Short running head: Sleep in Juvenile Fibromyalgia

SLEEP AND SLEEP COMPLAINTS IN JUVENILE FIBROMYALGIA SYNDROME

Clara Malattia, MD, PhD[1,2], Lorenzo Chiarella, MD[2,3], Miriam Sansone, MD[2,3], Angela Pistorio, MD[4], Claudio Lavarello, MD[1], Manuela Carpaneto, MD[5], Raffaele Ferri, MD[6], Angelo Ravelli, MD[2,4] and Lino Nobili, MD[2,3]

1. Clinica Pediatrica e Reumatologia, IRCCS Istituto Giannina Gaslini, Genoa, Italy;
2. Department of Neurosciences, Rehabilitation, Ophthalmology, Genetic and Maternal Infantile Sciences (DINOGMI), University of Genoa, Genoa, Italy.
3. Child Neuropsychiatry Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy.
4. Direzione Scientifica, IRCCS Istituto Giannina Gaslini, Genoa, Italy .
5. SS Antonio e Biagio e Cesare Arrigo Hospital, Child Neuropsychiatry Unit, Alessandria, Italy
6. Sleep Research Centre, Oasi Institute Research - IRCCS, Troina, Italy.

Corresponding author:

Dr.Clara Malattia,

Clinica Pediatrica Reumatologia

IRCCS Istituto G. Gaslini

Via G. Gaslini 5

16147 Genova Italy

Tel: +39-010-56362843

Fax: +39-010-5636211

e-mail: claramalattia@gaslini.org

Conflict of Interest Disclosures: The authors have no conflicts of interest relevant to this article to disclose.

Funding: This study was supported by the Italian Ministry of Health, 5x1000 project 2017 "SOLAR: Sleep disorders in children: an innovative clinical research perspective".

Key Indexing Terms: Juvenile Fibromyalgia, sleep, polysomnography, musculoskeletal pain, depression, fatigue.

Abstract

Objective: To investigate sleep quality in juvenile fibromyalgia syndrome (JFS) and its impact on the global burden of the disease.

Methods: Consecutive JFS patients who performed full-night polysomnography (PSG) were included in this cross-sectional study. JFS related symptoms, neuropsychiatric features, and sleep quality were assessed using self-report measures. PSG sleep parameters, including N3 distribution index, were obtained from patients and age-matched healthy controls.

Results: We included 25 patients (F 20, median age 15.7 years). Non restorative sleep was reported by 22/25 (88%) patients. JFS patients showed significantly longer Sleep Period Time (P=0.004) and increased wake time after sleep onset (P=0.03) compared to healthy peers. N3 sleep distribution index was significantly lower in patients than in control group (P=0.02). Subjective poor sleep quality was related to Widespread Pain Index (WPI) (r_s-0.65), symptom severity scale (r_s-0.64), depressive symptoms (r_s-0.58), fatigue (r_s-0.44), and symptoms severity upon awakening (r_s-0.65). N3 distribution index was correlated to depressive symptoms (r_s 0.41) and irritability (r_s 0.40). On multiple regression analysis, WPI was predicted by subjective sleep quality (β= -0.32, P=0.04), whereas depressive symptoms were predicted by subjective sleep measures (β= -0.32, P= 0.04) and PSG parameters (N3 min: β= -0.07, P=0.03).

Conclusions: Sleep complaints are a key hallmark of JFS and has significant impact on relevant clinical domains of the disease, such as pain and depression.

Introduction

Juvenile fibromyalgia syndrome (JFS) is a disabling condition characterized by widespread diffuse musculoskeletal pain, fatigue, mood disturbances that cause functional impairment and have a marked impact on the patients' quality of life [1]. JFS is more common in girls than in boys, and has a mean age at symptoms onset of 11.4-13.7 years [2]. The estimated prevalence of JFS ranges from 1.2 to 6.2% [3, 4], making this condition an emerging healthcare problem in female adolescents.

