Subjective and Objective Sleepiness in Monozygotic Twins Discordant for Chronic Fatigue Syndrome

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Study Objective: To examine the association of chronic fatigue syndrome (CFS) with measures of objective and subjective sleepiness.
Design: Monozygotic co-twin control study.
Setting: Academic medical center.
Patients and Participants: Twenty monozygotic twin pairs discordant for CFS.
Interventions: N/A.
Measurements and Results: All twins completed an Epworth Sleepiness Scale (ESS), 4 Stanford Sleepiness Scales (SSS), and underwent a standard 4-nap multiple sleep latency test. We compared the ESS scores, average SSS scores, and average sleep latency in CFS and healthy twins. The CFS twins reported more sleepiness as measured by mean scores on the ESS (10.9 vs 8.2; 95% confidence interval [CI] = 0.3–5.5; P = .03) and the SSS (3.4 versus 2.1; 95% CI = 0.7–1.9; P < .001). The mean sleep latency on the Multiple Sleep Latency Test was not significantly different between the CFS and healthy twins (8.9 vs 10.0 minutes; 95% CI -4.4–1.7; P = .33). Mean SSS scores increased among the CFS twins and decreased among healthy twins from nap 1 to nap 4 (P < .001). The individual ESS scores and mean sleep latencies on the Multiple Sleep Latency Test were negatively correlated for all the twins (Pearson's r = -0.40; P = .01), with a slightly stronger association among the healthy twins (Pearson's r = -0.42, P = .07) than the CFS twins (Pearson's r = -0.36, P = .15).
Conclusions: CFS twins reported significantly more subjective sleepiness than their healthy co-twins despite similar nonpathologic mean sleep latencies on the Multiple Sleep Latency Test. Patients with CFS may mistake their chronic disabling fatigue for sleepiness.
Key Words: chronic fatigue syndrome, twins, sleep, Multiple Sleep Latency Test, Epworth Sleepiness Scale, Stanford Sleepiness Scale
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INTRODUCTION

CHRONIC FATIGUE SYNDROME (CFS) IS A HETEROGENEOUS DISORDER CHARACTERIZED BY EXCESSIVE FATIGUE LASTING AT LEAST 6 MONTHS IN THE ABSENCE OF A PHYSICAL OR PSYCHIATRIC ETIOLOGY.[1] Unrefreshing sleep, a symptom criterion for CFS, may result in excessive daytime sleepiness.[2] Sleepiness, feeling unrested on rising, and diverse sleep-related symptoms are common complaints among patients with CFS.[3-5] Although primary sleep disorders are often overlooked in patients presenting with presumed CFS,[3,6] they are unlikely to fully account for the sleepiness experienced by individuals with this illness.[7]

Many measures of both subjective and objective sleep are genetically influenced. For example, twin studies have demonstrated strong heritabilities for self-reported daytime napping, habitual bedtime, sleep duration, and sleep quality.[8] Similarly, polysomnograms (PSGs) in twins have shown that body movements, stage 2 sleep, slow-wave sleep (stages 3 and 4), and rapid eye movement sleep density are largely genetically determined.[9-12] Sleepiness may also be under genetic control.[13] Taken together, these investigations underscore the influence of heritable factors on sleep. Previous studies of sleepiness among CFS patients have not controlled for such influences.[14]

For this analysis, we used a co-twin control methodology, which is a matched-pair comparison that adjusts for many genetic and environmental factors not generally considered in case-control studies.[15] This design offers a powerful alternative to traditional approaches that compare CFS patients to healthy control subjects. We address 3 questions: (1) Do subjective and objective measures of sleepiness differ between monozygotic twins with CFS and their healthy co-twins? (2) Do objective findings correlate with subjective reports in CFS and healthy twins? and (3) Is a specific pattern of sleepiness associated with CFS? We hypothesized that twins with CFS would report more sleepiness than their healthy co-twins but that objective measures of sleepiness would be similar within pairs.

