Chronic fatigue, unrefreshing sleep and nocturnal polysomnography

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Abstract

Background and purpose: To investigate the complaint of unrefreshing sleep with study of sleep electroencephalogram (EEG) in patients with chronic fatigue.

Patients and methods: Fourteen successively seen patients (mean age: 41.1 ± 9.8) who complained of chronic fatigue but denied sleepiness and agreed to participate were compared to 14 controls (33.6 ± 10.2 years) who were monitored during sleep recorded in parallel. After performing conventional sleep scoring we applied Fast Fourier Transformation (FFT) for the delta 1, delta 2, theta, alpha, sigma 1, sigma 2, beta EEG frequency bands. The presence of non-rapid eye movement (NREM) sleep instability was studied with calculation of cyclic alternating pattern (CAP) rate. Two-way analysis of variance (ANOVA) was performed to analyze FFT results and Mann–Whitney U-test to compare CAP rate in both groups of subjects.

Results: Slow wave sleep (SWS) percentage and sleep efficiency were lower, but there was a significant increase in delta 1 (slow delta) relative power in the chronic fatigue group when compared to normals (P < 0.01). All the other frequency bands were proportionally and significantly decreased compared to controls. CAP rate was also significantly greater in subjects with chronic fatigue than in normals (P = 0.04). An increase in respiratory effort and nasal flow limitation were noted with chronic fatigue.

Conclusions: The complaints of chronic fatigue and unrefreshing sleep were associated with an abnormal CAP rate, with increase in slow delta power spectrum, affirming the presence of an abnormal sleep progression and NREM sleep instability. These specific patterns were related to subtle, undiagnosed sleep-disordered breathing.

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Keywords: Chronic fatigue; Unrefreshing sleep; Slow wave sleep; Cyclic alternating pattern; Slow delta; Sleep-disordered breathing

1. Introduction

Complaints of chronic fatigue are common in general medical clinics, and relating the complaint to a specific medical entity is often difficult. Effort has been made to define ‘Chronic Fatigue Syndrome (CFS)’ to better investigate these patients. CFS is estimated to affect approximately 0.2–0.7% of the population in Western countries [1] and up to 800,000 Americans [2]. It is a medically unexplained illness and represents a socio-economic burden [2]. In association with the complaint of fatigue, sleep, musculoskeletal and somatic symptoms [3,4] are the most prevalent symptoms in CFS. Despite these clear symptoms, the pathophysiology underlying the complaint of chronic fatigue, or the so-called ‘chronic fatigue syndrome’ is still unclear. Immune system activation [5–8], neurocognitive and mental alterations [4,9,10], evidence of oxidative stress [8,11] and involvement of hypothalamic–pituitary axes (HPA) have also been described [1,5,6,12,13]. However, none of these findings are sufficient to fully explain the symptoms of chronic fatigue. Even the HPA alterations seem to be multifactorial and are not the primary cause of CFS. Rather they appear to be a consequence of the persistence of the symptomatology linked to CFS [12]. A recent study showed that the most prevalent complaint among subjects with idiopathic chronic fatigue is unrefreshing sleep [14]; however, using a Sleep Disorders Questionnaire® (SDQ), the study did not find any increased association between the complaint of chronic fatigue and excessive daytime somnolence or sleep apnea. The reported
prevalence of an association between an undiagnosed primary sleep disorder and the diagnosis of CFS varies between 0 and 50% [14,15]. Fisher [15] and Unger [14] emphasized the importance of excluding a treatable primary sleep disorder when evaluating patients with the complaint of chronic fatigue. Furthermore, clear controversies exist regarding the presence of specific abnormal sleep patterns in patients presenting with unexplained chronic fatigue. Several studies have described a sleep electroencephalogram (EEG) pattern known as ‘alpha–delta’ sleep (better called ‘delta–alpha’ based on successive appearance of the EEG frequencies) in patients suffering from CFS [16,17]. However, many believe that the ‘delta–alpha’ sleep pattern is not a specific marker of CFS [18] but instead is a non-specific pattern [19], and its association with CFS has been questioned [20,21].