Sleep disturbances are a well-known component of the clinical spectrum of fibromyalgia (FM), and are reported in 75-90% of adult patients [5-7] and in 67%-96% of JFS patients [1, 2, 8, 9]. Self-reported subjective sleep problems in FM and JFS include difficulty falling asleep, sleep fragmentation with multiple arousals, non-restorative sleep and excessive daytime somnolence [5-8]. These subjective sleep complaints are substantiated by objective sleep-wake patterns on polisomnography (PSG) examination. Indeed, PSG and EEG spectral analysis have revealed greater sleep-onset latency and an increased arousal index, decreased total sleep time (TST) and sleep efficiency (SE), reduced percentage of slow-wave sleep (SWS), and increased alpha wave activity during SWS (the alpha-delta sleep) in FM patients compared to control subjects [10-15]. These PSG findings suggest a disorder of homeostatic and circadian mechanisms during sleep in FM patients. Wide evidence indicates a significant relationship between sleep disturbances and FM-related symptoms, such as unrefreshing sleep, sleepiness, fatigue, lower pain thresholds, mood swings, and cognitive impairment [16-18].

In contrast to adults, JFS has been investigated less extensively in regard to sleep characteristics. Sleep assessment in children with chronic pain has primarily relied on subjective measures of sleep quality [8, 9, 19, 20] and, so far, only three studies have used PSG to investigate the patho-physiological bases of sleep disturbances in JFS [21-23]. Similarly to FM, abnormal sleep patterns in JFS included shortened TST, prolonged sleep latency, decreased SE, longer awake periods during sleep, and alpha intrusions into SWS [21, 22].

However, there is conflicting evidence regarding the impact of sleep disturbances on JFM-related symptoms. Roizenblatt et al. have reported an association between alpha-delta sleep with subjective sleep complains and musculoskeletal pain in 34 JFS patients [21]. These results have been recently questioned by Olsen et al. who found that alpha-delta sleep was unrelated to pain, disability, or subjective sleep difficulties in an observational study involving 10 JFS patients [23]. Overall, however, the available data is insufficient to establish a causal relationship between sleep quality and JFS-related symptoms.

The purposes of the present study are to investigate sleep quality and describe the PSG sleep patterns of adolescents with JFS. We also aimed to determine the impact of sleep disturbances on the global burden of the disease by exploring their relationships with JFS-related symptoms.

Methods

Patients with JFS by the 2010 American College of Rheumatology Adult Fibromyalgia Criteria [24, 25] were recruited from the Paediatric Rheumatology Department at the Gaslini Children's Hospital of Genoa, Italy. All consecutive patients who performed a full-night PSG between 2019-2020 were included in this cross-sectional study. Patients who had received sleep medications within one week prior the study or had co-morbid illnesses that could affect sleep were excluded.

The Widespread Pain Index (WPI), the Symptoms Severity scale (SS) as well as the total number of tender points [25] at the time of inclusion in the present study were recorded. The WPI includes a list of 19 painful areas and reflects the bodily distribution of pain. The SS comprises two parts: Part SS2a evaluates the severity of fatigue, waking unrefreshed, and cognitive symptoms using a 4-point Likert scale (total score range: 0 to 9). Part SS2b includes a checklist of 41 somatic symptoms (score range: 0-3, based on the number of symptoms complained by the patients: 0 symptoms (score of 0), 1 to 10 symptoms (score of 1), 11 to 24 symptoms (score of 2), and 25 or more symptoms (score of 3)). The SS is obtained from the sum of the SS2a and SS2b scores and ranges from 0 to 12 [25]. Tender point evaluation was performed at 18 standardized points by digital pressure.

Participants were asked to rate their average level of pain in the previous two weeks using the standard 100-mm pain Numerical Rating Scale (NRS) that ranges from 0 (no pain) to 100 mm (pain as bad as it can be) [26, 27]. Self-report measures (100 mm NRS) were also used to rate the severity of symptoms in the following domains: fatigue, headache, symptoms severity upon awakening, irritability and global assessment of disease severity.

Depressive symptoms were assessed using the Children's Depression Inventory (CDI), a self-report scale with a total score ranging from 0 to 54 [28]. A CDI score ≥19 is considered the cut-off to identify patients with clinically-significant depressive symptomatology. Anxiety symptoms were evaluated using the Multidimensional Anxiety Scale for Children (MASC), a self-report questionnaire which consists of 39 items. The total score is pathological if ≥ 60 [29]. Perceived sleep quality was assessed using the Sleep Condition Indicator (SCI), an eight-item, patient-reported questionnaire based upon DSM-5 criteria [30]. Scores of these eight components are summed to obtain a global score ranging from 0 to 32; a score ≤ 16 identifies an insomnia disorder [30]. Daytime sleepiness was assessed using the Epworth Sleepiness Scale-Children and Adolescents (ESS-CHAD), a self-administered eight-item questionnaire. The total score is marked out of a maximum of 24, and a score > 10 is considered abnormal and indicative of excessive daytime sleepiness [31].

