Pain and the Alpha-Sleep Anomaly: A Mechanism of Sleep Disruption in Facioscapulohumeral Muscular Dystrophy

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Abstract

Objective. To measure the presence of the alpha-sleep anomaly in facioscapulohumeral muscular dystrophy (FSHD) and to evaluate the association between the sleep electroencephalogram (EEG) pattern and the presence of musculoskeletal pain.

Setting. Sleep laboratory.

Subjects. Fifty-five consecutive adult FSHD patients, 26 women and 29 men, age 49.6 ± 15.1 years (range 18–76).

Interventions. Questionnaires and polysomnography.

Outcome Measures. Patients were asked to indicate if in the 3 months before the sleep study they presented persisting or recurring musculoskeletal pain. Patients who reported pain were asked to fill in the Italian version of the Brief Pain Inventory and the McGill Pain questionnaire, and a 101-point visual analog scale (VAS) for pain intensity. Polysomnographic recordings were performed. EEG was analyzed by means of Fast Fourier Transform. Four power spectra bands (δ 0–4 Hz, θ 4–8 Hz, α 8–14 Hz, β 14–32 Hz) were computed. Sleep macrostructure parameters and alpha/delta EEG power ratio during non rapid eye movement (NREM) sleep were compared between patients with and without pain.

Results. Forty-two patients in our sample reported chronic pain. VAS mean score was 55.2 ± 23.8 (range 10–100), pain rating index score was 13.8 ± 10.2, and present pain intensity was 2.5 ± 0.8. The statistical analysis documented an increased occurrence of the alpha and beta rhythms during NREM sleep in FSHD patients with pain. Significant correlations were observed between the alpha/delta power ratio during NREM sleep and pain measures.

Conclusions. Chronic musculoskeletal pain is frequent in FSHD patients, and it represents a major mechanism of sleep disruption.

Key Words. Alpha-Sleep Anomaly; Facioscapulohumeral Muscular Dystrophy; Sleep; Pain; Polysomnography
Introduction

Facioscapulohumeral muscular dystrophy (FSHD) is a slowly progressive dystrophic myopathy with predominant involvement of facial and shoulder girdle musculature. FSHD is the second most frequent form of muscular dystrophy in adults, after myotonic dystrophy [1]. FSHD is an autosomal dominant muscular dystrophy; the gene for the disease has been mapped to the long arm of chromosome 4 (region 4q35) [2]. In this region, a long stretch of 3.3 kb KpnI repeat units, called D4Z4, has been identified. To present, no transcript derived from this locus has been identified. The clinical features of FSHD develop when the number of the KpnI repeat units in D4Z4 falls below a critical threshold [3]; moreover, the number of KpnI repeats left on the shortened chromosome 4 inversely correlates with the severity of the disease [4,5]. The phenotypic spectrum of FSHD is wide and heterogeneous. The severity of muscular impairment ranges from mild forms in which the patient can be unaware of the disease to severe muscular impairment in wheelchair-bound patients. For a detailed review of the clinical features of FSHD, see Tawil and Van Der Maarel [6].

Sleep disorders have a high prevalence in patients with neuromuscular diseases [7]. Several factors may explain sleep disruption in neuromuscular diseases; in particular, sleep may be disturbed by apneas (either central or obstructive), hypoventilation, reduced motility in bed, and chronic pain [7–9]. In a previous report, we have observed poor sleep quality in a large sample of FSHD patients, in whom perceived sleep quality was inversely related to the severity of the muscular impairment [10]. Moreover, our polysomnographic (PSG) study in FSHD patients documented a high prevalence of sleep-disordered breathing (SDB) [11] and a marked reduction of spontaneous nocturnal body movements [9].

It can be hypothesized that a further possible mechanism of sleep disruption in FSHD might be musculoskeletal pain. Pain is frequent in neuromuscular diseases, and it represents a well-known cause of sleep disruption [12]. Pain is frequent also in FSHD; it may be present in a vast majority of the patients (up to 89%) [13], it may be disabling, and it may interfere with a number of activities of daily living [12–15]. Electroencephalogram (EEG) recordings may be a useful tool to investigate the effects of pain on sleep. Pain may interfere with the process of cortical synchronization, and the hallmark of this interference is the increase of fast-frequency rhythms (namely, cortical synchronization, and the hallmark of this interference is the increase of fast-frequency rhythms (namely, 14–32 Hz) during non rapid eye movement (NREM) sleep [16]. The increased amount of alpha activity in the EEG during NREM sleep, in particular during deep slow-wave sleep (SWS, sleep stage N3) is defined “alpha-sleep anomaly,” previously known as “alpha-delta sleep” [17,18]. PSG recordings have demonstrated that the alpha-sleep anomaly, although not specific [19], may reflect the impact of a variety of painful conditions on sleep [16,20–22].

