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SLEEP DISTURBANCE IN CHRONIC FATIGUE SYNDROME

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Abstract—Sleep and fatigue characteristics were evaluated in 72 patients who met major criteria for the chronic fatigue syndrome (CFS), 57 multiple sclerosis (MS) patients preselected for fatigue complaints, and 40 healthy controls. Using previously validated rating scales, CFS patients had significant elevations in fatigue and sleep disturbance compared to the MS and healthy control groups. To confirm these subjective measures, polysomnography was carried out in a subgroup of CFS patients who included sleep disturbance as one of their symptoms on initial clinical interview. In 10 of 16 (62.5%) polysomnography revealed clinically significant and potentially treatable sleep abnormalities. Their sleep disorders included periodic movement disorder (4), excessive daytime sleepiness (3), apnea (2), and narcolepsy (1). We conclude that subjective sleep disturbance is common in CFS and some CFS patients may have objective sleep disorders.

INTRODUCTION

FATIGUE may be a manifestation of a variety of neurologic and medical disorders, but its precise pathogenesis is unknown. Research on fatigue and a possible relationship to sleep disorders has been stimulated by the 1988 formulation of a case definition for chronic fatigue syndrome (CFS) [1]. This definition refers to overwhelming fatigue which is independent of any recognized medical disorder, and includes sleep disturbance as one of its 11 minor symptom criteria [1]. However, little work has been done to characterize the associated sleep disturbance in patient populations who experience profound fatigue.

In this report we evaluated sleep disturbance, fatigue, and depressive symptoms in CFS, multiple sclerosis (MS) patients and healthy controls. Subjective sleep disturbance in a subset of CFS patients was further investigated using polysomnography. We hypothesized that due to the overlap between fatigue, poor sleep, and depression, subjective sleep disturbance would be common in patients with CFS and that in some individuals pathophysiological abnormalities of sleep would be present. Given the strong association of depression in CFS compared to other medical conditions, we expected self-reported sleep disturbance and depression to be relatively elevated compared to both healthy controls and to a central neurological disorder associated with severe fatigue, MS.

METHODS

Subjects

Seventy-two CFS out-patients (mean age 44 ± 11 yr, 67% women) were evaluated with complete general and neurologic examinations. They had been referred by their primary care physician or by the local CFS support group. All patients met both major criteria for CFS. They had new onset of severe

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fatigue, which interfered with their activities of daily living, and which could not be explained by any concurrent or past medical disorder. All satisfied at least 5 of the 11 minor symptom criteria for CFS. A mean of 8 ± 2 criteria were satisfied by the total group. Patients were symptomatic for an average of 4 yr (maximum 22 yr). No patient at the time of their clinical evaluation had physical signs of CFS (fever, adenopathy, or reddened throat). All but one patient with cerebral palsy and spastic diplegia since birth had otherwise normal general and neurologic examination. Laboratory studies, including complete peripheral blood cell count, thyroxine level, thyroid stimulating hormone, electrolytes, Lyme titer, and erythrocyte sedimentation rate, did not reveal any other diagnosable disorder that could cause fatigue. Seven patients had past medical conditions from which they had fully recovered 7 months prior to the onset of their fatigue and sleep symptoms [Lyme disease (6), aseptic meningitis (1)].

Although several patients had major depression or anxiety disorders, in most cases these were considered to be concurrent with the chronic fatigue rather than the primary or exclusive cause of symptoms.

Of the 72 CFS patients, 16 (22%) were selected for polysomnography because they included sleep disturbance in addition to fatigue on the initial clinical interview. However, in all cases their chief complaint was severe fatigue. This polysomnography group consisted of nine women and six men with a mean age of 42 ± 16 yr. They were not significantly different from the larger chronic fatigue group with respect to age and sex distribution.

The MS control group consisted of clinically definite MS patients as determined by the criteria of Poser and colleagues [2], who included severe fatigue among their symptoms when evaluated on University Hospital Multiple Sclerosis Comprehensive Care Center. Healthy controls were drawn from volunteers unfamiliar with the clinical study. They were screened by telephone interview and excluded from the study if they reported any medical or psychiatric condition known to produce fatigue.

Subjective assessments

Subjective reports of sleep disturbance were measured with a modified version of the St. Mary's Sleep Questionnaire [3]. This 14 item self-report questionnaire specifically refers to the sleep status for the preceding night. Responses to individual items as well as the total set of questions (sleep disturbance score) were computed for all subjects using a numerical rating system from 1 (least sleep disturbance) to 6 (maximum sleep disturbance). In addition, the percentage of subjects answering affirmatively (scores of 4 or more) to each question was analyzed.