Patients underwent a full-night PSG recording at their home. The recording montage included: F4-M1, C4-M1, O2-M1, F3-M2, C3-M2, O1-M2 electroencephalograms, right and left electrooculograms for eye movement detection and REM sleep identification, a bipolar mental electromyogram (EMG) for muscle tone measurement, nasal airflow, chest, abdominal and leg movements (piezo-electric bands), arterial oxygen saturation and a bipolar electrocardiogram (ECG). Patients were set up in the morning in the clinic, and the device recording time was lined up with the patients' usual sleep schedule. After this procedure, patients spent the night at home in order to avoid the first-night effect.

All recordings were computed and scored using RemLogic software, in accordance with the scoring rules proposed by the American Academy of Sleep Medicine (AASM) [32]. PSG variables included:

Sleep Period Time (SPT), Total Sleep Time (TST), Sleep Onset Latency (SOL), Wake After Sleep Onset (WASO), Sleep Efficiency (SE), Sleep staging with total minutes of NREM (N1, N2, N3) and REM sleep stages, Awakening index. N1 corresponds to light transitional sleep, N2 to fully developed sleep and occurs throughout the sleep period, N3 (also referred to as delta sleep or Slow Wave Sleep) corresponds to deep sleep, it is thought to be the most restful form of sleep and it is more represented in the first part of the sleep period. Time spent in Stages N1, N2, N3 and REM was analyzed and expressed as a percentage of TST and SPT. In addition, wake-time was defined as a relative percentage in the SPT that was computed as the elapsed time from sleep onset through to the last epoch of sleep. TST was computed as the total duration of epochs scored as asleep. SOL was computed as duration of time from light off to falling asleep. WASO, defined as the duration of night-time awakenings, was computed as the total duration of epochs scored as wake after initial sleep onset and prior to final awakening. SE was computed as the proportion of time scored as asleep relative to the total time in bed. Arousals were defined as an abrupt shift in EEG frequency lasting from 3 to 14 seconds and accompanied by one or more following changes in recording signals: increased chin or EMG activity, increased heart rate, ECG distortion, and distortion of the respiratory signals. Awakenings were computed as a shift from a sleep stage epoch to a wake epoch. Awakening index was the number of awakenings per hour of sleep.

We also investigated the distribution of N3 in the course of the night calculating the N3 distribution index defined as ([number of epochs of N3 in the first half of SPT - number of epochs of N3 in the second half of the SPT]/total number of N3 epochs) [33]. The N3 distribution index ranges from -1 to 1, with higher values being correlated with predominance of N3 sleep in the first half of the night, as expected in physiological sleep. All the aforementioned PSG variables were also extracted from a population of 27 control subjects (CSs) matched for age and sex with patients. CSs underwent a full-night PSG recording at their home. All CSs had a negative history of musculoskeletal pain and underlying medical conditions including cardiac, neurological, or respiratory diseases that are known to have an impact on sleep architecture. None of them reported current sleep disturbances.

This study was approved by the Institutional Review Board for human subject's research (CER Liguria: 333/2022 - DB id 12460). All participants and legal guardians provided the appropriate informed consent/assent for the use of recordings for research and publications purposes.

Statistical methods

Descriptive statistics were first performed; categorical data were reported in terms of absolute frequencies or percentages, whereas continuous quantitative data were reported in terms of medians, first and third quartiles (1^{st} -3^{rd} q). Comparison of quantitative data was made by means of the non-parametric Mann-Whitney U test. Correlation between quantitative data was evaluated by means of the non-parametric Spearman's correlation coefficient (r_S); correlations were considered high if > 0.70, moderate if 0.40–0.69, and low if < 0.40 [34].

We hypothesized that in a multivariate model, increased pain, symptom severity scale, and anxiety/depressive symptoms could be predicted by poorer sleep quality. Multiple regression models for different outcomes (i.e WPI, SS scale, fatigue, CDI, MASC etc.) and selected independent variables (i.e subjective and objective sleep indicators) were performed. Independent variables that were clinically relevant or were linearly correlated to the outcomes were included in multivariable models. Beta coefficients and Standard Errors (SE) of the models were calculated and reported for each model and the classical t-tests were used to evaluate the Beta coefficients. R^2 was used as an indicator of goodness-of-fit.