The aim of the present study was to measure the presence of the alpha-sleep anomaly in FSHD and to evaluate the association between this sleep EEG pattern and the presence of musculoskeletal pain.

Methods

Patients

The present observation concerns 55 consecutive adult patients affected by FSHD, 26 women and 29 men, mean age 49.6 ± 15.1 years, range 18–76. Patients were recruited consecutively from the Centre for Neuromuscular Disorders of the Catholic University, Rome, Italy. Inclusion criteria were: adult age (>18 years), genetically confirmed diagnosis of FSHD, and consent to participate in the study. Exclusion criteria were: other concomitant medical, neurological or psychiatric diseases, assumption of central nervous system active drugs in the month prior to the study, PSG evidence of SDB, defined as apnea-hypopnea index >10 events/hour and/or oxygen desaturation index >15 events/hour.

The diagnosis of FSHD was made on clinical basis and confirmed by genetic tests, described elsewhere [23,24]. All patients underwent a full medical and neurological evaluation. Muscle strength was evaluated by using the manual muscle testing (MMT), and a score was assigned according to the Medical Research Council Scale [25]. MMT score ranges from 0 = “no movement, no visible or palpable contraction” to 5 = “segment movement through full range of motion against gravity and ability to hold against resistance.” In order to measure the clinical severity of the muscular impairment, a 10-grade clinical severity scale (CSS) [5] was adopted. The CSS score ranges from 0.5 = “facial weakness,” to 5 = “wheelchair bound.” According to this scale, CSS score ≤2 was assigned to patients with facial and shoulder muscles weakness, whereas higher scores (>2) were assigned to patients showing also pelvic and lower limb muscles weakness.

Subjective evaluation of sleep quality was performed by the Pittsburgh Sleep Quality Index (PSQI) [26]. PSQI is a self-rated questionnaire that assesses sleep quality and disturbances. The questionnaire consists 19 items divided into seven components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. A global PSQI score greater than 5 yielded a diagnostic sensitivity of 89.6% and specificity of 86.5% (kappa = 0.75, P < 0.001) in distinguishing good and poor sleepers [26].

For the evaluation of daytime sleepiness, the validated Italian version of the Epworth Sleepiness Scale (ESS) was applied [27]. The ESS is a self-administered eight-item questionnaire that has been proposed as a simple method for measuring daytime sleepiness in adults. Higher scores indicate increased propensity to sleep. The cut-off value for excessive daytime sleepiness is
Pain in FSHD

9 points. The questionnaire had a high level of internal consistency as measured by Cronbach’s alpha (0.88) [28]. PSQI and ESS were administered in the sleep lab, just before the PSG recording. All patients enrolled in the present study underwent a full-night, laboratory-based attended PSG with recording of respiratory parameters. Because the presence of SDB can increase the amount of fast-frequency EEG activity during sleep [29], only FSHD patients without PSG evidence of SDB were enrolled in the present study. The study was approved by the local Ethical committee, and all patients gave their written consent to participate.

Evaluation of Pain

Patients were asked to indicate if they presented intermittent or continuous musculoskeletal pain in the previous 3 months, with a frequency of at least once per week [30]. If they answered “yes,” they were asked to indicate the localizations of the pain by drawing in a schematic representation of their body (Figure 1), and then, they were invited to fill in a 101-point (0 = no pain, 100 = worst pain imaginable) visual analog scale (VAS) and the Italian version of the McGill Pain questionnaire [31–33]. The McGill questionnaire includes the choice of adjectives for the pain in the following modalities: sensory, affective, evaluative, and miscellaneous, which allow to calculate a pain rating index (PRI). Moreover, the questionnaire requires to evaluate the present pain intensity (PPI) with a score ranging from 0 to 5. The higher the pain score, the greater the pain. Values for test–retest reliability in patients with musculoskeletal pain for total, sensory, and affective scores are, respectively, 0.75, 0.76, and 0.62 [34]. Pain questionnaire have been administered in the sleep lab, in the evening, before starting the PSG montage. The patients in the nonpain group did not complete the pain questionnaire.