METHODS

CFS Twin Registry Construction and Recruitment

Twins were recruited for participation in a CFS Twin Registry through patient support-group newsletters (58%), electronic bulletin board notices (15%), physicians and researchers familiar with CFS (11%), twin organizations and researchers (6%), relatives and friends (3%), and other sources (8%). We mailed 600 intake questionnaires; 426 (71%) were returned, and complete intake data were available for both members of 193 twin pairs. Each twin filled out a booklet that included data on demographics, zygosity, habits, lifestyle, distress, physical health conditions, and a checklist of the symptoms of CFS.[1] For the nonfatigued twin, we used a control version of the booklet without the questions pertaining to fatigue. Informed consent was obtained

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on all Registry participants in accordance with our institution's Human Subjects Office. A more complete description of the Registry can be found elsewhere.[16]

Participant Selection

From the CFS Twin Registry, 22 sets of monozygotic twins discordant for CFS were chosen for a 7-day in-person evaluation based on registry information and additional telephone screenings. Twins were required to (1) be at least 18 years of age; (2) be reared together; (3) be discordant for CFS (1 twin met the Centers for Disease Control and Prevention CFS criteria, the other was healthy); (4) be negative for HIV; (5) abstain from alcohol and caffeine and, based on their personal physicians' advice, discontinue all medications at least 2 weeks prior to the evaluation; and (6) travel to Seattle together.

To determine if a twin met CFS criteria, we used responses to the CFS symptom checklist, diagnoses generated by the Diagnostic Interview Schedule (Version III-A),[17] and information from review of his or her medical records. The same inclusion and exclusion criteria (eg, body-mass index, specific psychiatric disorders) and review processes were applied to the fatigued and healthy twins. Medical records covering the last 5 years were reviewed by a physician knowledgeable about CFS for exclusionary medical conditions. A psychologist and an infectious disease specialist also independently reviewed the twins' medical charts to verify health status and approve twins for participation. Prior to the scheduled visit, we confirmed that the ill twin still met CFS criteria and the control twin was healthy and not fatigued.

Zygosity was initially determined using validated self-report methods,[18,19] then confirmed by restriction fragment length polymorphisms. DNA was extracted from peripheral blood mononuclear cells, digested with *Hae lll*, separated by agarose electrophoresis, blotted onto a nylon membrane, and hybridized with 6 variable-number tandem repeat probes to determine monozygosity with a certainty of over 99.9%.[20]

Demographics and Psychiatric Disorders

Demographic variables available in the CFS registry included age in years, sex, race, marital status, and employment. The Diagnostic Interview Schedule (Version III-A) was administered via telephone interview to Registry participants to determine current and lifetime psychiatric diagnoses such as major depression. This instrument assigns diagnoses by computer algorithm based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Version III-Revised*.[21] A trained research assistant administered modules on major depression, dysthymia, generalized anxiety, panic, agoraphobia, posttraumatic stress disorder, mania, bipolar affective disorders, schizophrenia, eating disorders, somatization, and substance abuse or dependence.

Objective Sleep Measures

Travel to Seattle occurred at least 4 nights prior to the acclimatization night, 5 nights prior to the PSG night, and 6 nights prior to the multiple sleep latency test (MSLT). We performed a research PSG with a full recording montage for 2 nights (an acclimatization night followed by the PSG). Measured parameters included central and occipital electroencephalogram, left and right electrooculogram, mental and submental electromyography, chest and abdominal respiratory effort (piezoelectric belts), nasal and oral airflow (thermistor), left and right anterior tibialis electromyography, pulse oximetry, electrocardiogram, body position, and snoring (microphone). Data were recorded on an ALICE 3™ digital system (Respironics/Healthdyne Technologies, Murrysville, Penn). A single technician blinded to illness status used Rechtschaffen and Kales criteria[22] to score the PSGs for clinically significant sleep disorders, sleep fragmentation, and abnormalities in sleep architecture, latency, and efficiency.