Fatigue was quantitatively assessed with a self-report 29 item fatigue questionnaire which included the fatigue severity scale (FSS) [4]. The FSS is a nine-item scale scored from 1 (no fatigue) to 7 (severe fatigue). Its clinical utility, reliability, and validation criteria have been previously reported [4].

Depressive symptomatology was measured with the center for epidemiologic studies depression scale (CES-D) [5]. This is a 20-item self-report inventory scored from 0 to 60 in which a score greater than 15 suggests depressive symptomatology. It is specifically designed to measure the affective component of depression, and scores above 15 suggest more severe depressive symptoms. The scale has been extensively validated in clinical and epidemiologic studies [6–8]. The CES-D is a screening instrument and does not generate a clinical diagnosis. Therefore, chronic fatigue subjects who underwent sleep studies and who had CES-D scores of 15 or above were additionally evaluated with the structured clinical interview for diagnosis of DSM-III-R disorders (SCID) [9] by a psychiatrist or psychologist.

Polysomnography

Polysomnography was performed overnight at University Hospital and was followed the next day with the daytime multiple sleep latency test (MSLT) [10]. The polysomnography procedure involved nocturnal recordings of the electroencephalogram, electrooculogram, submental electromyogram, and electrocardiogram. Included were measures of nasal and oral airflow, measures of thoracic abdominal respiratory movement, and anterior tibial electromyogram. All recordings were made on Grass Model polygraphs calibrated to 50 uV/10 mm with a paper speed of 10 mm/second recording.

Statistics

Analysis of variance with planned contrasts was used to test for statistical differences among the patient groups and controls. A chi-square (χ^2) analysis was used to examine differences on specific sleep questions comparing CFS separately to MS and healthy controls.

RESULTS

Sleep assessment

The responses to the specific items on the questionnaire by the CFS patients were compared to the healthy controls and MS patients. Sleep in CFS was much more

disrupted than in controls. CFS patients, compared to healthy controls, reported that they slept lightly (37% (25 of 68) vs 10% (2 of 20), df = 2, $\chi^2 = 8.5$, $p < 0.01$) and badly (15% (10 of 68) vs 5% (1 of 20), df = 2 $\chi^2 = 13.7$, $p < 0.001$), were bothered by early morning waking (27% (17 of 62) vs 0% (0 of 18), df = 1 $\chi^2 = 6.3$, $p < 0.001$), and still felt drowsy upon awakening (76% (48 of 63) vs 35% (7 of 20), df = 2 $\chi^2 = 14.5$, $p < 0.001$). In contrast, on most sleep questions CFS and MS patients did not differ. However, CFS slept more lightly (37% (25 of 68) vs 10% (3 of 29), df = 2 $\chi^2 = 8.4$, $p < 0.01$), and more frequently reported feeling drowsy upon awakening (76% (48 of 63) vs 48% (14 of 29), df = 2 $\chi^2 = 8.5$, $p < 0.05$).

Relationship between sleep, fatigue and depressive symptoms

To determine the relationship between sleep disturbance in CFS to other symptoms we compared the CFS patients sleep disturbance score and their reports of fatigue and depressive symptoms to the MS and healthy control groups. As shown in Table I, CFS patients had significantly higher sleep disturbance scores compared to MS patients (21 vs 18, $p < 0.04$) and healthy controls (21 vs 15, $p < 0.0005$). Increased sleep disturbance in CFS was associated with elevated fatigue severity. The fatigue score for the CFS patient of 6.1 was significantly elevated compared to MS patients 5.1 ($p < 0.0001$) and healthy controls 2.8 ($p < 0.0001$). Depressive symptoms were also more elevated among the CFS patients compared to the MS group, (20 vs 16, $p < 0.005$), or healthy controls, (20 vs 9, $p < 0.0001$).

TABLE I.—ASSESSMENT OF FATIGUE, SLEEP AND DEPRESSION IN CHRONIC FATIGUE PATIENTS AND CONTROLS*

Group (*N*)	Chronic fatigue syndrome [Group A] (72)	Multiple sclerosis [Group B] (57)	Healthy controls [Group C] (40)	*p*
Age	40 ± 14	44 ± 11	32 ± 10	A = B A > C $F = 6.14$, $p < 0.01$
% Female	64%	77%	70%	A = B = C
FSS	6.1 ± 0.8	5.1 ± 1.4	2.8 ± 1.2	A > B, $F = 25.5$, $p < 0.0001$ A > C, $F = 218$, $p < 0.0001$ df = 1
CES-D	20 ± 10	16 ± 11	9 ± 7	A > B, $F = 8.3$, $p < 0.005$ A > C, $F = 39.3$, $p < 0.0001$ df = 1
Sleep disturbance score†	21 ± 8	18 ± 6	15 ± 5	A > B, $F = 4.5$, $p < 0.04$ A > C, $F = 13$, $p < 0.0005$ df = 1

