J. Sleep Res. (2008) 17, 427–431 Chronic fatigue syndrome: Sleepy or tired?

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Are patients with chronic fatigue syndrome just 'tired' or also 'sleepy'?

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SUMMARY It is presently unclear whether chronic fatigue syndrome (CFS) patients exhibit daytime sleepiness in addition to fatigue. Both, fatigue, such as that seen in CFS patients, and excessive daytime sleepiness, such as in sleep apnea–hypopnea syndrome (SAHS), remain poorly understood. Both daytime conditions are generally related to unrefreshing sleep and show affective symptoms. This study's objective was to contribute to the understanding of the relationship between fatigue and sleepiness in CFS patients not co-morbid for primary sleep or psychiatric disorders. We compared 16 untreated CFS patients (mean age 32.8, all females) with 13 untreated SAHS (mean age 47.7, all females) patients and 12 healthy controls (mean age 32.2, all females). Objective sleepiness was measured using multiple sleep latency tests (MSLT). Subjective sleepiness and fatigue were assessed with the Epworth Sleepiness Scale and the Fatigue Severity Scale, respectively. Mean Sleep Latency (SL) on the MSLT was significantly shorter in SAHS patients than in CFS patients and CFS patients showed significantly shorter mean SL than matched controls but within normal range. Subjective sleepiness was greatest in SAHS patients and subjective fatigue was highest in CFS patients. Affective symptoms showed highest intensities in CFS patients. While higher than the control group on all measures, compared to SAHS, the CFS group had higher subjective fatigue and lower subjective and objective sleepiness. Despite possible overlap in symptoms and signs of both daytime conditions, our data indirectly support the clinical distinction between fatigue and sleepiness.

KEYWORDS chronic fatigue syndrome, multiple sleep latency test, sleep apnea–hypopnea syndrome, sleepiness

INTRODUCTION

Patients with chronic fatigue syndrome (CFS) present with fatigue as their main symptom. However, it is unclear whether they also experience excessive daytime sleepiness (EDS). The semiological distinction of fatigue and sleepiness is difficult both for patients and clinicians, leading to possibly imprecise diagnostic formulations (Pigeon *et al.*, 2003). Moreover the relationships of sleepiness or fatigue to sleep remain insufficiently understood (Pigeon *et al.*, 2003; Shen *et al.*, 2006).

The main objective of this study was to investigate objective and subjective sleepiness in a fatigue-associated condition such as CFS and to compare them to a sleepiness-associated condition such as sleep apnea–hypopnea syndrome (SAHS). The intensity of subjective fatigue and affective symptoms were also measured in both conditions.

Assessment of objective sleepiness with multiple sleep latency tests (MSLT) has been used in several previous CFS studies (Le Bon *et al.*, 2000; Reeves *et al.*, 2006; Watson *et al.*, 2004). Despite finding that 30% of patients have a mean sleep latency (SL) of less than 10 min in an uncontrolled CFS study (Le Bon

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et al., 2000), previous papers did not mention a significantly lower mean SL compared to control subjects (Reeves *et al*., 2006; Watson *et al*., 2004). However, previous studies did not exclude CFS patients with co-morbid primary sleep disorders (Le Bon *et al*., 2000; Reeves *et al*., 2006), which can influence both fatigue and sleepiness and, hence, muddle the general picture.

To our knowledge the degree of sleepiness has never been described before in a carefully selected untreated sample of CFS patients without primary sleep disorders or co-morbid psychiatric diagnoses.