Patients seen in a subdivision of rheumatology dealing with the complaint of unexplained chronic fatigue were regularly referred for objective investigation of their sleep once all other possible etiologies for their complaint of chronic fatigue had been ruled out. Clinical sleep evaluation obtained for these patients did not reveal any abnormalities that could explain their subjective complaints. The only consistent finding in the polysomnograph recordings have been a decrease in slow wave sleep (SWS), despite the fact that an increase in stage 4 NREM sleep has been mentioned in at least one report [22], but this finding is non-specific. We have performed several investigations using the cyclic alternating pattern (CAP) scoring system in other patients with abnormal SWS findings. Based on these preliminary clinical findings of the other patients with abnormal slow wave sleep, this study was designed as a prospective investigation of the potential relationship between the complaint of chronic fatigue, unrefreshing sleep and abnormal slow wave sleep (SWS). The study was based on one night of polysomnography and specifically evaluated SWS. Prior to this study we performed several investigations using the CAP scoring system in patients with abnormal SWS findings. The goal of this study was to compare the CAP rate seen in patients with fatigue to matched controls and to explore the relationship between CAP pattern and quantitative EEG measured during the same night as one of the central EEG derivations (C4/A1). This report presents the results of this investigation on subjects referred to the sleep clinic with an unexplained complaint of chronic fatigue and unrefreshing sleep, who agreed to undergo all steps of the investigation. All who enrolled signed informed consent forms for anonymous usage of their data for research.

2. Methods

2.1. Subjects

Fourteen patients (3 men and 11 women), with a mean age of 41.1 ± 9.8, who had been evaluated by the specialized rheumatologic clinic and found to have unexplained chronic fatigue, were referred for sleep investigation. They were compared to 14 controls (3 men and 11 women) aged 33.6 ± 10.2-year-old (P = 0.06) recruited from the community; the controls were professionals and had a socio-economic background that was similar to those presented by the patients. Controls were matched for gender and age as closely as possible. The need to monitor patients and controls nearly simultaneously to avoid effect of seasonal change with variable light intensity, time change, respiratory allergy, school schedule for children, etc. was in part responsible for a small discrepancy in age between groups. Controls were excluded if they had a complaint of chronic fatigue or suffered from a sleep disorder. Additionally, controls had to report that they were in good health and took no medications, and sign the informed consent form.

2.2. Evaluation

Patients and controls underwent the same evaluation. They all filled out standard questionnaires, including the Epworth sleepiness scale (ESS) [23] and the fatigue severity scale (FFS) [23]. The former is a scale with eight questions and four possible responses evaluating degree of sleepiness in specific situations. The latter is a validated fatigue scale designed to assess functional outcomes related to fatigue. It is a 9-item scale scored from 1 to 7, where 1 indicates no impairment and 7 indicates severe impairment. Its clinical utility, reliability and validation criteria have been reported. Higher scores suggest greater fatigue [23]. Fatigue in CFS patients and in disorders of sleep continuity have been associated with increased scores on the FFS [24,25]. Sleep logs indicating bed time, wake time, and sleep interruption were obtained for 15 days prior to the recording and included 2 weekend or days off each week. Patients were given pre-stamped envelopes and were asked to mail their sleep logs every 3 days.

Medical data obtained from evaluation at the chronic fatigue/fibromyalgia clinic in the rheumatology division was reviewed, and blood tests were repeated if they had been obtained more than 2 months prior to the sleep clinic investigation. All patients and controls had normal blood tests, and no evidence of infections or immunologic disorders.

2.3. PSG recording

Every subject went to bed at the usual bedtime and had a minimum of 7 1/2 h of PSG recordings. The following sleep variables were collected and stored using a dedicated computerized 32-channel sleep system with a sampling rate of 256 Hz per channel: a total of 20 EEG leads, two electrooculogram (EOG) channels, two electromyogram (EMG) channels (chin and both legs), and an electrocardiogram (ECG) channel. Respiration was monitored with a nasal cannula-pressure transducer system, mouth thermocouple,
2.4. EEG fast Fourier transformation (FFT) analysis