The morning after the PSG, twins underwent a standard 4-nap MSLT that included a central and occipital electroencephalogram, left and right electrooculogram, and mental and submental electromyography, snoring microphone, and electrocardiogram.[23] Sleep latency was defined as the time between lights out and any epoch of sleep. Twins were awoken after 3 consecutive epochs of any stage of sleep. The MSLT values were averaged for each person across all 4 naps (ie, 4-nap average), and were also evaluated longitudinally as repeated measurements per person over time.

Subjective Sleep Measures

The twins completed the Epworth Sleepiness and Stanford Sleepiness Scales; both are well-known validated instruments for assessing subjective sleepiness.[24,25] Just before beginning the MSLT, each twin completed a standard 8-item Epworth Sleepiness Scale that inquired about how likely they were to doze or fall asleep recently in any of 8 situations (0 = would never doze, 3 = high chance of dozing). Scores over 10 indicate significant subjective sleepiness.[24] In addition, before each of the 4 MSLT naps, twins filled out the 7-item Stanford Sleepiness Scale. In contrast to the Epworth, which measures recent propensity to sleep, the Stanford Sleepiness Scale measures feelings of sleepiness at a particular time;[25] higher scores signify greater subjective sleepiness. As with the MSLT, the Stanford Sleepiness Scale was evaluated as each person's overall 4-nap average and also as longitudinal measurements over time. Finally, to identify sleep deprivation as a potential cause of daytime sleepiness, all twins recorded total nightly sleep time on a 2-week sleep diary prior to coming to Seattle. The sleep-diary information was summarized as the proportion of nights each twin reported getting at least 7 hours of sleep.

Statistical Analysis

Initial descriptive statistics used matched pair *t* tests and McNemar tests to compare means and proportions between CFS and healthy twins for demographic factors, depression, and self-reported sleep from the sleep diary. We used 2-level mixed-effects linear regression models [26] to compare the Epworth Sleepiness Scale, the 4-nap averages for the Stanford Sleepiness Scale, and the 4-nap averages for the MSLT in CFS and healthy twins, including a random effect for twin pair and a fixed effect for CFS status. This technique accommodates the nested structure of the data (2 people per twin pair). We examined preliminary models adjusting for depression and the proportion of nights with at least 7 hours of sleep as reported in the sleep diary. The CFS fixed effect was included in all models, but the depression and sleep-diary fixed effects were only included in the final models if they were significant in the preliminary analyses. We calculated Pearson correlation coefficients to evaluate the correla-

tion of objective sleepiness (MSLT 4-nap averages) and subjective sleepiness (Epworth Sleepiness Scale and Stanford Sleepiness Scale 4-nap averages). Coefficients were calculated for the entire group and for CFS and healthy twins separately. Mean time to sleep onset was further evaluated by applying Cox survival analysis with the robust variance estimator to the MSLT 4-nap averages.[27]

To compare the longitudinal sleepiness measures (MSLT and Stanford Sleepiness Scale) across all 4 naps, we used 3-level mixed-effects linear regression models (4 naps per person, 2 people per twin pair), including categorical fixed effects for CFS status and nap and random effects for twin pair and individual within twin pair. As described for the Epworth Sleepiness Scale and 4-nap averages, we examined preliminary models adjusting for depression and the sleep diary information, as well as the CFS by nap interaction. The CFS and nap fixed effects were included in all models, but the depression, sleep diary, and interaction effects were included in the final models only if they were significant in the preliminary analyses.

We limited our analysis to twin pairs in which each twin had complete data on all sleepiness measures. One CFS twin and 1 healthy twin had missing sleepiness data. After excluding the twins with missing data and their co-twins, there were 20 complete pairs left for this analysis. All analyses were completed for women alone and for the entire sample; since the inclusion of the 2 male pairs did not alter our results, we present findings for the entire sample. Analyses were conducted in Stata version 7.0 (STATA Inc., College Station, Tex), SAS version 8.2 [28] and MIXOR.[29]

RESULTS

Demographics, Depression, and Sleep Diary

The twins were on average 41 years old, 18 pairs (90%) were female, and all were White. Fifty-seven percent of both CFS and healthy twins were married. CFS twins had higher frequencies of unemployment (57% vs 10%, $P = .26$) and current depression (19% vs 0%, $P < .001$). According to the sleep diaries, 39% of the CFS and 48% of the healthy twins reported sleeping at least 7 hours each night in the 2 weeks prior to the MSLT, but this difference was not statistically significant ($P = .33$).