METHODS

Patients and subjects

From November 2005 to October 2006, patients exhibiting only CFS were selected prospectively among the patients referred to our sleep laboratory. They were referred to the sleep unit after a full medical check-up (total body CT or MRI scan, functional brain imaging, several ultra-sonograms, several effort measures and numerous blood tests). Center for Disease Control criteria were used for the first selection of CFS patients (Fukuda *et al*. 1994). In order to avoid the overlaps with primary sleep disorders or psychiatric disorders, further exclusion criteria were: (1) Apnea–Hypopnea Index (AHI) or Periodic Limb Movement index (PLMI) $\geq 5\ h^{-1}$, clinical criteria for narcolepsy or idiopathic hypersomnia (HI); (2) all DSM-IV axis 1 diagnoses. During the same period, SAHS patients were referred from the pneumonology department of the same hospital, for a clinically suspected nocturnal breathing disorder. Inclusion setting of AHI for SAHS patients was AHI $> 15\ h^{-1}$. Healthy Controls (HC) were locally recruited healthy volunteers who received 120 Euros from private funding at the end of the study. Regular Sleep–Wake schedules were required and no shift working was allowed. Control patients had no significant somatic conditions and no current or past mental disorders. Further exclusion criteria were identical to patients groups. In order to avoid gender mismatch, only female subjects were studied.

All patients and subjects were free of neuropsychopharmacological treatment for at least 2 weeks prior to recording. Daytime napping, outside of MSLT, was not allowed in the sleep unit. All patients and controls filled out a sleep diary 2 weeks prior to sleep recording to assess regular sleep–wake schedule, received a standard physical examination (DN), structured clinical interview for DSM IV (American Psychiatric Association, 1994) (DN, GH, OL) and psychometric assessment (DN).

The study was conducted in accordance with the rules and regulations for clinical trials stated by the World Medical Assembly in Helsinki.

Material

Polysomnograms

All participants admitted to the sleep unit were recorded for two consecutive nights of polysomnogram (PSG) with MSLT following the first night. Participants were prepared for the PSG recordings between 22:00 h and 23:00 h and allowed to retire when they wished. Morning arousal was spontaneous. The minimum threshold for total sleep time (TST) on the first night of polysomnogram was 360 min for all subjects.

The recordings included six electroencephalograms recorded from Fp2-A2, Fp1-A1, C3-A1, C4-A2, O1-A1, O2-A2 sites, two electrooculograms, submental and bilateral anterior tibial electromyograms. Oral and nasal airflow were recorded by a oro-nasal cannula (Pro-Flow Plus™ Pro-Tech®, Mukilteo, WA, USA), respiratory effort was measured by thoracic and abdominal belts (Pro-Tech® CT2™, Mukilteo, WA, USA). Capillary oxygen saturation was monitored by photosensitive finger-oxymetry (Nonin® FlexiForm® II 7000A Nonin Medical Inc, Mineapolis, MN, USA and LINOP® Adt Masimo corp. Irvine, CA, USA). All (PSG and MSLT) recordings were analyzed on 21″ screens displaying 30-s polysomnograph epochs (Respironics Inc™ Alice® 4 and 5, Murrysville, PA, USA). Classical criteria were used for sleep stage scoring (Rechtschaffen and Kales, 1968).

Multiple sleep latency tests

Multiple sleep latency tests were carried out during the second day of the stay in the lab after the first night of polysomnogram recording. The time schedule for all patients and controls was the same. Four MSLTs were recorded (10.00, 12.00, 14.00, 16.00 h) and were always supervised live and in real time by the same investigator (DN). Subjects usually went for a walk in the park next to our laboratory between MSLT 2 and 3 and between MSLT 3 and 4. Residual light intensity during MSLT, as measured by photometry (Respironics Inc™ Alice®), varied between 12 and 15 Lux. MSLT was stopped after 1 min of sleep stage 1 or after 30 s of sleep stage 2, respectively, or after one epoch of any other sleep stage. The intention was to avoid power napping that could significantly influence the validity of the second night's polysomnogram recording. Maximum duration of recording time was 20 min (Table 1). Formerly, the International Classification of Sleep Disorders (ICSD) suggested a mean SL less than 10 min on the MSLT to indicate moderate to severe sleepiness and a mean SL above 10 as a mild or normal sleepiness. Current cut-offs, according to the ICSD, suggest a mean SL above 10 min as a normal sleepiness and below 8 as pathological.