All statistical tests were 2-sided, and P values less than 0.05 were considered statistically significant. The software "Statistica" (release 9.0, StatSoft Corporation, Tulsa, OK, USA) was used for descriptive and bivariate analyses.

Results

Twenty-five consecutive patients with JFS, whose demographic and clinical features are reported in table I, were included in the study. Twenty patients were not receiving any medications before and

during PSG. Of the remainder patients, 2 discontinued their medications (one amitriptyline and one amitriptyline plus clonazepam) 7 days before the study and 3 elected to continue their medications (one sertraline, one gabapentin, and one duloxetine).

We also included 27 CSs (19 females and 8 males, median age 15.3 years, 1st -3rd q: 14.9- 16.0 years). Eighteen JFS patients (72%) complained of subjective poor sleep quality according to the SCI. Sleeping problems included difficulties initiating sleep or frequent awakenings, as reported in table II. Non-restorative sleep (i.e., awakening tired with the sensation of not having slept during the night) was reported by 22 patients (88%). Although excessive daytime sleepiness was reported in only 4 patients (16%), 9 patients (36%) reported regular napping in the afternoon.

Table III shows the comparison of full-night PSG between JFS patients and age-matched CSs. JFS patients showed a significant longer SPT (P=0.004) and increased WASO (P=0.03) compared to their healthy peers. No differences in SE, number of arousals and sleep latency were found in JFS patients compared to healthy controls. Although the time spent in N3 sleep stage did not differ between patients and controls, the N3 distribution index was significantly lower in JFS patients (0.5) than in the control group (0.6, P=0.02), indicating a higher number of epochs of N3 during the second part of the night.

As reported in table IV, subjective poor sleep quality and daytime sleepiness were related to bodily distribution of pain (r_S -0.65 and 0.50, respectively), increased symptom severity scale (r_S -0.64 and 0.61, respectively), depressive symptoms (r_S -0.58 and 0.54, respectively), fatigue (r_S -0.44 and 0.51, respectively) and symptoms severity upon awakening (r_S -0.65 and 0.49, respectively). Reduced N3 sleep stage was related to symptoms severity scale (N 3 min: r_S -0.41; N3 SPT: r_S -0.46) and Children's Depression Inventory scale (N3 min: r_S -0.40). The N3 distribution index correlated to depressive symptoms (r_S 0.41) and irritability (r_S 0.40).

On multiple regression analyses (table V), the number of painful body regions (WPI) was predicted by subjective poor sleep quality (β= -0.32, P=0.04), whereas depressive symptoms were predicted by

both subjective poor sleep quality (β= -0.32, P= 0.04) and objective PSG measures (N 3 min: β= -0.07, p=0.03; N 3 Distribution Index: β= 11.54, P= 0.002).

Discussion

This study confirms that disturbed sleep is a key hallmark of JFS and provides important insights into the impact of sleep complaints on relevant clinical domains of the disease, such as pain and depression. In line with previous studies [1, 2, 8, 9], the majority of our patients complained of difficulties in falling asleep, frequent awakenings, non-restorative sleep, and excessive daytime somnolence. More than 70% of patients had an abnormal SCI score and satisfy the criteria for insomnia disorder according to DSM 5.

Of note, these results do not appear to be fully reflected by the objective measures of sleep obtained from PSG recording. In contrast to previous studies [21, 22], our patients did not differ in SE, number of arousals, sleep onset latency, and sleep staging from controls, except for wake after sleep onset. Although the last variable was significantly increased in our patients as compared to healthy controls, the TST appeared to be preserved, resulting in an overall increase in the total SPT.

The discrepancy between subjective and objective sleep variables suggests the presence of a certain amount of sleep misperception in JFM patients. This should be always kept in mind when evaluating these patients especially when considering the pharmacological treatment of sleep complaints in this population.

Although JFM might present with a distinct set of symptoms and PSG findings than adult forms, we cannot exclude that the preservation of the TST might disappear as disease progresses, leading to the same PSG changes described in adult patients. In support of this hypothesis, Roizenblatt et al. found that PSG alterations are less prominent in children with JFS than in their affected mothers, which suggested that sleep disturbances may worsen over time [21]. In line with these observations, the short disease duration of our patients might explain in part the lack of major alterations in sleep macrostructure as revealed by PSG examinations. As TST and total N3 sleep appear to be

quantitatively similar to controls, morning symptoms complained by patients can not be explained by sleep deprivation. Although sleep macrostructure was preserved, sleep EEG in our patients showed a significantly different distribution of N3 sleep stage throughout the night. In fact, although the time spent in N3 was similar between patients and the controls, the N3 distribution index was significantly lower in JFS patients, indicating a higher representation of N3 sleep during the second part of the night.

