Sleep Medicine 12 (2011) 179–185

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Gender specificity of the slow wave sleep lost in chronic widespread musculoskeletal pain

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ARTICLE INFO

Article history:
Received 8 April 2010
Received in revised form 20 July 2010
Accepted 27 July 2010
Available online 21 January 2011

Keywords:
Chronic widespread pain
Sleep and pain
Napping
Slow wave activity
Sleep intensity
Delta activity
Electroencephalography
Heart rate variability

ABSTRACT

Objectives: The majority of patients suffering from musculoskeletal chronic widespread pain (CWP) are females, and they tend to report poor sleep. We tested the hypothesis that the poor sleep of female patients reporting CWP is gender specific for changes in (1) electroencephalograph (EEG) features and (2) heart rate variability (HRV).

Methods: Twenty-four normal sleepers were compared to 24 patients with CWP who complained of poor sleep. Patients were referred from general practice and were matched for age (41–47 years) and gender (25 W, 23 M). Sleep variables and spectral EEG activity analyses were performed during 1 night of sleep recording. Time-domain cardiac RR interval and spectral autoregressive analyses were also performed from the same data set.

Results: Compared to normal females, female patients with CWP had significantly shorter sleep duration (−68 min), lower sleep efficiency (−9.9%), twice the awakenings and a trend for more periodic limb movements per hour of sleep. Daytime napping was reported by 78% of CWPs. Compared to all controls, females with CWP had significantly less power in the EEG delta band in the first and second non-REM sleep cycle. Although RR interval analysis revealed that CWP patients had a faster heart rate, neither the sympathetic nor sympathovagal analysis reached statistical significance for gender or pain status comparisons.

Conclusions: Female CWP patients have shorter sleep duration with many awakenings and lower sleep EEG delta activity without gender difference in HRV.

1. Introduction

About 1 in 4 adults in the general population report chronic pain lasting for at least 3 months [1–6]. Poor sleep and pain interaction can be bidirectional or circular in chronic pain patients. Moreover, a poor night of sleep can be followed by more pain the next day, and a day with more pain can be followed by a night of poor sleep [7].

Chronic widespread musculoskeletal pain, a sensory condition afflicting several body sites, is experienced by about 8–12% of the population, with females accounting for as much as 80% of this group [8,9]. In general medical practice, the risk (odds ratio) that a chronic widespread musculoskeletal pain (CWP) patient will report poor sleep quality and fatigue is 3.1 and 3.5 times higher than in control subjects, respectively [10]. Patients with CWP, i.e., clinically diagnosed with fibromyalgia, report poor quality sleep, which may be due to increased awakenings, transient sleep arousals, and disrupted delta sleep or sleep stage N3 [11–14]. A recent comparative study on the sleep macrostructure revealed that female patients with fibromyalgia had more sleep stage shifts and longer stage N2 sleep duration, possibly due to more rapid transition toward sleep stage N3, a variable that also contributed to explain higher pain reports the next day [15].

The power of SWA over consecutive non-REM to REM sleep cycles is used to estimate sleep homeostasis and regulation by means of

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doi:10.1016/j.sleep.2010.07.015

electroencephalography (EEG) delta band frequency spectral analysis [16–19]. In a comparative ambulatory home recording study done in female patients only, spectral autoregressive EEG analysis revealed that patients with fibromyalgia presented lower intensity in the delta and theta sleep frequencies with higher dominance of the faster ranges, i.e., alpha and sigma [18,19]. The lower powers of delta and theta EEG frequencies differed significantly from controls across the first three consecutive non-REM to REM cycles.

Heart rate variability (HRV) analysis of the RR signal is another indirect method to assess autonomic cardiac activity during wake and sleep [20]. HRV-related changes in sympathovagal balance were estimated in the sleep of patients with fibromyalgia, revealing an overnight dominant sympathetic activity when compared to controls [21,22].

The aim of this retrospective sleep laboratory analysis was to assess gender differences in the dynamics of EEG and HRV activity between normal subjects and clinical patients (i.e., no medication washout) reporting musculoskeletal chronic widespread pain (CWP). We tested the hypothesis that differences previously observed in the sleep of patients reporting CWP are gender specific for changes in (1) EEG features and (2) HRV across consecutive non-REM to REM sleep cycles.

2. Methods

2.1. Sampling method

In this retrospective clinical study, the data of 24 normal subjects and 24 CWP patients were retrieved from our sleep laboratory data bank. Subjects in the two groups were matched for age (±5 years) [10] and had a similar proportion in genders (controls: 12 females, 12 males; CWP: 13 females, 11 males). The study was conducted in compliance with the institution's ethical guidelines.