Sleepiness and fatigue scales

The Fatigue Severity Scale (FSS) is a self-reporting tool used to assess levels of fatigue and its effect on daily functioning (Krupp *et al*., 1989). The FSS has been used in many studies, including those studying CFS (Olson *et al*., 2003). The Epworth Sleepiness Scale (ESS) is one of the most widely used scales of subjective sleepiness. Scores above 10 are commonly interpreted as increased daytime sleepiness (Johns, 1991).

Table 1 (a) Age and BMI; (b) Key sleep variables, corrected for Age and BMI; (c) Measures of objective and subjective sleepiness, subjective fatigue and affective symptoms, corrected for Age and BMI

	CFS (n = 16)	*SAHS* (n = 13)	*Controls* (n = 12)	ANOVA (P)	*Ctrls/CFS Fisher PLSD* (P)	*Ctrls/SAHS Fisher PLSD* (P)	*CFS/SAHS Fisher PLSD* (P)
(a)							
AGE	32.8(10.2)	47.7 (7.5)	32.2 (9.6)	.0001	NS	.0001	.003
BMI	23.1 (4.3)	31.1 (7.9)	21.3 (1.9)	.0001	NS	.0001	.005

(b)				ANCOVA (P)	*Ctrls/CFS contrast* (P)	*Ctrls/SAHS contrast* (P)	*CFS/SAHS contrast* (P)
SEI	90.1 (8.4)	90.2 (4.2)	89.1 (6.2)	NS			
SOL	24.2 (10.4)	27.3 (16.4)	21.2 (4.3)	.042	NS	.015	.027
WASO	44.7 (35.1)	34.0 (12.5)	51.8 (35.0)	NS			
SWS [%]	25.2 (10.1)	18.9 (9.5)	22.0 (11.8)	NS			
AHI	1.7 (1.2)	18.7 (3.9)	1.1 (1.3)	.0001	NS	.0001	.0001
MAI	29.4 (16.2)	32.8(7.6)	11.9 (6.1)	.0001	.0001	.013	NS

(c)				ANCOVA (P)	*Ctrls/CFS contrast* (P)	*Ctrls/SAHS contrast* (P)	*CFS/SAHS contrast* (P)
ESS	10.5 (5.8)	12.8 (2.4)	3.5 (2.2)	.0001	.0001	.0001	NS
FSS	6.2 (0.9)	3.5 (1.4)	1.7 (1.1)	.0001	.0001	.020	.001
BDI	10.2 (5.4)	6.8 (3.2)	0.3 (0.6)	.0001	.0001	.024	.008
HAMA	17.6 (4.7)	10.1 (3.7)	3.2 (1.6)	.0001	.0001	.027	.0001
MSLT 1	16.5 (4.7)	12.2 (3.6)	17.8 (4.2)	.050	NS	.018	.029
MSLT 2	14.6 (2.1)	10.4 (3.3)	18.7 (2.1)	.001	.011	.0001	.016
MSLT 3	13.8 (5.3)	8.6 (2.5)	16.0 (3.9)	.027	NS	.008	.043
MSLT 4	14.5 (4.9)	11.5 (3.4)	18.4 (3.4)	.029	.028	.017	NS
MSLT MEAN	14.6 (3.0)	10.6 (1.8)	17.7 (1.3)	.0001	.005	.0001	.0001

Ctrls: Controls; CFS: chronic fatigue patients; SAHS: sleep apnea–hypopnea patients; ESS: Epworth Sleepiness Scale; FSS: Fatigue Severity Scale; BDI: Beck Depression Inventory (Short Form 13 items); HAMA: Hamilton Anxiety Scale; MSLT: Multiple Sleep latency Test in minutes (A sleep latency test without sleep is noted as a sleep latency of 20 min); SEI: sleep efficiency index (=TST: total sleep time/SPT: sleep period time); TST = SPT – WASO; SOL: sleep onset latency (minutes); WASO: wake after sleep onset (minutes); SWS: slow wave sleep, percent of the sleep period time; AHI: apnea–hypopnea index per hour of sleep; MAI: micro arousal index per hour of sleep. Values are presented as means with (standard deviation); Trends are marked in brackets (). Descriptive sleep data illustrate the second polysomnogram recording (following the MSLT).