N3 stage, also referred to as delta sleep or SWS, is the deepest and most restorative sleep stage. Physiologically episodes of N3 are longer at the beginning of the night and shorten gradually as the night progresses [32]. The altered distribution of N3 sleep in our patients could be related to the increased length of wakefulness periods during the night. An alternative hypothesis is that the higher amount of N3 epochs during the second part of the night might be the expression of an impairment in the process of physiological release of the homeostatic drive to sleep. Regardless of the mechanism, this shift of N3 sleep could contribute to explain the severity of morning symptoms complained by our patients. Indeed, an increased amount of N3 sleep during the second part of the night might enhance the physiological phenomenon of sleep inertia, thereby exacerbating transitory hypovigilance, confusion, and impaired cognitive and sensory-motor performance that physiologically follows awakening [35].

In support of the major role of N3 in the restorative process, we found a significant inverse correlation between N3 sleep duration and the symptom severity scale, which evaluates the severity of fatigue, waking feeling unrefreshed, and cognitive symptoms. The relationship of FM symptoms with N3 sleep deprivation is well established in adult patients [6, 7, 10, 11, 21]. Our results confirm the pivotal role of N3 sleep for energy restoration, providing a reasonable explanation to non-restorative sleep in JFS.

We found that self-reported sleep complaints were significantly and independently correlated to the WPI, which reflects the distribution of pain throughout the body. Similarly, Roizemblatt et al. found that alpha-delta sleep was significantly associated with the number of tender points and inversely

related to pain thresholds in JFS patients [21]. Moreover, there is preliminary evidence that multidisciplinary pain treatment programs, including intensive physical exercise, produce subjective improvement in sleep quality in JFS patients [23]. Collectively, these results confirm the interplay between sleep and pain, and provide support to nonpharmacological treatment strategies aimed at enhancing sleep quality in JFS. This approach could also help to reduce the risk and the severity of co-morbid psychiatric disorders, such as anxiety and depression, which represent a significant problem in JFS [1, 8, 36]. In fact, anxiety and depression disorders have been correlated with school absenteeism and functional disability in JFS [37, 38]. The alarming finding is that depression and anxiety have been recently associated with a high risk of suicide in a cross-sectional study involving 31 JFS patients [39]. Therefore, identification of predictors of anxiety and depressive symptoms in JFS, is of utmost importance to improve treatment outcomes.

Our results suggest a relationship between sleep disturbances and depressive symptoms in JFS. In fact, both subjective and objective sleep measurements were significantly and independently correlated with the CDI score. They also confirm the results of previous studies in FM, which provided evidence of a bidirectional link between sleep disorders, depression and anxiety [40, 41]. Such a link could be mediated by common pathophysiological mechanisms, including alterations in serotoninergic activity and melatonin secretion [42, 43] although further studies are needed to establish the degree of this possible bidirectional relationship. Because sleep complaints and depressive symptoms are known to have a significant impact on daily activities and pain thresholds [37, 38, 41], studies examining the interrelationship between these variables over time could help to develop more effective therapeutic strategies for JFS.

There are some limitations of our study that should be addressed in future research. Firstly, the statistical power is limited by the small sample size. Secondly, spectral analysis was not performed and, thus, data on sleep microstructure is lacking. Such data could improve our understanding of the mechanisms underlying poor sleep quality in JFS, in the light of the previous descriptions of alpha-delta sleep phenomenon in FM [10, 11]. This altered sleep pattern is well described in adult FM

patients, but not in the juvenile form of the disease. Thirdly, a potential influence of medications on the study results cannot be excluded despite discontinuation of therapies before patient inclusion into the study. Finally, we only made single time-point PSG recordings. Longitudinal interventional studies are needed to elucidate whether interventions addressing sleep disturbances may improve pain, mood disorders and emotional dysfunction in adolescents with JFS. The strengths of our analysis include the use of objective measurements of sleep quality and the age and sex-matched control group used for PSG examinations. This requirement is essential due to the differences in sleep patterns related to age and pubertal status [44].

