Comparison of Subjective and Objective Measures of Insomnia in Monozygotic Twins Discordant for Chronic Fatigue Syndrome

Nathaniel F. Watson, MD; Vishesh Kapur, MD, MPH; Lester M. Arguelles, MS; Jack Goldberg, PhD; Douglas F. Schmidt, PhD; Roseanne Armitage, PhD; Dedra Buchwald, MD

1Department of Neurology and Sleep Disorders Center, University of Washington; 2Department of Medicine and Sleep Disorders Center, University of Washington; 3Epidemiology and Biostatistics Division, University of Illinois at Chicago; 4Department of Epidemiology, University of Washington and VA Vietnam Era Twin Registry, Seattle, WA; 5Virginia Mason Sleep Disorders Center, Seattle, WA; 6Department of Psychiatry and Sleep Study Unit, University of Texas Southwestern Medical Center at Dallas; and the 7Department of Medicine, University of Washington

INTRODUCTION

CHRONIC FATIGUE SYNDROME (CFS) IS A HETEROGENEOUS DISORDER OF EXCESSIVE FATIGUE OF GREATER THAN 6 MONTHS’ DURATION IN THE ABSENCE OF A CLEAR PHYSICAL OR PSYCHIATRIC ETIOLOGY.1 Unrefreshing sleep is 1 of 8 possible symptom criteria for this syndrome.1 Many individuals with CFS suffer from insomnia, defined as a disorder of initiating and maintaining sleep.2 The inability to fall or stay asleep, inadequate sleep time, feeling unrested on rising, and sleepiness are among the most frequent complaints of CFS patients.3-5 In prior studies, however, the unrefreshing sleep suffered by patients with CFS has typically been unconfirmed by objective means or its association with objective abnormalities was poorly described. For example, CFS patients have been shown to exhibit polysomnographic characteristics of poor sleep, such as low sleep efficiency and more time awake after sleep onset,6 but the precise relationship of these objective findings to perceptions of sleep were not examined. In some cases, primary sleep disorders have been detected in these patients.3,4 Twin studies of sleep indicate that subjective reports of sleep, including daytime napping, habitual bedtime, sleep duration, and subjective sleep quality, exhibit strong heritability.7 Polysomnography (PSG) in twins also has shown that body movements, stage 2, slow wave sleep (stages 3 and 4), and rapid eye movement (REM) density are all largely genetically determined.8-11 Genetic similarities make twin studies useful for detecting subtle environmental effects when studying diseases of unknown etiology; when the appropriate control group is unknown; or when the domain of interest, such as sleep, is under genetic influence.12 The purpose of the current study was to examine objective and subjective measures of sleep disturbances in monozygotic twins where 1 twin had CFS and the other twin did not. This co-twin control design effectively controls for genetic variability in sleep disturbances. We hypothesized that CFS twins would have more insomnia-related complaints than their healthy co-twins but that objective measures of sleep quality would not differ substantially.

METHODS

Registry Construction and Subject Recruitment

Twins were recruited through patient support-group newsletters (58%), electronic bulletin board notices for CFS (15%), physicians and researchers familiar with CFS (11%), twin organizations and researchers (6%), relatives and friends (3%), and other sources (8%). A total of 600 twins were mailed an intake questionnaire, 426 (71%) were returned, and complete intake data were available for both members of 193 twin pairs. Each twin filled out a questionnaire on demographics, zygosity, habits, lifestyle, distress, physical health conditions, and a checklist of the symptoms of CFS.1 For the nonfatigued twin, a control version of the intake questions was used that did not reference fatigue. A more complete description of the Registry can be found elsewhere.13 Informed consent was obtained on all Registry participants in accordance with our institution’s Human Subjects Office.

Disclosure Statement

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Address correspondence to: Nathaniel F. Watson, MD, University of Washington Sleep Disorders Center, Box 359803, 325 Ninth Avenue, Seattle, WA 98104-2499; Tel: 206-731-4999; Fax: 206-731-5657; E-mail: nwatson@u.washington.edu


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The Diagnostic Interview Schedule Version III-A,14 a structured interview based on the Diagnostic and Statistical Manual of Mental Disorders, Version III-Revised,15 was administered by telephone to all Registry twins. Sections included major depression, dysthymia, generalized anxiety, panic, agoraphobia, posttraumatic stress disorder, mania, bipolar disorders, schizophrenia, eating disorders, somatization, and substance abuse and dependence.