Once visual scoring had been performed, EEG spectral analysis was applied on the C4-A1 channel, with a sampling rate of 256 Hz per channel. Visual inspection eliminated movement artifacts and awakening segments longer than 10 s. Absolute and relative power was assessed for each classical EEG frequency bands, defined by delta 1 (0.25–2 Hz), delta 2 (2.25–4 Hz), theta (4.25–8 Hz), alpha (8.25–12 Hz), sigma 1 (12.25–14), sigma 2 (14.25–16), and beta (16–20). Results were given in relative power. The FFTs were performed on averaged, non-overlapping, four-second windows, with a Hanning window, free of artifacts and arousals >10 s of EEG segments during the total PSG recording. The window results were averaged to obtain a 60-s value, and analysis covered the total sleep.

2.5. Data analysis

2.5.1. Scoring criteria

All records were to be scored following the international sleep scoring criteria of Rechtshaffen and Kales [26]. Short EEG arousals and respiratory events were also defined using the American Sleep Disorders Association (ASDA) and American Academy of Sleep Medicine (AASM) recommendations [27,28]. Monitoring of respiratory variables allowed recognition and typification of sleep apneas and hypopneas. A hypopnea is defined as a decrease of nasal cannula pressure transducer signal by at least 30% associated with an oxygen drop of 3% or an EEG arousal of 3 s or longer. Flow limitation is defined as a drop of nasal flow compared to prior recording between 3 and 30% with a ‘flattening’ of the curve as described, for at least four breaths, associated with changes in Pes. An abnormal respiratory effort was identified with the presence of Pes crescendos or continuous sustained effort, terminated by an abrupt return to normal effort which is referred to as a Pes reversal [29]. Visual scoring of sleep stages and recognition of respiratory events were performed blindly on both patients and controls. This scoring process also included identification of all sleep phenomena such as body or leg movements. The different respiratory criteria allowed scoring of an apnea–hypopnea index (AHI) based on the calculation of apneas and hypopneas per hour of sleep, and a respiratory disturbance index (RDI) with integration of flow limitation events, respiratory event-related arousal, and Pes events terminated by a Pes reversal [29].

2.5.2. Cyclic alternating pattern (CAP)

Automatic detection of CAP [30,31] was applied to C4-A1 and visually corrected, based on the international atlas rules [32]. A CAP [31,33] is formed by electrocortical events indicated by periodic EEG activity occurring during non-rapid eye movement (NREM) sleep, and characterized by transitory events that recur at regular intervals in the range of seconds during NREM sleep. These events are clearly distinct from the background EEG rhythm as abrupt frequency shifts or amplitude changes. Two phases (A and B) are present that are part of a CAP cycle and recur within 2–60 s. When none of the phases (A and B) are identifiable, sleep has reached a new stable state [32,33]. Phase A is identified by transient events typically observed in NREM sleep. It includes EEG patterns of higher voltage, slower frequency and faster-lower voltage than the background EEG (with an increase in amplitude by at least 1/3 compared to the background EEG). Phase A has been subdivided into three subtypes based on the presence in association with high amplitude slow waves (delta waves) and the presence of faster and lower amplitude activity that can mimic for phase A3 what has been described as delta–alpha EEG pattern. Phase B, which follows, is defined by an EEG pattern of less EEG amplitude with EEG figures of stages 1, 2 NREM sleep. If there is difficulty reaching a new stable state during NREM sleep passing from wake to REM sleep, the CAP rate will increase with the greater the number of cycles (i.e. the greater the number of Phases A and B, or CAP rate) signifying a greater instability of NREM sleep.

Phase A was analyzed as a whole; i.e. subtypes of phase A were not considered in this study. Main sleep EEG patterns recognized in this detection were delta bursts, also called delta-cluster, sequences of K-complexes, vertex sharp wave, and polyphasic bursts of slow and fast frequencies. The parameters analyzed were CAP rate (time occupied by CAP sequences over total NREM sleep time expressed in percent) and CAP time.

2.6. Statistical analysis

One-way analysis of variance (ANOVA) was performed to compare sleep stages and demographic parameters between fatigue and controls. Comparison of relative and absolute power between patients and controls was done with t-test, and comparison of CAP rate and CAP time with Mann–Whitney U-test (after Kolmogorov–Smirnov test).