PSG

Full-night, laboratory-based PSGs were recorded in acclimatized, sound-proof rooms, following adaptation. Recording montage included: EEG leads filled with electrolyte applied to following locations: F3, F4, C3, C4, O1, and O2; reference electrodes placed on the left (A1) and right (A2) mastoids (the reference used for spectral analysis was A1 + A2); two electro-oculographic (EOG) electrodes applied to the outer ocular canthus and referred to the contralateral mastoid; surface electromyography (EMG) of submental and intercostal muscles; airflow measured by nasal-cannula pressure transducers; thoracic and abdominal effort; electrocardiogram; and peripheral hemoglobin saturation measured by a clip sensor placed on a finger or on the earlobe. Continuous audio and video recording was performed by means of infrared cameras. For the EEG recording, impedances were kept below 5 KΩ before starting the recording and checked again at the end of the recording. Sampling frequency was 256 Hz, analog-to-digital conversion was made at 16 bit, preamplifier amplitude range was ±3,200 μV, and prefilters were set at 0.15 Hz. Sleep recordings were analyzed on computer monitor, and sleep stages were visually classified according to the criteria of the American Academy of Sleep Medicine (AASM) [35].

Power Spectral Analysis

EEG frequency analysis was performed during quiet wake prior to sleep and in all NREM and rapid eye movement (REM) sleep stages. Spectral analysis was performed on 2-second windows, with a frequency resolution of 1 Hz, using a discrete Fast Fourier Transform algorithm. Four power spectra bands (δ 0.5–4 Hz, θ 4–8 Hz, α 8–14 Hz, β 14–32 Hz; total power: 0–32 Hz) were computed for each EEG electrode for the entire recording period. Moreover, the ratio of the spectral power of the alpha and delta bands—ω/δ ratio—was calculated. In order to compensate for variability among subjects and across the night in EEG power, the spectra were normalized: value in each frequency bin was divided by the total power, and therefore, the relative power spectrum was calculated. The same software (low-resolution electromagnetic tomography, LORETA) [36] was used for power spectral analysis and for the statistical comparison between groups. Spectral analysis was performed after the traditional, visual sleep scoring, by means of a dedicated software (Rembrandt SleepView, Medcare® Systems, Inc, Buffalo, NY, USA). Each 30-second epoch was visually scored according to the established criteria [35] screened for artifacts (EOG, EMG, temporary disconnect spikes, sweating, body movements), and all epochs containing whatever artifact were removed from the analysis. Also, epochs in which a respiratory event occurred (apneas or hypopneas, either central or mixed or obstructive,
hemoglobin desaturations, respiratory event-related arousals) were excluded from the analysis. The remaining data were extracted from the scored sleep data file, and EEG data were converted and stored in separate American Standard Code for Information Interchange data file suitable for the analysis by means of the LORETA software [36].

A major end point of this study was to detect and quantify the "alpha-sleep anomaly." As specified, this consists of an abnormal sleep EEG pattern characterized by the persistence of alpha activity (8–13 Hz) during NREM sleep [37]. In wake EEG, the alpha band is topographically prevalent on the parietal and occipital leads; nevertheless, during drowsiness and light sleep, and, in particular, during arousals, alpha rhythm can spread on the anterior regions. Moreover, most of the EEG patterns that allow the recognition and scoring of sleep stages (v-waves, spindles, k-complexes, saw-tooth waves) are mostly represented on the central derivations [38]. For this reason, EEG frequency analysis was performed using the following monopolar scalp derivations: F4, C4, and O2 referred to the contralateral mastoid A1 or F3, C3, O1 referred to A2. This choice is in accordance with the recommendation of the AASM [35].