Selection of the Clinical Sample

From the Registry, 22 sets of monozygotic twins were chosen for a 6-day evaluation. Twins were required to: 1) be at least 18 years of age; 2) have been reared together; 3) be discordant for CFS (ie, 1 twin met the Centers for Disease Control and Prevention criteria and the other was healthy and denied chronic fatigue); 4) provide evidence of a recent negative HIV-1 antibody test; 5) discontinue alcohol, caffeine, and all medications known to affect sleep, cognition, and immune function at least 2 weeks prior to the evaluation; and 6) be able to travel to Seattle at the same time.

Both the ill and the healthy twins were rigorously screened. CFS was defined in accordance with the Centers for Disease Control and Prevention CFS criteria.1 For fatigued twins, the symptom checklist and diagnoses generated by the Diagnostic Interview Schedule were used to determine whether CFS criteria were initially met. Next, all medical records for the previous 5 years were reviewed by an internist for exclusionary conditions. Health issues were resolved by telephone or physician contact. Laboratory tests were performed prior to the evaluation. A psychologist and an infectious disease specialist independently reviewed the charts and approved the twins for participation. Just before the scheduled visit, screening questions were readministered to document that the ill twin still met CFS criteria and the co-twin was healthy. Monozygosity was initially determined using previously validated self-report methods16,17 and confirmed using molecular biology techniques.18

Measures of Sleep

The assessment of sleep and insomnia had 3 components: a Sleep Disorders Questionnaire, 2 nights of PSG, and a post-PSG survey of sleep. Each is described in detail below.

Sleep Questionnaire. Both twins filled out a 175-item Sleep Disorders Questionnaire that explores a person’s subjective themes or beliefs regarding sleep.19 The following 8 items were selected for use in this study based on their relevance to insomnia: “I often have a poor night’s sleep,” “I wake up often during the night,” “My night’s sleep is often restless and disturbed,” “I feel that my sleep is abnormal,” “I have trouble getting to sleep at night,” “I have been unable to sleep at all for several days,” “I feel that I have insomnia,” and “I take a prescription drug to help me sleep.” The response categories for these items are 1 = disagree or never, 2 = rarely, 3 = sometimes, 4 = usually, 5 = true or always.

Polysomnography. PSG with a full recording montage was performed during 2 nights, including central and occipital electroencephalogram, left and right electrooculogram, mental and submental electromyogram, chest and abdominal respiratory effort, nasal and oral airflow, left and right anterior tibialis electromyogram, pulse oximetry, electrocardiogram, body position, and microphone-detected snoring. Data were recorded on an ALICE 3TM digital system (Respiromics/Healthdyne Technologies, Murrysville, PA 15668-8550). Visual PSG scoring was performed according to standard Rechtschaffen and Kales criteria by a single technician blinded to illness status.20 All data were derived from the second night, with the first night being used for acclimatization to the sleep-lab environment. Twins had traveled to Seattle at least 4 nights prior to the acclimatization night and 5 nights prior to the study night. The following sleep-related parameters were calculated: total sleep time, sleep latency, REM latency, sleep staging, sleep efficiency, hypnogram awakenings, arousal number, and arousal index.

Sleep latency was defined as lights out to the first epoch of any 3 consecutive epochs of sleep or to the first epoch of stage 2, 3, 4, or REM, whichever came first. REM latency was defined as sleep onset to the first epoch of REM sleep. Hypnogram awakenings represented the total number of awakenings for the night as calculated by a sleep medicine physician (NFW) tallying the number of times the patient went from a stage of sleep to wakefulness for at least 1 epoch, as evident on the post-PSG hypnogram. We also evaluated each twin for clinically significant sleep disorders, such as obstructive sleep apnea or periodic limb movement disorder; none were evident.

Post-PSG Survey. The morning following the PSG night, a brief survey was administered to all twins. This survey asked the twins to subjectively report their total sleep time and the number of times they awakened during the night. In addition, they were asked if they slept well and if they felt rested.