All normal subjects, used as controls for the analysis, were free of any medical condition, chronic pain and sleep complaints. Data from control subjects are derived from our data bank since they all participated in ongoing studies in the sleep laboratory. A one-night sleep laboratory recording excluded normal subjects with sleep apnea–hypopnea, insomnia, periodic limb movement, bruxism, etc. Presence of CWP was confirmed during the sleep laboratory interview and examination. The patient reported complaint and presence of several tender points related to widespread musculoskeletal pain in the shoulder, lower back, neck, or leg (for 3 months or more) of at least moderate intensity present in the last month with concomitant complaint of unrefreshing sleep [9,10,23–26]. Such criteria are strong predictors of widespread pain in relation to poor sleep [14,27]. Note that all CWP subjects were referred to our university based sleep clinic by their family physician or rheumatologist to further investigate complaints of poor sleep in a one-night polygraphic sleep recording.

Because our goal was to compare a population of CWP as seen in regular medical practice, no CWP subjects were excluded if they had a history of restless legs syndrome (RLS) or periodic limb movements (PLM) during sleep. No medication washout was requested, similar to a previous study in consecutive physician-referred individuals [28]. Subjects who regularly used opioids were excluded.

At the time of sleep recording, 5 of the 13 female patients with CWP were taking non-steroidal anti-inflammatory pain medications, 7/13 antidepressant or anxiolytic or hypnotic, 4/13 antihypertensive or cardiac-related medications, and 3/13 hormones or thyroid medications (3/13). Of the 11 males with CWP, 4 were taking non-steroidal analgesics, 8/11 antidepressants, anxiolytic, or hypnotics, and 2/11 antihypertensives or cardiac-related medication. None of the normal subjects were taking analgesics on the night of sleep laboratory recording, but 1 female was under an anxiolytic/hypnotic; 1 female and 1 male were under an antihypertensive or a cardiac-related medication, and 1 female was under hormonal therapy for menopausal symptoms.

2.2. Polysomnographic recordings

Polysomnographic recordings included surface EEG (C3–A2 and O2–A1), electrocardiogram (ECG), electrooculogram (EOG), and electromyogram (EMG) of leg and chin muscles. To detect respiratory disorders, a chest belt, an oxymetry, and nasal airflow monitors were used. Audio and video recordings helped exclude subjects with movement disorders such as snoring and tooth grinding. All signals were processed at 128 Hz for offline analysis using Harmonie software (Stellate corp, Montreal) with a 16-bit resolution (National Instruments, PCI-6033E, USA).

2.3. Sleep and heart rate variables

Visual and semi-quantitative data scoring from a computer screen provided estimates for three types of sleep variables: (1) sleep duration, sleep efficiency, sleep latency, and REM latency; (2) number of awakenings/hr, micro-arousals/hr, and sleep stage shifts/hr; (3) percent of sleep stage, periodic limb movements during sleep (PLMS) index, and sleep apnea–hypopnea index (called apnea index). Sleep stages were scored according to the criteria of Rechtschaffen and Kales (since data were collected before 2007) using modified 20-s epochs [29]. PLMS, sleep apnea–hypopneas, and micro-arousals were scored according to standard criteria [30–33].

Analyses were performed blind to subjects status (normal or CWP). During a given sleep stage, we selected sections in which at least 20 s passed without any sign of arousal (increased EEG, HR, or EMG activity of chin or tibialis). EEG data were compared for gender effects and controlled for the influences of napping habit, as reported by subjects at the clinical interview since presence of nap influenced EEG dynamic [17].

2.4. EEG quantification

Data from five subjects were rejected for EEG analysis because the EEG signal was too contaminated by technical artifacts, preventing valid power analysis. Therefore, 22 control subjects (11 female, 11 male) and 21 CWP patients (12 female, 9 male) were included in the analysis. Sections of stable EEG of at least 4 s derived from C3–A2 were selected from non-REM and REM sleep for the compressed band array analysis, according to Achermann's formula [34]. Consecutive series of 4 non-REM sections and 1 REM sleep episode from sleep onset to wake time are presented. Twenty non-REM and 5 REM sections were selected from each non-REM and REM cycle. Because the mean number of ultradian sleep cycles was low for CWP patients (less than 4 cycles in 50% of patients) compared to normal subjects (see Table 1), only the first three consecutive non-REM to REM cycles were analyzed for all subjects. In non-REM sleep, cycles were labeled C1N1 to C3N4, where C1 to C3 denotes sleep sub-cycles and N1 to N4 denotes sequence in non-REM periods (non-REM divided in 4 sections). During REM cycles, sub-cycles were labeled C1R to C3R, where R denotes each REM cycle (only one REM cycle per sleep cycle).

For the EEG power spectral analysis, a cosine window was used to decrease leakage or activity spillover at a given frequency range followed by the use of the Fast Fourier Transform (FFT). EEG signals were quantified to estimate the power value of the following bands: delta (0.50–4.00 Hz; plus low and high sub-analysis divided at 2.00 Hz), theta (4.00–8.00 Hz; plus low and high sub-analysis divided at 6.00 Hz), alpha (8.00–13.00 Hz; plus low and high sub-analysis divided at 10.00 Hz), sigma-spindle activity (12.75–15.00 Hz), low beta (13.00–22.00 Hz), and high beta (22.00–32.00 Hz).