Statistical Analysis

On the basis of the response to the pain question, the study population was split in two groups: with pain (Pain, N = 42) and without pain (No Pain, N = 13). Further data analysis was performed in three successive steps. In the first step, clinical and PSG data (including muscular evaluation, subjective sleep measures, and PSG scores) in the two groups were compared by means of the Mann–Whitney U-test. This nonparametric test was used because its interpretation does not depend on the population fitting any parameterized distribution. In case of multiple comparison in order to avoid family-wise type-I errors, a formal Bonferroni correction was applied to each family of comparisons by dividing the limit of significance by the number of comparisons represented in Figure 1. The most common localization was the low back (47%), followed by the limbs (40%) and the cervical spine (18%). The Pain and No Pain did not show significant differences concerning age, sex, and length of the deleted fragment. The Pain group was characterized by a more severe muscular impairment as expressed by the CSS score (Pain 3.3 ± 1.0; No Pain 2.5 ± 1.4; Mann–Whitney U-test P = 0.029). Clinical and demographic details and results of the statistical comparison between the Pain and No Pain groups are reported in Table 1. The results of the pain measures (mean ± SD) are reported in Table 2.

Pain Measures

Forty-two patients reported persistent musculoskeletal pain in the 3 months before the sleep study (Pain group); 13 were pain free (No Pain group). The localizations of pain reported by all patients in the study are schematically represented in Figure 1. The most common localization was the low back (47%), followed by the limbs (40%) and the cervical spine (18%). The Pain and No Pain did not show significant differences concerning age, sex, and length of the deleted fragment. The Pain group was characterized by a more severe muscular impairment as expressed by the CSS score (Pain 3.3 ± 1.0; No Pain 2.5 ± 1.4; Mann–Whitney U-test P = 0.029). Clinical and demographic details and results of the statistical comparison between the Pain and No Pain groups are reported in Table 1. The results of the pain measures (mean ± SD) are reported in Table 2.

Subjective Sleep Measures

As concerns the subjective sleep evaluation, 26 patients presented PSQI scores equal or above the cut-off value (five points), indicating poor sleep quality. PSQI scores were higher in the Pain group, although the difference was
not statistically significant (Pain 6.3 ± 3.3; No Pain 5.4 ± 2.7; Mann–Whitney U-test \( P = 0.099 \)). The mean ESS score did not differ in the two groups. Only one patient (in the No Pain) had an ESS score above the cut-off value (ESS score = 13). The results of statistical comparison of subjective sleep measures in the Pain and No Pain groups are reported in Table 1.

**PSG**

Useful PSG recordings were obtained in all patients. Results of the PSG study and comparison between the Pain and No Pain groups are reported in Table 3. No significant differences were found in sleep latency, sleep duration, sleep efficiency, and amount of wake after sleep onset. As concerns sleep stages composition, patients in the Pain group showed reduced deep SWS (N3: Pain 15.6 ± 10.5%; No Pain 22.5 ± 9.1%; Mann–Whitney U-test \( P = 0.026 \)) and increased index of arousals in REM (Pain 7.0 ± 6.6%; No Pain 3.2 ± 2.7%; Mann–Whitney U-test \( P = 0.025 \)). Detailed data concerning sleep macrostructural parameters in the two groups are displayed in Table 3.

The alpha-sleep anomaly defined according to established criteria [38] was measured by means of EEG spectral analysis (Figures 2, 3) and was expressed as the ratio of the relative (or absolute) powers of the alpha and delta bands (\( \alpha/\delta \) ratio). The LORETA analysis documented that the Pain and No Pain groups showed similar spectral power in the delta and theta bands. A mild, not significant, trend toward the reduction of the delta power band could be detected in the Pain group (\( t = 0.139; P > 0.05 \)). As concerns the fast-frequency spectral components, the LORETA analysis showed a significant increase of the power of the alpha band (8–13 Hz; \( t = 1.780; P < 0.001 \)) as well as of the beta band (13.5–32 Hz; \( t = 2.010; P < 0.001 \)) in the Pain patients (Figure 3). Finally, in the Pain group, the correlation analysis did not reveal significant relationships between sleep macrostructure and pain measures but allowed to confirm that the alpha-sleep anomaly showed a positive linear correlation with pain indexes. In fact, the ratio of alpha/delta power during SWS was directly related with the all pain indexes: the VAS score \( (r(40) = 0.528; P < 0.001) \), the PRI \( (r(40) = 0.505; P < 0.001) \), and the PPI \( (r(40) = 0.972; P < 0.001) \). In the Pain group, the correlation analysis showed no significant

