, reinforces the hypothesis that the influence of steroidal and nonsteroidal antiinflammatory drugs (NSAID) on sleep is less deleterious than the effects of the inflammatory process[46-48]. It is well known that NSAID have potential effects on melatonin secretion, and that they may theoretically cause phase shifting and enhance nighttime alertness in healthy subjects[49], but these data cannot be extended to patients with pain, in whom pain and the disease process per se may also disrupt sleep[27]. Although healthy subjects using NSAID exhibit reduction in SWS and REM, in patients with RA these drugs do not seem to yield to objective sleep changes; on the contrary, patients report improvement in sleep evaluation[30,48]. Nevertheless, we cannot exclude that the prolonged treatment of the JRA patients could partially explain the changes in sleep EEG that we found.

We observed abnormal sleep patterns in children with JRA experiencing chronic pain and/or functional impairment. A followup study is needed to evaluate the implications of sleep disruption on the natural course of the disease, as well as on patients' quality of life and response to treatment.

ACKNOWLEDGMENT

The authors are grateful to Jaques Belik, MD, for revision of the manuscript, to Marcia Pradella Hallinan, MD, for sleep scoring, and to Agostinho A. Rosa, PhD, for spectral analysis of the recordings.

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