3. Results

3.1. Patient history, subjective complaints, sleep logs, and scales

Social variables: all patients and controls worked outside of the home. Three women in the patient group and four in the controls worked part-time only. Three chronic fatigue
and three control subjects had no children. There was a
difference between the two groups in the age of the patients’
children, with the youngest child in the chronic fatigue

group being 9-year-old compared to the youngest child
being 2-year-old in the control group. Overall the youngest
child in the family tended to be younger in controls than in
chronic fatigue patients, despite the fact that if all ages of
children were tabulated no significant difference between

groups could be shown, as large SD existed.

Chronic fatigue patients had complaints of continuous
fatigue during the day, which impaired their social and
professional life and had been present for a mean of 6 ± 4.3
years (range 2–12 years). This fatigue was present upon
awakening and was associated with a feeling of unrefreshing
sleep. Fatigue was present on weekdays as well as
weekends and did not diminish after a longer time was spent
in bed, which usually occurred on weekends.

On their 15-day sleep logs, chronic fatigue patients
reported 7.38 h ± 24 min of time in bed during weekdays
but spent as much as 12 h in bed on weekends. The reported
time in bed during weekdays was not significantly different
in chronic fatigue patients than controls (7.14 h ± 35 min).
However, on weekends, time spent in bed was much greater
in patients with fatigue than in controls (mean difference on
weekend: 190 ± 29 min). Eleven chronic fatigue subjects
had a complaint of nocturnal disrupted sleep, and sleep logs
indicated a mean of 1.8 ± 9 episodes of awakening during
sleep. The mean duration of these reported awakenings was
14 ± 9 min. None of the chronic fatigue patients considered
themselves an ‘insomniac’, but six of them mentioned
muscle pain at awakening. Four had nocturia, but related it
to a prior awakening.

With regard to their complaint of fatigue, 12 chronic
fatigue patients reported difficulty concentrating during the
daytime and at work. Seven of them believed that their
fatigue was responsible for limitation in job performance,
and all reported great curtailment in social activities due to
their symptoms. None of the patients smoked and 8/14
reported they did not consume alcohol. The remaining six
patients stated they consumed alcohol only on social
occasions, with one alcoholic beverage every 4–6 weeks.
Caffeine intake was variable but always limited to morning
hours and was usually limited to 1–2 cups of coffee or tea.

Chronic fatigue patients had all previously consulted
internists in search of a solution for their problems, and had
tried to live as ‘healthy’ as possible with regular schedules
to improve their condition. None of the patients took any
medications for the prior 10 months. Chronic fatigue
patients who had tried pharmacotherapy in the past
(10/14) had used polyvitamins, or specific vitamin
supplements, preparation such as ATP, 5-HTP, calcium or
magnesium supplements. No benefit was derived from any
of these therapies and all had been discontinued. In addition,
6/14 had previously been placed on a low dosage of a
Tricyclics or selective serotonin reuptake inhibitors (SSRI)
from their general practitioners for symptomatic treatment.

Two men had undergone treatment with a low dosage of
testosterone for unclear reasons, as their endocrinologic
evaluation was normal. Despite the variety of pharmaceu-
tical agents, none of these medications had any positive
effect on symptoms. As mentioned, all medication intakes
had been stopped many months before the referral.

Krupp et al.’s FSS scores [24] were 4.9 ± 1.2 and 2.1 ±
0.8, P < 0.01 for fatigue patients versus controls, indicating
the presence of abnormal fatigue in chronic fatigue patients.

Though two women with chronic fatigue had signs and
symptoms for fibromyalgia, they did not fulfill the
examination criteria for this condition.

At clinical evaluation, body mass index (BMI) was
similar for both groups (24.6 ± 2.4; 22.1 ± 4.5 kg/m²;
fatigue and controls, respectively; P = 0.14). No explanation
for chronic fatigue had been found after in-depth evalu-
ations at the rheumatologic clinic, which included normal
endocrine and immunological tests.