### Table 1

Demographic and clinical variables in facioscapulohumeral muscular dystrophy patients and comparison between Pain and No Pain

<table>
<thead>
<tr>
<th>Clinical and Demographic Data</th>
<th>Anchor Values</th>
<th>Pain (N = 42)</th>
<th>No Pain (N = 13)</th>
<th>Mann–Whitney U-Test (( P ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.3 ± 15.2</td>
<td>47.4 ± 14.9</td>
<td>0.548</td>
<td></td>
</tr>
<tr>
<td>CSS score</td>
<td>0–5</td>
<td>3.3 ± 1.0</td>
<td>2.5 ± 1.4</td>
<td>0.029</td>
</tr>
<tr>
<td>KpnI (Kb)</td>
<td>&lt;40</td>
<td>23.3 ± 6.2</td>
<td>24.8 ± 5.3</td>
<td>0.578</td>
</tr>
<tr>
<td>PSQI</td>
<td>0–21</td>
<td>6.3 ± 3.3</td>
<td>5.4 ± 2.7</td>
<td>0.099</td>
</tr>
<tr>
<td>ESS score</td>
<td>0–24</td>
<td>4.2 ± 2.8</td>
<td>3.6 ± 4.8</td>
<td>0.619</td>
</tr>
<tr>
<td>Sex</td>
<td>24 M—18 F</td>
<td>5 M—8 F</td>
<td>0.389</td>
<td></td>
</tr>
</tbody>
</table>

**CSS** = clinical severity scale; **ESS** = Epworth Sleepiness Scale; **KpnI** = size of the deleted fragment; **PSQI** = Pittsburgh Sleep Quality Index.

Data are expressed as mean ± standard deviation.

### Table 2

Results of the pain measures in the Pain group (N = 42 subjects)

<table>
<thead>
<tr>
<th>Anchor Values</th>
<th>Musculoskeletal Pain [32]</th>
<th>FSHD Mean</th>
<th>FSHD SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual analog scale</td>
<td>0–100</td>
<td>41 ± 16</td>
<td>50.93</td>
</tr>
<tr>
<td>Pain rating index</td>
<td>Sensory</td>
<td>0–19</td>
<td>5.36</td>
</tr>
<tr>
<td></td>
<td>Affective</td>
<td>0–9</td>
<td>2.67</td>
</tr>
<tr>
<td></td>
<td>Evaluative</td>
<td>0–8</td>
<td>3.28</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous</td>
<td>0–6</td>
<td>1.71</td>
</tr>
<tr>
<td></td>
<td>Total pain rating index</td>
<td>0–42</td>
<td>15.7 ± 11.9</td>
</tr>
<tr>
<td></td>
<td>Present pain intensity</td>
<td>0–5</td>
<td>2.3 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>Alpha/delta power ratio</td>
<td>0–1</td>
<td>0.07</td>
</tr>
</tbody>
</table>

**FSHD** = facioscapulohumeral muscular dystrophy; **SD** = standard deviation.

In the "Musculoskeletal Pain" column, we report data measured in a population of patients with musculoskeletal pain [32].
correlations between the \( \alpha/\delta \) ratio and the PSQI \( r(40) = 0.034 \), \( \alpha/\delta \) ratio and CSS \( r(40) = -0.156 \), between \( \alpha/\delta \) ratio and ESS \( r(40) = 0.122 \). The correlation between \( \alpha/\delta \) ratio and length of the deletion showed a trend toward a positive relation \( r(40) = 0.247 \), which however did not reach statistical significance. Due to the low number of patients, no correlations were measured in the No Pain group. Graphic representations of the correlations between the alpha-delta ratio and pain measures are reported in Figure 4. In the pain group, the median value of the relative \( \alpha/\delta \) was 0.58. This value allowed to split the Pain group into two subgroups: high \( \alpha/\delta \) and low \( \alpha/\delta \). The high \( \alpha/\delta \), compared with the low \( \alpha/\delta \) group, showed higher VAS (U-test 322.5, \( P = 0.010 \)), higher PPI (U-test 307.5, \( P = 0.022 \)), and higher PRI (U-test 420.5, \( P < 0.001 \)).