*Group A refers to chronic fatigue patients; Group B includes patients with multiple sclerosis, a neurologic disorder in which fatigue is frequent; Group C includes healthy volunteers unfamiliar with the clinical study. FSS refers to the fatigue severity scale which is scored from 1 (no fatigue) to 7 (severe fatigue); CES-D depression scale is scored from 0 to 60 with > 15 indicating high depressive symptomatology. The sleep disturbance score was generated from computing 8 of the 14 questions on the St Mary's Sleep Questionnaire with a 1–6 scale in which a higher score indicates greater sleep disturbance. Data is expressed as the arithmetic mean ± SD.

†The sleep disturbance score was calculated in 69 of Group A, 29 of Group B, and 20 of Group D.

To determine the relative contribution of fatigue and depressive symptoms to sleep disturbance, the correlations between these measures was assessed. For the entire set of CFS, MS, and healthy control subjects the sleep disturbance score was significantly correlated with fatigue severity ($r = 0.22, p < 0.002$). The sleep disturbance score was also significantly correlated with the CES-D measure of depressive symptoms ($r = 0.29$, $p < 0.0001$). However, these levels of correlation were sufficiently small that neither depressive symptoms nor fatigue severity contributed to more than 10% of the variance of sleep disturbance. Furthermore, when the CFS subgroup was analyzed only depressive symptoms significantly correlated with sleep disturbance, ($r = 0.26$, $p < 0.03$). Again, despite the statistical significance, the level of correlation between depressive symptomatology and sleep disturbance is such that even in the CFS group, only 7% of the variance in sleep disturbance can be attributed to depressive symptoms.

Polysomnography findings

To determine whether subjective sleep complaints in CFS were associated with objective abnormalities on polysomnography, 16 CFS patients underwent overnight sleep recordings. The polysomnography group had a somewhat higher sleep disturbance score than the other chronic fatigue patients ($F = 5.78$, $p < 0.05$). Patients selected for polysomnography also had a high mean CES-D score, 25 ± 9, but this was not significantly different from those CFS patients who did not undergo polysomnography (21 ± 11, N.S.). Eleven of the polysomnography group had CES-D scores greater than 15 and underwent psychiatric interview. A diagnosis of concurrent major depression was confirmed in six patients, panic disorder in one, and no AXIS 1 disorder in the remaining four.

Polysomnographic findings for the 16 chronic fatigue patients studied are shown in Table II. The sleep efficiency (ratio of number of hours of sleep documented on polysomnography to number of hours in bed) for the group was poor, 80%. In 10 of the 16 patients, polysomnography revealed abnormalities of potential clinical significance. Two patients met criteria for sleep apnea (more than five apneas or hypopneas per hour) [10]. One had 29 disordered breathing events per hour (DBR) with a mean minimum oxygen desaturation of 54%; the other had 61 DBR with a mean minimum oxygen desaturation of 78%. Eight patients had periodic leg movements associated with arousal. In four they were sufficiently frequent, greater than 90 times during the night, (463, 146, 94, and 93 respectively) to meet criteria for the clinical diagnosis of periodic leg movement disorder [10]. Three other patients had excessive daytime sleepiness with MSLTs of 5.5 min or less. Of these three, two patients had one or more episodes of REM sleep onsets. Both complained of persistent excessive somnolence. Another patient, with similar symptoms of daytime sleepiness, had a MSLT of 8.5 min, but she experienced a total of three REM sleep onset episodes. This patient was subsequently found to be DR2 positive and is considered to have narcolepsy. However, neither she nor the other patients with shortened MSLT had cataplexy, sleep paralysis or hypnogogic hallucinations.

Two patients had alpha wave intrusions during slow wave sleep. One of these patients also had periodic movement disorder while the other patient had no other polysomnographic abnormality. Of the six patients with major depression, two had shortened REM latencies (≤ 60 min).