### 3.2. Sleep, sleep stages and, respiratory parameters

Pre- and post-sleep questionnaires obtained in the
laboratory indicated that all chronic fatigue patients felt
that their day had been of poor quality, with constant
fatigue, which impaired their professional activities. In the
morning, these patients reported the presence of awakenings
which matched polysomnography findings. In addition, they
reported very unrefreshing sleep with significant tiredness
which was equal or greater to what they felt at the previous
bedtime. Despite the impression of their sleep being of poor
quality, none complained of ‘insomnia’.

Sleep stage analyses: as shown in Table 1, patients with
complaint of chronic fatigue had a significantly lower
percentage of Stages 3, 4 NREM sleep, lower sleep
efficiency, and a similar AHI (0.9 ± 0.6 versus 0.7 ± 0.9;
p = ns) but higher RDI compared to normal subjects (Table 1).

<table>
<thead>
<tr>
<th>PSG parameters</th>
<th>Fatigue (n = 14)</th>
<th>Controls (n = 14)</th>
<th>F(1,27)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDI</td>
<td>4.7 ± 3.3a</td>
<td>1.0 ± 1.4</td>
<td>11.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Lowest O2 Satsuration</td>
<td>92.6 ± 2.8</td>
<td>92.0 ± 2.1</td>
<td>0.34</td>
<td>n.s.</td>
</tr>
<tr>
<td>TST (min)</td>
<td>398.8 ± 72</td>
<td>377.2 ± 75.5</td>
<td>2.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>84.1 ± 9.4a</td>
<td>90.6 ± 4.6</td>
<td>4.2</td>
<td>0.06</td>
</tr>
<tr>
<td>REM sleep (%)</td>
<td>17.2 ± 6.1</td>
<td>19.4 ± 4.7</td>
<td>0.88</td>
<td>n.s.</td>
</tr>
<tr>
<td>Stages 3, 4</td>
<td>13.9 ± 7.2a</td>
<td>25.4 ± 6.7</td>
<td>15.1</td>
<td>0.01</td>
</tr>
<tr>
<td>NREM sleep (%)</td>
<td>6.7 ± 1.2a</td>
<td>9.4 ± 2.1</td>
<td>0.06</td>
<td>n.s.</td>
</tr>
<tr>
<td>Arousal index/ hour of sleep</td>
<td>9.5 ± 3.8</td>
<td>9.3 ± 5.2</td>
<td>0.006</td>
<td>n.s.</td>
</tr>
<tr>
<td>Eapworth sleepiness scale</td>
<td>10.3 ± 4.7</td>
<td>8.9 ± 2.4</td>
<td>0.37</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

RDI, respiratory disturbance index; TST, total sleep time; Fatigue: chronic
fatigue patients; Number of subject involved: 28.

* One-way ANOVA.
3.3. CAP parameters

CAP time and CAP rate were significantly higher in chronic fatigue patients despite similar NREM sleep time (as measured in minutes) in both subject groups. (Table 2) Further phase A analyses were not performed.

3.4. Sleep EEG spectral power frequencies

There was a significant increase in slow delta (delta 1) power in chronic fatigue patients compared to normal controls as shown in Tables 3A and 3B. This was found when considering relative and absolute power (Tables 3A and 3B and Fig. 1).

4. Discussion

We studied subjects complaining of unexplained fatigue and unrefreshing sleep lasting for several years. In many reports, patients with ‘chronic fatigue syndrome’ have normal sleep including sleep stage distribution by polysomnography despite their sleep complaints [34]. Others have reported sleep stage changes, with increase in stage 2 NREM sleep and decreases or increases in slow wave sleep [22,35,36]. A sleep pattern called ‘delta–alpha’ has also been associated with fibromyalgia and fatigue, but publications reporting it have been criticized due to lack of specificity of this pattern [19]. The real issue, we believe, is not the specificity of the polysomnographic pattern: It is the fact that patients with chronic fatigue syndrome have an abnormal sleep EEG pattern of shorter duration than the one used for sleep staging. This abnormal sleep EEG pattern is not recognized by the conventional scoring methods of polysomnography, and critics of the finding should have raised the question of the underlying problems behind the presence of delta–alpha sleep disturbances [14].