In conclusion, our study is amongst the first to combine self-reported measurements and PSG examinations in the evaluation of sleep quality in JFS, and to demonstrate the impact of sleep disruption on the global burden of the disease. Although we found a discrepancy between subjective sleep measures and PSG findings, our results revealed consistently that more sleep alterations were associated with more severe symptoms across a variety of disease-related domains, especially those concerning pain and depression. Elucidation of the influence of sleep complaints on disease severity could provide insights for the development of more comprehensive therapeutic approaches. Longitudinal studies are needed to demonstrate whether treatment of sleep disturbances may help to decrease the severity of JFS-related symptoms and improve disease otucome.

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Table I. Description of the study patients [N=25].

JFS	N=25
Male n (%)	5 (20 %)
Female n (%)	20 (80 %)
Age at diagnosis (years)	14.8 [12.8-15.5]
Age at study visit (years)	15.7 [13.5-17.3]
Disease duration (years)	0.8 [0.2-1.9]
Patient's global assessment (NRS)	6.5 [5.5-7.5]
Headache (NRS)	6.5 [3-8]
Fatigue (NRS)	7.5 [6-9]
Symptom severity upon awakening (NRS)	7.5 [6.5-8]
Musculoskeletal pain (NRS)	7.5 [6-8]
Irritability (NRS)	6.5 [3.5-8.5]
Widespread Pain Index	9 [5-12]
Symptom Severity scale	8 [6-10]
Trigger Points	10 [6-14]
Child's Depression Inventory	17 [11-24]
Multidimensional Anxiety Scale for Children	50 [40-58]
Sleep Condition Indicator	14 [9-17]
Epworth Sleepiness Scale for Children and Adolescents	5 [3-7]

Values are median [1st-3rd q] unless otherwise indicated.
JFS: Juvenile Fibromyalgia Syndrome; q: quartile; NRS: numerical rating scale.

Table II. Results of Sleep Condition Indicator in the 25 JFS patients. Last column represents the percentage of patients whose answers are within the pathological range.

Items	Options	No. (%)	Pathological range No. (%)
1 - How long does it take you to fall asleep?	> 60 minutes	3 (12)	
	46-60 minutes	5 (20)	12 (48)
	31-45 minutes	4 (16)	
	15-30 minutes	6 (24)	
	0-15 minutes	7 (28)	
2 - If you wake up during the night, how long are you awake for in total?	>60 minutes	3 (12)	
	46-60 minutes	3 (12)	10 (40)
	31-45 minutes	4 (16)	
	15-30 minutes	6 (24)	
	0-15 minutes	9 (36)	
3 - How many nights a week do you have problem with sleeping?	5-7 nights	13 (52)	
	4 nights	4 (16)	20 (80)
	3 nights	3 (12)	
	2 nights	1 (4)	
	0-1 nights	4 (16)	
4 - How would you rate your sleep quality?	Very poor	3 (12)	
	Poor	11 (44)	22 (88)
	Average	8 (32)	
	Good	3 (12)	
	Very good	0 (0)	
5 - Thinking about the last month, to what extent has poor sleep affected your mood, energy, and/or relationships?	Very much	2 (8)	
	Much	10 (40)	20 (80)
	Somewhat	8 (32)	
	A little	2 (8)	
	Not at all	3 (12)	
6 - Thinking about the last month, to what extent has poor sleep affected your concentration, productivity	Very much	3 (12)	
	Much	10 (40)	18 (72)
	Somewhat	5 (20)	
	A little	5 (20)	

and/or ability to stay awake?	Not at all	2 (8)	
7 - Thinking about the last month, to what extent has poor sleep troubled you in general?	Very much	2 (8)	
	Much	6 (24)	16 (64)
	Somewhat	8 (32)	
	A little	6 (24)	
	Not at all	3 (12)	
8 - How long have you had a problem with your sleep?	> 1 year	15 (60)	
	7-12 months	3 (12)	21 (84)
	3-6 months	3 (12)	
	1-2 months	2 (8)	
	I don't have a problem / <1 month	2 (8)	

Table III. Results of the full-night polysomnographic recording: ccomparison between JFS patients [N = 25] and controls [N = 27].