Affective symptoms scales

All patients completed the 13-item short form of the Beck Depression Inventory (BDI, Beck, 1961) on the first day of their stay in our laboratory before the first night of polysomnogram between 17:00 h and 19:00 h All subjects were rated with the Hamilton anxiety (HAMA, Hamilton, 1959) scale between 11:00 h and 13:00 h by the same interviewer (DN) on the second day of their stay in our laboratory after their first night of polysomnogram recording. Generally proposed cut-offs, for anxiety disorders and depression, are scores > 20 on the HAMA and scores > 13 on the BDI, respectively.

Statistics

All variables in each of the groups were compatible with the use of parametric tests.

Between-group comparisons involving continuous data were computed using MANCOVA with single factor (diagnostic group) and two covariates (Age and BMI). Contrast tests between the groups were performed when ANCOVAS showed significant outcomes. Hypotheses tests were two-sided and carried out at a 5% significance level. Trends are marked between brackets at a 10% level. All results are expressed as mean ± standard deviation. Analyses were computed using SPSS 13® (SPSS Inc., Chicago, IL, USA).

RESULTS

Estimated TST from sleep diaries (data not shown) showed no differences among groups (F: 1,128; $P = 0.338$).

Among descriptive variables, age and BMI were shown to present with significant differences (Table 1a). Patients in the SAHS group were older and had a higher BMI than the two other groups (CFS and HC), who showed no significant difference between them. For this reason, both variables were introduced as covariates in the multivariate analyses.

A first MANCOVA was performed to compare key sleep variables between the three groups. Pillai's Trace was highly significant for subject groups (1.206; F: 8.095; $P = 0.0001$). CFS patients showed more microarousals per hour than

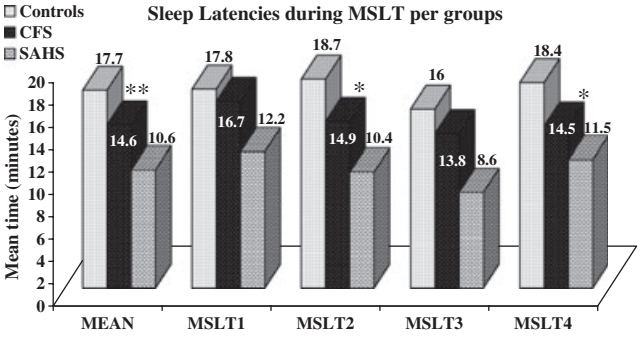

Figure 1. Significance CFS versus Controls: * $P = .01$; ** $P = .003$. Values are mean sleep latencies in minutes, standard deviations and are given in Table 1.

controls. They showed less apneas–hypopneas and a shorter sleep-onset-latency (SOL) than SAHS patients. The latter showed more apneas–hypopneas, more micro-arousals and a longer SOL than controls (Table 1b).

A second MANCOVA was applied to MSLTs and subjective scales for sleepiness and fatigue (Pillai's Trace: 1.378; F: 8.305; $P = 0.0001$ for subject groups). CFS patients showed significantly shorter mean SL and significantly shorter SL in MSLT 2 and MSLT 4 than HC. SAHS patients presented with shorter SL than CFS patients or HC in all cases, excepted for MSLT 4, which showed no significant difference between the two clinical conditions (Table 1c).

Observation of the means showed (mean) SL, on the MSLT, to be generally stable across groups (Fig. 1). CFS patients systematically presented with intermediate values between SAHS patients and HC.

All four subjective scales showed both patients groups with significantly more complaints than controls. Comparing patients groups, no significant difference in subjective sleepiness (ESS) was observed. Severity of fatigue, anxiety and depression symptoms were higher in the CFS group.

DISCUSSION

This is, to our knowledge, the first study comparing objective and subjective measures of sleepiness as well as subjective measures of fatigue between CFS, SAHS and control subjects.