Table 1—Group means for objective and subjective sleepiness measures in CFS and healthy twins

Sleepiness Measure	CFS Twins	Healthy Twins	(95% CI)	*P* value
Objective				
MSLT sleep latency, *min*	8.9	10.0	(-4.4 – 1.7)	.33
Subjective				
Stanford Sleepiness Scale, *score*	3.4	2.1	(0.7 – 1.9)	< .001
Epworth Sleepiness Scale, *score*	10.9	8.2	(0.3 – 5.5)	.03

CI refers to confidence interval for difference between chronic fatigue syndrome (CFS) and healthy group means; MSLT, Multiple Sleep Latency Test.

Objective Measures of Sleepiness

As shown in Table 1, mean MSLT 4-nap averages in the CFS and healthy twins were similar (8.9 vs 10.0 minutes; $P = .33$). Likewise, Kaplan-Meier survival curves did not differ in mean time to sleep onset for the CFS and healthy twins ($P = .28$; Figure 1). In the longitudinal analysis, mean sleep latency times decreased from nap 1 to nap 3 and increased from nap 3 to nap 4 in both groups (Figure 2). Except for nap 4, CFS twins had shorter sleep latencies than the healthy twins in the longitudinal analysis, but these differences were not significant ($P = .22$). Depression, the CFS by nap interaction, and the sleep diary information were not significantly associated with sleep latency in preliminary models for the 4-nap averages or the longitudinal data and were not included in the final regression models. On the research PSG, the overall mean total sleep time in both groups was 6.3 hours. With the exception of 1 CFS twin who had obstructive sleep apnea (Ball, in press), no other sleep disorders were detected in either group.

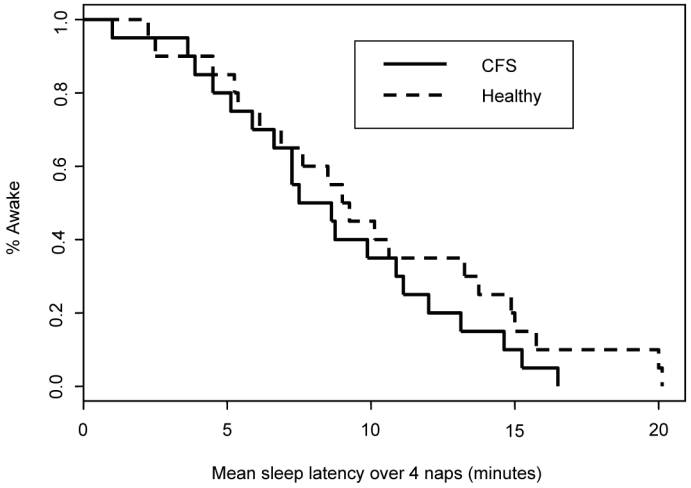

Figure 1—Kaplan-Meier survival curves for twins with chronic fatigue syndrome (CFS) and healthy twins.