TABLE II.—CLINICAL CHARACTERISTICS OF PATIENTS UNDERGOING POLYSOMNOGRAPHY*

Patient number	Age/sex	Duration of fatigue (months)	Sleep efficiency sleep abnormality	Past medical history	Psychiatric diagnosis	Sleep diagnosis
1	72/M	15	84%	none	Major depression	Normal
2	49/F	180	67% PLM 463 per hr	none	PMD/ panic disorder	PLM disorder
3	46/M	6	83% PLM 146 per hr	Lyme disease	Not done	PLM disorder
4	45/M	60	92% MSLT 5.5	Lyme disease	Normal	Excessive day time sleepiness
5	34/F	168	62% None	Cerebral palsy	Major depression	Normal
6	57/M	24	89% 61 DBE † MSLT 4.7	none	Major depression	Obstructive sleep apnea
7	60/M	12	87% 29 DBE ‡	none	Not done	Obstructive sleep apnea
8	56/F	12	58% none	none	Major depression	Normal
9	23/F	15	95% 90 PLM	none	Major depression	PLM disorder
10	16/F	12	95% 3 REM SO MSLT 8.5	Aseptic meningitis	Normal	Narcolepsy
11	47/F	240	64% none	none	Not done	Normal
12	32/M	96	79% MSLT 5.2	none	Not done	Excessive day time sleepiness
13	30/F	92	89% alpha wave intrusion	none	Normal	PLM disorder & Alpha wave intrusion
14	54/M	48	98% none	none	Normal	Normal
15	31/F	12	82% alpha wave intrusion	none	Normal	Alpha wave intrusion
16	19/F	12	53% none	none	Major depression	Normal

*MSLT refers to multiple sleep latency test; PLM, periodic leg movements associated with arousals; alpha, alpha wave intrusions as defined by Moldofsky [11], DBE, disordered breathing events.

† associated with a mean minimum oxygen desaturation of 75% ‡ associated with mean minimum oxygen desaturation of 54%, REM SO, REM sleep onsets (a finding seen in narcolepsy).

DISCUSSION

In this preliminary study, subjective reports of sleep and associated symptoms of depression and fatigue were compared in CFS to another disease control group, MS patients with fatigue, and to healthy volunteers. CFS patients had significantly

elevated sleep disturbance, depression, and fatigue compared to the two control groups. This observation is particularly striking since MS is a well recognized cause of persistent severe fatigue [12–14].

Sleep disturbance in CFS was not significantly correlated with fatigue severity. In contrast, the correlation between sleep disturbance and depressive symptoms did reach statistical significance. The correlation between sleep disturbance and depressive symptoms in the CFS patients was only 0.26 which suggests that depressive symptoms could account for 7% of the variance of sleep disturbance. The overlap of depressive symptoms with sleep disturbance underscores the need to consider psychological factors associated with CFS.

To confirm the subjective reports of sleep difficulty in CFS, 16 CFS patients who included sleep difficulty among their major symptoms were additionally evaluated with polysomnography. Ten of the 16 (62.5%) had associated pathophysiologic abnormalities of sleep which may have contributed to their fatigue and sleep symptoms. Although the precise causal relationship between fatigue, sleep irregularity, and other CFS symptoms will require additional investigation, the polysomnographic studies clearly revealed a variety of clinical disorders of sleep. These included periodic movement disorder, excessive daytime sleepiness, narcolepsy, and apnea. Two patients had alpha wave intrusion. This latter finding has been associated with fibromyalgia [11], a condition which overlaps considerably with CFS [15, 16]. The lack of polysomnographic data on the healthy controls limits the ability to generalize from these findings. However, the sleep studies did reveal that several of the CFS patients met established criteria for specific sleep disorders, a finding which suggests that in some patients in whom fatigue is attributed to CFS, a treatable polysomnographic disorder of sleep is present. For example, as a direct result of polysomnography the diagnosis of CFS in one patient was changed to narcolepsy. This patient subsequently had dramatic improvement with appropriate pharmacologic treatment. In the other patients, the inter-relationship of their chronic fatigue and sleep abnormality was less straight-forward. For example, of the two patients treated for sleep apnea one had significant improvement while the other had only a partial therapeutic response, possibly due in part to refractory concurrent depression.

Consistent with the elevated depression symptom levels in CFS was the finding that among the group of sixteen patients studied with polysomnography six were diagnosed on psychiatric interview with major depression. However, only two patients had shortened REM latencies, a polysomnographic finding noted in depression [17]. Nonetheless, any evaluation of sleep and fatigue in these patients should also consider possible associated psychological factors such as depression. In the current study no single sleep abnormality was found to be characteristic of chronic fatigue suggesting that in addition to psychological factors a variety of sleep disorders might in a susceptible individual contribute to CFS.

In conclusion, in addition to severe fatigue and frequent depressive symptomatology, patients with chronic fatigue report considerable disturbance of sleep. Problems with sleep may play a larger role in CFS than has been previously recognized, and this should be kept in mind when evaluating such patients.

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