Chronic fatigue syndrome patients presented with normal sleep latencies on the MSLT, but higher levels of fatigue and sleepiness than controls on the subjective scales. They complained of more fatigue than SAHS patients but expressed a similar degree of subjective sleepiness. They showed more anxiety and depression than both SAHS and controls. SAHS patients presented with shorter sleep latencies on the MSLT and higher levels of fatigue and sleepiness than controls on the subjective scales. They also showed higher anxiety and depression levels than controls.

Sleep apnea–hypopnea syndrome patients are thus sleepy and tired. CFS patients are tired with a more ambiguous picture on sleepiness. While scoring for it on the subjective scale, their sleep latencies were within the normal range (Arand *et al*., 2005), so that CFS patients should not be considered as objectively sleepy. Interestingly however, their values were significantly shorter than in controls studied under identical conditions. CFS patients are not likely to belong to the group of people described by Harrison and Horne (1996), who can easily relax and, therefore, show lower but normal SL. A higher ability to relax would indeed be surprising here, considering the high subsyndromal intensity of anxiety symptoms shown in the present (Table 1c), and in previous studies (Fischler, 1999; Skapinakis *et al*., 2003). Such intermediate SL values could thus indicate a vigilance degree halfway in the continuum between sleepiness and normality.

Analyses of the means of the subjective scales showed CFS patients to be the most tired, and SAHS, the most sleepy. These data confirm the subjective clinical picture and support the theoretical distinction between fatigue and sleepiness. However, these distinctions are not clear-cut, especially for sleepiness, and the data confirm the likely overlap in the perception and operationalization of sleepiness and fatigue (Pigeon *et al*., 2003). This, combined with the puzzling and well-known discordance between objective and subjective sleepiness, should stimulate us in finding more precise tools and analyses.

The most interesting descriptive polysomnographic finding was the high level of idiopathic microarousal index (MAI) in the CFS group. This is consistent with previous studies from our group, on other groups of patients (Le Bon *et al*., 2007; Neu *et al*., 2007). The MAI level found in CFS patients was almost as high as in the SAHS group. What is interesting is that elements usually associated with more microarousals, such as periodic limb movements or sleep apneas–hypopneas were excluded in this group. Also, elements usually associated with EDS, such as lowered SWS or lower sleep efficiency are lacking in the CFS group. This higher level of MAI is thus presently not associated with any known factor or variable except group diagnosis.

Limitations

The age difference between the SAHS and the two other groups is a limitation to the generalization of the present findings. Age has been shown to be associated with an increase of the SL on MSLT (Arand *et al*., 2005). The moderate EDS and mean SL on the MSLT in our SAHS group probably emphasize this point. However, we wanted to compare groups with no interference by gender. As CFS females are epidemiologically largely predominant, we selected only females as controls and SAHS patients. Young females with severe apnea–hypopnea syndrome are not very frequent and have not been studied extensively so far in the literature.

Time in bed (TIB) was not held constant in this study (also see Methods section), but all subjects had a minimum of 360 min of TST and data analysis showed no differences in TIB among groups (data not shown).

The time course for MSLT recording between two PSGs should not affect the data, as PSG in general has not been shown to influence the outcome of MSLT (Wichniak *et al*., 2002). The mean SL of our HC group is relatively high, regarding age related normative data (Arand *et al*., 2005). This may be due to slight differences in study conditions (time schedule, residual light intensity and afternoon walk, see also Methods section) than in the aforementioned paper. However, the study conditions were identical for the three groups, hence the observed differences remain valid.

CONCLUSIONS

Speculations about somato-sensory misperception were made regarding the intense complaints of non-recovering sleep, fatigue, daytime sleepiness, and the relative lack of objective sleep findings in CFS patients (Neu *et al*., 2007). Future objectives should focus on sleep microstructure and attempt to bridge the gap between subjective complaints underlined by high scores on psychometric or physical scales and the apparent absence of objective findings in polysomnographic studies.

Complaints of fatigue and sleepiness can overlap in patients, but should be taken into account separately as they may express very different aetiologies and may imply different treatment considerations. Contributions to the study of fatigue and sleepiness should extend to other comparative models of related clinical conditions.

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