### Discussion

The results of the study suggest that chronic musculoskeletal pain was present in a majority of our FSHD patients; moreover, the increased amount of alpha EEG activity during SWS in the group of patients with pain, as compared with patients without pain, suggests that pain might interfere with the process of cortical synchronization during sleep.

It is known that chronic pain may be a significant problem in many persons with neuromuscular diseases, in particular in all forms of muscular dystrophy [8,40,41]. Chronic musculoskeletal pain has been previously observed in FSHD patients [12,15]. In accordance with these previous studies [12], pain was highly prevalent in our patients with

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**Table 3** Results of PSG recordings and comparison between Pain and No Pain

<table>
<thead>
<tr>
<th>Sleep PSG Parameters</th>
<th>Pain (N = 42)</th>
<th>No Pain (N = 13)</th>
<th>Mann–Whitney U-Test (( P ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIB (minute)</td>
<td>485.9 ± 64.4</td>
<td>468.2 ± 67.6</td>
<td>0.627</td>
</tr>
<tr>
<td>SEI (%)</td>
<td>84.3 ± 11.6</td>
<td>84.0 ± 9.5</td>
<td>0.656</td>
</tr>
<tr>
<td>Awakenings &gt;1 minute</td>
<td>9.1 ± 5.6</td>
<td>10.0 ± 5.3</td>
<td>0.487</td>
</tr>
<tr>
<td>WASO (minute)</td>
<td>85.8 ± 67.6</td>
<td>72.8 ± 44.7</td>
<td>0.634</td>
</tr>
<tr>
<td>Sleep latency (minute)</td>
<td>40.4 ± 40.2</td>
<td>30.9 ± 17.9</td>
<td>0.976</td>
</tr>
<tr>
<td>REM (%)</td>
<td>15.1 ± 4.7</td>
<td>12.5 ± 4.9</td>
<td>0.071</td>
</tr>
<tr>
<td>N1 (%)</td>
<td>12.0 ± 10.0</td>
<td>9.8 ± 3.3</td>
<td>0.843</td>
</tr>
<tr>
<td>N2 (%)</td>
<td>40.5 ± 13.4</td>
<td>38.4 ± 10.2</td>
<td>0.613</td>
</tr>
<tr>
<td>N3 (%)</td>
<td>15.6 ± 10.5</td>
<td>22.5 ± 9.1</td>
<td>0.026</td>
</tr>
<tr>
<td>Arousal index</td>
<td>8.6 ± 5.6</td>
<td>5.8 ± 3.2</td>
<td>0.071</td>
</tr>
<tr>
<td>Arousal NREM</td>
<td>8.9 ± 5.5</td>
<td>6.3 ± 3.3</td>
<td>0.125</td>
</tr>
<tr>
<td>Arousal REM</td>
<td>7.0 ± 6.6</td>
<td>3.2 ± 2.7</td>
<td>0.025</td>
</tr>
</tbody>
</table>

SEI = sleep efficiency index; TIB = time in bed; WASO = wake after sleep onset; PSG = polysomnographic; REM = rapid eye movement; NREM = non-REM.

Data are expressed as mean ± standard deviation.

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**Figure 2** Results of polysomnographic recording in a patient. Upper plot: sleep hypnogram; middle plot: frequency spectrum; lower plot: time course of the alpha power during sleep. One sleep cycle is showed. Intrusion of alpha frequency within slow-wave sleep is visible in the color frequency plot (arrows). Signals labels are on the left.
Pain in FSHD

FSHD; it occurred in 42 out of 55 patients in the sample (76%). Pain could involve all body segments, often with multiple localization. The most common localization was the low back (47%), followed by the limbs (40%) and by the cervical spine (18%) (Figure 1). These localizations are consistent with the findings of previous studies [41]. Pain in neuromuscular diseases can interfere with a number of activities of daily living. It has been demonstrated that chronic pain may have a severe impact on the quality of life in general [42] and in particular on the perceived quality of sleep [12]. In the study by Jensen et al. [12], pain needed specific drug treatment in more than 50% of the patients. Treatments consisted in most cases in nonsteroidal anti-inflammatory drugs, opioids, gabapentin, and muscle relaxants. A possible pathogenic mechanism for pain in FSHD could be inflammation. Although FSHD is an inherited disease, a contribution of inflammation to its pathogenesis, has been hypothesized. Recently, it has been observed that turbo inversion recovery recovery magnitude imaging indicated an inflammatory component of the disease [43]. Also, T2-short tau inversion recovery (STIR) hyperintense FSHD muscles are more similar to inflammatory myopathies than to T2-STIR normal FSHD muscles or other muscular dystrophies [44]. Moreover, Frisullo et al. [45] found by immunohistochemistry inflammatory infiltrates mainly composed by CD8(+) T cells in muscles showing hyperintensity features on T2-STIR magnetic resonance imaging sequences.