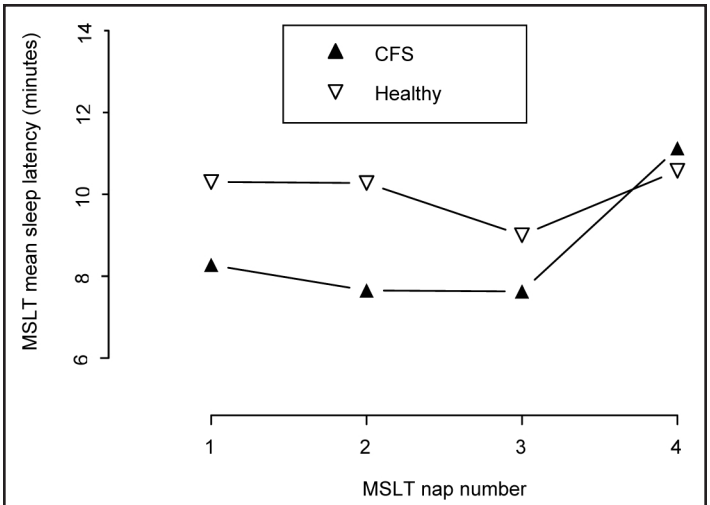

Figure 2—Mean sleep latency on the Multiple Sleep Latency Test (MSLT) for twins with chronic fatigue syndrome (CFS) and healthy twins by nap number.

Subjective Measures of Sleepiness

CFS twins reported significantly higher scores for all subjective sleepiness measures compared to healthy twins. As seen in Table 1, CFS twins reported more sleepiness on the Epworth Sleepiness Scale (mean scores: CFS = 10.9 vs healthy = 8.2; P = .03) and Stanford Sleepiness Scale (mean 4-nap averages: CFS = 3.4 vs healthy = 2.1; $P < .001$). CFS twins were subjectively sleepier than their healthy co-twins before all 4 naps, and in the longitudinal regression analysis, mean Stanford Sleepiness Scale scores increased among the CFS twins and decreased among healthy twins from nap 1 to nap 4 ($P < .001$) (Figure 3). As with the MSLT, depression, the CFS by nap interaction, and the sleep diary information were not significantly associated with any of the subjective sleepiness scores and were not included in the final regression models.

Correlation of Subjective and Objective Measures of Sleepiness

The Epworth Sleepiness Scale was negatively associated with the MSLT 4-nap average for all twins combined (Pearson's r = -0.40; P = .01). A subgroup analysis showed these measures tended to be slightly less correlated among the CFS twins (r = -0.36; P = .15) than the healthy twins (r = -0.42; P = .07). The Stanford Sleepiness Scale 4-nap average and MSLT 4-nap average did not show significant correlation for all twins combined (r = -0.21; P = .21), the CFS twins (r = -0.16; P = .51), or the healthy twins (r = -0.15, P = .54).

DISCUSSION

We found that CFS twins experienced more subjective sleepiness than their healthy co-twins as measured by both their recent propensity to fall asleep (Epworth Sleepiness Scale) and current feelings of sleepiness (Stanford Sleepiness Scale). Furthermore, our CFS twins had a mean Epworth Sleepiness Scale score that was in the abnormal range, an observation not explained by either self-reported (sleep diary) or objectively documented (PSG) differences in sleep duration or restriction between the ill and healthy twins. Although these subjective differences are of questionable clinical significance, they do point toward a heightened sense of sleepiness among the CFS twins.

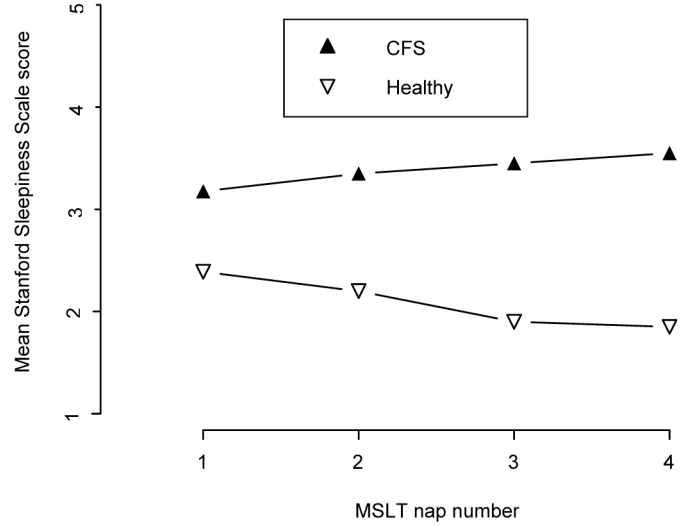

Figure 3—Stanford Sleepiness Scale scores for twins with chronic fatigue syndrome (CFS) and healthy twins by nap number.