Our study addressed the question of unrefreshing sleep using new tools. None of our patients had secondary gain to their claim of fatigue, and all were greatly handicapped by their syndrome. These patients tried to treat their fatigue by staying in bed on weekends and days off, despite the negative impact it had on their social and family lives. They denied ‘sleepiness’, and their ESS was borderline normal. Several of the sleep logs showed some nocturnal sleep disruption, though all patients denied having ‘insomnia’, defined as difficulty falling asleep at sleep onset or difficulty returning to sleep if awakened during the night. The major complaint of the patients was of ‘unrefreshing sleep’ and a continuous feeling of fatigue that was described as ‘exhaustion’ by a few, which was already present at the time of morning awakening. In our study the subjective investigations did not yield important findings. Sleep staging analyses did not account for the reported fatigue. Though there were subtle abnormalities, a decrease in sleep efficiency and a decrease in stages 3, 4 NREM sleep (SWS) compared to normal controls as already mentioned by others [36], these findings are interesting but are not specific. Additionally, experiments with short-term sleep deprivation and recovery have shown that sleep duration appears to be more important for daytime alertness than SWS content [37] and total sleep time, which were similar in our fatigue patients and controls. We also failed to demonstrate alterations in sleep consolidation and fragmentation parameters. Our fatigue patients had similar arousal indices compared to normals. Notably, this study did not find an increase in alpha EEG frequencies (fast frequencies), primary components of delta–alpha pattern and of arousals from sleep. The lack of sleep fragmentation may explain

### Table 3A
Sleep EEG frequency bands relative power

<table>
<thead>
<tr>
<th>EEG frequencies</th>
<th>Fatigue (n = 13)</th>
<th>Controls (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta 1 (%)</td>
<td>0.74 ± 0.14</td>
<td>0.47 ± 0.18</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Delta 2 (%)</td>
<td>0.15 ± 0.07</td>
<td>0.26 ± 0.09</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Theta (%)</td>
<td>0.07 ± 0.04</td>
<td>0.12 ± 0.04</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Alpha (%)</td>
<td>0.02 ± 0.03</td>
<td>0.06 ± 0.03</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Sigma 1 (%)</td>
<td>0.01 ± 0.02</td>
<td>0.04 ± 0.03</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Sigma 2 (%)</td>
<td>0.01 ± 0.01</td>
<td>0.03 ± 0.09</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Beta (%)</td>
<td>0.003 ± 0.009</td>
<td>0.01 ± 0.01</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

*Significantly different with t-Test analysis.

### Table 3B
Sleep EEG frequency bands absolute power (μV²)

<table>
<thead>
<tr>
<th>EEG frequencies</th>
<th>Fatigue (n = 13)</th>
<th>Controls (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delta 1</td>
<td>1459.3 ± 1113.2</td>
<td>516.7 ± 394.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Delta 2</td>
<td>294.0 ± 154.1</td>
<td>247.5 ± 129.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Theta</td>
<td>89.3 ± 41.8</td>
<td>127.57 ± 59</td>
<td>n.s.</td>
</tr>
<tr>
<td>Alpha</td>
<td>41.7 ± 18.0</td>
<td>57.33 ± 24.75</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sigma 1</td>
<td>35.0 ± 24.8</td>
<td>37.0 ± 20</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sigma 2</td>
<td>22.3 ± 17.6</td>
<td>16.7 ± 13.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Beta</td>
<td>6.7 ± 3.3</td>
<td>14.36 ± 7.05</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

t-Test (one CD with recording data unreadable, n = 27). Fatigue, chronic fatigue patients.

* Significantly different with t-Test analysis.
why these patients were not sleepy during the daytime but complained only of chronic fatigue.