In previous studies, we have observed that FSHD patients have poor sleep quality due to a variety of mechanisms [9–11]. The present study suggests that in FSHD patients, the presence of pain is associated with substantial modification of sleep, involving both the macrostructure (reduced duration of stage N3) and, particularly, the EEG frequencies. Notably, we did not observe any significant correlation between subjective sleep measures and pain measures, and no differences in sleep quality and sleepiness scores in the groups Pain and No Pain. Because pain and sleep disturbances are highly prevalent in FSHD patients and they can have various pathogenesis, it seems likely that subjective scores may fail to reveal this association.

In sleep studies, an attempt has been made to measure the effect of chronic pain on sleep by means of EEG frequency analysis. Sleep is initiated and maintained by complex interactions between subcortical and cortical neuronal networks, which promote progressive cortical synchronization, resulting in a progressive increase of amplitude and reduction of frequency of scalp EEG. During sleep, the generators of cortical electrical shift from the production of low-amplitude high-frequency EEG activity, typical expression of the activation of cortical cells, to the production of high-amplitude low-frequency EEG activity, indicating a widespread synchronization of the cortical neurons [46]. Several studies suggest that chronic pain is associated with an increased amount of alpha activity during NREM sleep [16,22,47–49]. The alpha EEG patterns include phasic and tonic alpha EEG sleep as well as periodic K-alpha complexes [16]. This abnormal intrusion of alpha during NREM, previously defined “alpha-delta sleep” [17], was initially considered as a sleep marker of chronic rheumatologic diseases [22], in particular Fibromyalgia syndrome [50,51]. At present, the alpha-sleep anomaly is considered as a rather nonspecific sleep pattern [19,52], as it can be observed in a wide variety of medical and psychiatric conditions [53–57]. Although nonspecific, the alpha-sleep anomaly is highly prevalent in patients with chronic pain, and it is associated with poor sleep quality and poorly refreshing and restoring sleep [58]. In the present study, we found an increase of fast-frequency rhythms during sleep in subjects with chronic pain, and a close relation between EEG alpha band relative power and the scores of intensity of chronic pain. Moreover, patients with high α/β relative power showed higher pain indexes than those with low α/β power. The presence of fast-frequency rhythms indicates increased level of arousal and suggests that pain might act as a tonic arousing stimulus during sleep.

Study Limitations

We believe that the main methodological limitation of the present study is the relatively small number of patients included in the No Pain group. This was due to the high prevalence of pain in FSHD. As a consequence, some statistical measures and, in particular, the correlations within the No Pain group could not be computed. Another limitation is the use of self-report data for pain, which could suffer from a recall bias. Sleep measures (subjective and objective) were compared with subjective pain measures. It is known that subjective evaluation of sleep duration and quality may be biased by sleep misperception [59], and on the other hand, no instrumental evaluation of pain (i.e., laser evoked potentials) was obtained. Finally, the treatment of pain and the successive amelioration of sleep should be the ultimate confirmation of the role of pain in sleep disturbances in FSHD.
Conclusions

Taken together, and within the earlier mentioned limitations, these findings suggest that chronic musculoskeletal pain is frequent in FSHD patients, and it may act as a mechanism of sleep disruption. In this regard, our results confirm observations reported in previous literature [8,10,12,15,42]. In addition, the correlation between alpha spectral power and pain suggests that measuring the alpha intrusion into NREM sleep may provide a tool to quantify the impact of pain on sleep.

Figure 4 Graphics of the correlations between the alpha/delta ratio in non-rapid eye movement sleep and the pain indexes: visual analog scale, pain rating index, and present pain intensity.
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