Traditionally, fatigue is defined as weariness or exhaustion from labor, exertion, or stress, whereas sleepiness is a sluggish lethargic state associated with a readiness to fall asleep. Given only the subjective data derived from the Epworth and Stanford Sleepiness Scales, we could not establish whether the sleepiness reported by the CFS twins was attributable to their use of the terms *fatigue* and *sleepiness* interchangeably or if CFS was associated with true objective sleepiness. The MSLT, which was performed to answer this question, revealed that CFS and objective sleepiness were not associated.

The CFS twins, however, had slightly lower, though not statistically different, mean sleep latencies than their healthy co-twins. Although pathologic sleepiness (mean sleep latency under 5 minutes) was not observed, both the CFS and healthy twins had MSLT values less than the 11.5 minutes reported for normal subjects.[30] This finding might be explained by sleep restriction, as documented by short sleep durations on the both the research PSG and the 2-week sleep diary for the CFS and healthy co-twins.[31] Other than 1 CFS patient with obstructive sleep apnea, no sleep disorders were present in either group to explain this mild sleepiness.

The Epworth Sleepiness Scale correlated with the individual mean MSLT sleep latency for all twins, a finding consistent with published normative data.[32] Independent examination of the groups revealed this association was slightly stronger for the healthy twins than the CFS twins. We have previously demonstrated a similar divergence in CFS between subjective and objective measures of other aspects of sleep such as insomnia.[7] Furthermore, consistent with data on normal subjects[33] and time-of-day-variation of MSLT sleep latency,[34] self-reported sleepiness (as measured by the Stanford Sleepiness Scale) decreased early in the day among the healthy twins but not the CFS twins. Again, the more sustained subjective sleepiness reported by the CFS group was not confirmed by the MSLT, which revealed the expected biphasic circadian pattern of sleepiness for both groups. This finding suggests that CFS may be associated with an altered circadian pattern of subjective sleepiness. Alternatively, persons with CFS may experience a generally heightened perception of sleepiness or may be unable to distinguish fatigue and sleepiness, perhaps due to their severe underlying fatigue.

This co-twin control study has a number of limitations. First, CFS twins had a higher prevalence of current depression than their healthy co-twins, and depression is known to cause disorders of initiating and maintaining sleep and sleepiness.[35,36] However, depression was not associated with our outcomes. Second, solicitation by advertisement resulted in a volunteer sample of twin pairs with the potential for ascertainment problems. Unfortunately, the more desirable strategy of identifying twins from an American population-based twin registry is not possible. Third, although we examined data from the sleep diaries and the twins arrived in Seattle at least 5 days prior to the sleep studies, chronic sleep habits or acute sleep disruptions resulting from travel (eg, jet-lag) may have affected our data in unknown ways. Fourth, we cannot rule out subtle and unmeasured differences between twin pairs in objective sleep parameters despite our use of the co-twin control design. Lastly, studies such as this cannot address questions of mechanism and etiology, such as the nature of the biologic underpinnings of perceptional differences in sleepiness. A related caveat is that passive standard examinations of neurobiologic processes may be insensitive to disorders

like CFS in which abnormalities may only become apparent when active, challenging, or stressful tasks are performed.

In summary, our twins with CFS experienced greater subjective sleepiness than their healthy co-twins despite similar mean sleep latencies. Both the CFS and healthy twins had reduced, though nonpathologic, MSLT values potentially resulting from sleep deprivation. Although primary sleep disorders should be ruled out in many patients suspected of having CFS, clinicians also should be aware that patients with this disorder may report both chronic disabling fatigue and subjective sleepiness. Future studies should examine the mechanisms of the discrepancy between self-reported and measured sleep parameters in CFS and consider the use of challenge protocols. Sleep-challenge protocols, including partial or total sleep deprivation, may unveil unanticipated and previously undetected sleep disruption in CFS.

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