However, the CAP analyses and quantitative EEG analyses changes were significant compared to controls. These changes suggest one should analyze the polysomnograms of patients complaining of fatigue differently. In our chronic fatigue patients, there was a significant increase in slow delta power despite an overall decrease in SWS compared to normals. Some of the findings are close to those observed with parasomnias [38–42], including an increase in CAP rate and CAP time as observed here. Such increases are associated with complaint of unrefreshing sleep and sleep disorders [31,33,43]. In our analysis we did not dissociate the different phases A of CAP because we believe that the important question here is not related to types of phase A but instead to the following: why are the phases A interrupted and why is there a return to phase B instead of a normal progression toward consolidated SWS? The presence of an increase in slow delta indicates presence of ‘delta burst’ or ‘delta-cluster waves’ [44]; however, the decrease in overall delta power and slow wave sleep indicates that the ‘delta stage’ cannot be maintained during NREM sleep, leading to ‘instability of NREM sleep’ as emphasized by Terzano et al. [32,33]. Instability of NREM sleep has been seen with a variety of different syndromes and is a non-specific finding but raises the question of why such instability is present. We believe NREM sleep instability suggests an impairment of the normal homeostatic process.

Increase in CAP rate is associated with the presence of increased respiratory effort and of flow limitation events as shown with nasal cannula and esophageal pressure measurements. With these combined recording techniques, which are not routinely used in most sleep laboratories, we found a significant increase in the RDI (an index very different from the well-known AHI calculated in obstructive sleep apnea) in chronic fatigue subjects compared to controls. The main complaint of patients, particularly premenopausal women, with upper airway resistance syndrome (UARS [45]) is ‘chronic fatigue’. The difference between patients labeled ‘chronic fatigue’ or UARS appears mainly dependant on the referral route of patients rather than their clinical complaint. Initially, UARS patients were sent to the sleep clinic because of snoring, but it is well-known that UARS may be present without snoring [45]. The main complaint of patients in this study was ‘chronic fatigue’, which led them to be referred and evaluated by rheumatologists. Despite the diagnosis ‘chronic fatigue’ or ‘UARS’ both groups of patients share similar sleep disturbances that result in similar consequences. There are now a series of reports that show abnormal breathing without obstructive apneas, and hypopneas may be associated with changes in sleep EEG. Chervin et al. showed that in both children and adults [46,47] EEG changes may be seen with each abnormal breath and each increase in respiratory effort by utilizing a much more sophisticated technique than visual sleep stage scoring. There is now an array of reports that demonstrate the importance of intact sensory input from the oro-pharynx and upper larynx to avoid the development of the obstructive sleep apnea syndrome [48]. The presence of a local neuropathy appears to be associated with OSAS, but persistence of normal local sensory input seems to be inducing UARS, with its cortege of daytime fatigue [48], abnormal CAP rate and changes of sleep EEG at quantitative EEG analyses.

In 1999, Lentz et al. showed that SWS sleep disruption resulting in an increase in fatigue and a decrease in pain threshold [49]. Vergara et al. [50] reported that an important predictor of subjective quality of sleep and sleep depth is related to delta maximum power measured with quantitative EEG analysis. Instability of NREM sleep is associated with changes in delta power from the first to the last NREM–REM cycle as demonstrated in investigation of chronic sleepwalkers [42]. Subtle sleep-disordered breathing (UARS type) leads to these changes in delta power. The challenges now are to understand why similar breathing disorders during sleep lead to different clinical presentations, why subjects with similar sleep disturbances have
different types of parasomnia, or just a complaint of chronic fatigue. Could it be that the type of anatomical problem presented by these patients (nasal impairment versus base of tongue impairment, versus pharyngeal impairment) plays a role on the severity of the sleep EEG disturbance? Is an increase in nasal resistance more detrimental in creating an anxiety response than a base of tongue narrowing? These are unanswered questions but are important to consider as the types and number of sensory receptors are very different depending on the region of the upper airway that is the primary site of narrowing. The projections of these sensors and their association with certain regions of the brain may also be important: again an abnormality in the nose passage may not have the same impact as one behind the base of tongue. There will also be the need to explore whether subtle disruption of other biological functions leads to some subtle disturbances of sleep and complaints of chronic fatigue due to the impact on SWS and appearance of NREM sleep instability. In the recent past, the use of investigative approaches such as quantitative EEG, CAP scoring, or complex algorithms such as the one used by Chervin et al. [46,47], have demonstrated that much more information could be extracted from the sleep EEG of patients with complaint of ‘fatigue’, and these approaches may reveal much more than simple sleep staging.

References