	JFS Patients [N= 25]	**Controls [N = 27]**	
	Median (1st-3rd q)	**Median (1st-3rd q)**	**P§**
SPT	526.5 (500.4-567.7)	484 (450-520.5)	0.004
TST	489.5 (440.4-548.5)	462 (427-499.5)	0.12
WASO	26.1 (18.2-44.3)	16.5 (6-30)	0.03
SE	92.5 (85.4-95.3)	91.3 (87.2-93.8)	0.88
SOL	21.5 (10.0-27.9)	10.5 (6.3-21.8)	0.11
N1 sleep min.	24.5 (16-34)	21.5 (17-31)	0.65
N2 sleep min.	244.5 (205-281)	242 (211.5-268)	0.88
N3 sleep min.	127 (98.5-139)	108 (92.5-129.5)	0.11
REM min.	95 (78-109.5)	92.5 (71-106.5)	0.99
N1%TST	4.9 (3.7-7)	5.2 (3.4-7.3)	0.91
N1%SPT	4.5 (3.5-6.8)	5 (3.4-6.8)	0.71
N2%TST	49.7 (45.9-58.2)	51.8 (48.5-56.5)	0.50
N2%SPT	45.8 (42.5-55)	49.6 (44.4-55.3)	0.16
N3%TST	24.9 (22.6-29.2)	23.9 (20.2-26.7)	0.23
N3%SPT	23.5 (19.3-27.3)	22.3 (19.7-24.9)	0.49
REM%TST	19.7 (15.2-22.5)	19.7 (15.4-22.9)	0.63
REM%SPT	18.7 (13.6-20.6)	19.3 (14.4-21.9)	0.42
W%SPT	5.2 (3.4-8.1)	3.4 (1.2-7)	0.08
AWN-h	1.5 (1.1-2.4)	1.2 (0.8-3.9)	0.91
N3 Index	0.5 (0.2-0.6)	0.6 (0.5-0.7)	0.02

P[§]: P value refers to the Mann-Whitney U test. SPT, sleep period time; TST, total sleep time; WASO wake after sleep onset; SE, sleep efficacy efficiency, SOL, sleep onset latency; REM, rapid eye movement; W, wake; AWN-h awakening per hour.

Table IV. Correlations between subjective and objective sleep quality measures and the JFS-related symptoms.

	WPI	SS	CDI	MASC	Patient Global Assessment	Fatigue	Symptoms upon awakening	Irritability
CDI		0.62	-	0.70	0.73	0.41	0.40	0.72
MASC			0.70	-	0.46			0.82
SCI	-0.65	-0.64	-0.58		-0.55	-0.44	-0.65	
ESS	0.50	0.61	0.54	0.46	0.55	0.51	0.49	0.48
N3min		-0.41	-0.40					
N3-SPT		-0.46						
N3 Index			0.41					0.40

CDI, Child's Depression Inventory; MASC, Multidimensional Anxiety Scale for Children; SCI, Sleep Condition Indicator; ESS, Epworth Sleepiness Scale; N3 min, N3 minutes; N3-SPT, N3 % in sleep period time; WPI, widespread pain index; SS, symptom severity scale.

Table V. Multiple regression analyses

Independent variables	Beta	SE of Beta	P	R^2
Outcome: WPI				0.44
CDI	0.003	0.16	0.98	
MASC	-0.04	0.09	0.65	
SCI	-0.32	0.14	0.04	
ESS	0.33	0.27	0.24	
Outcome: SS				0.67
CDI	0.09	0.07	0.25	
MASC	-0.03	0.04	0.51	
SCI	-0.11	0.07	0.01	
ESS	0.22	0.13	0.10	
N3-SPT	-0.15	0.07	0.045	
Outcome: CDI				0.80
MASC	0.31	0.08	< 0.001	
SCI	-0.32	0.14	0.04	
ESS	0.21	0.30	0.51	
N3 Sleep min	-0.07	0.03	0.03	
N3 Distribution Index	11.54	3.28	0.002	
Outcome: MASC				0.52
CDI	0.96	0.29	0.003	
ESS	0.60	0.61	0.34	
Outcome: Fatigue				0.30
CDI	0.03	0.06	0.65	
SCI	-0.06	0.07	0.39	
ESS	0.18	0.13	0.19	
Outcome: Musculoskeletal Pain Intensity				0.18
ESS	0.16	0.09	0.07	
N3-Index	0.92	1.24	0.47	

CDI, Child's Depression Inventory; MASC, Multidimensional Anxiety Scale for Children; SCI, Sleep Condition Indicator; ESS, Epworth Sleepiness Scale; N3-SPT, N3 % in sleep period time; N3 Sleep min, N3 sleep minutes; WPI, widespread pain index; SS, symptom severity scale .