Measurement of Mood

The Positive and Negative Affect Schedule (PANAS)21 was used to obtain a continuous measure of current mood from all twins. This instrument asks subjects to rate the intensity with which they have experienced 20 emotions or feelings within the last 10 minutes from 1 (not at all or very slightly) to 5 (extremely). The responses yield 2 scales: positive and negative affect. The PANAS was used to adjust for mood in the analysis.

Statistical Analysis

Mean levels of the sleep measures in CFS and healthy co-twins were compared using a paired t-test. As an indicator of familial clustering for the continuously distributed objective sleep measures, we used the intraclass correlation coefficient derived from mixed-effects regression modeling for twin data.22 Values of this statistic that are close to 1.0 indicate a strong familial influence on the phenotype. Subjective data from the Sleep Disorders Questionnaire were dichotomized, where twins answering disagree or never or rarely were combined into a single “no” group and twins answering sometimes, usually, or true or always were combined into a single “yes” group. Analysis was performed via the signed-rank test. For categorical measures derived from the post-PSG survey, percentages were estimated in the CFS and healthy co-twins; formal statistical testing used McNemar’s chi-square test. We also repeated all our analyses after using the PANAS scales to adjust for the effects of positive and negative mood. These analyses used regression methods and, since in no case did the adjustment make a difference in the findings, we present only the unadjusted results.

RESULTS

Subject Recruitment and Selection

Of 193 twin pairs screened, 119 (62%) were discordant for 6 or more months of fatigue. Of these, 67 (56%) were monozygotic and had complete data available; however, 14 fatigued twins had a CFS exclusionary psychiatric illness, 4 had a CFS exclusionary medical disorder, 1 had a body mass index greater than 45, and 9 did not meet CFS symptom criteria. In 4 pairs, the nonfatigued twin had a condition exclusionary for CFS (eg, cancer), and 6 additional pairs were excluded for other reasons (eg, inadequate English, pregnancy). Of the 29 remaining pairs in which 1 twin met the criteria for CFS and their co-twin was healthy and denied chronic fatigue, 22 (76%) completed the study, 1 (3%) refused, 2 (7%) could not be scheduled, and 4 (14%) could not discontinue medications. There were no differences in measures of physical or mental functioning as assessed by the SF-36 Health Survey23 between the 22 twin pairs with CFS who traveled to Seattle and the 7 who did not.

Demographic and Clinical Characteristics

The twins’ mean age at the time of the study was 41.4 years, 20 pairs...
were female, and all were white and raised together. There were no differences between the CFS and healthy twins in the proportion that were married (59% vs. 59%). A small, statistically significant difference in the average years of schooling (CFS 14.0 vs. healthy 14.7; \( p \leq 0.05 \)) was noted. The CFS twins had a mean duration of illness of 7.0 years.

**Sleep Questionnaire**

There were significant differences in all 8 measures of insomnia from the Sleep Disorders Questionnaire (Table 1). The largest effects observed were for the use of a prescription drugs for sleep, trouble getting to sleep at night, waking up often during the night, and feelings that sleep is abnormal, poor, restless, and disturbed. More modest differences between twins were noted for the inability to sleep for several days and feelings of insomnia.

**Polysomnography Measures**

Virtually all of the objective measures of sleep obtained from the PSG were remarkably similar in both the CFS and healthy twin pairs (Table 2). For example, the mean total sleep time was 6.3 hours for both the CFS and healthy twins. The overall index of sleep efficiency was virtually identical in the CFS (88.3%) and healthy co-twins (88.6%). Twins with CFS did have a higher percentage of REM sleep than did their co-

### Table 1—Selected subjective measures of sleep from the Sleep Disorders Questionnaire

<table>
<thead>
<tr>
<th>Subjective Measures</th>
<th>CFS Twins (% yes)</th>
<th>Healthy Twins (% yes)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>I wake up often during the night</td>
<td>81.8</td>
<td>31.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>My nights sleep is often restless and disturbed</td>
<td>81.8</td>
<td>19.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I feel that my sleep is abnormal</td>
<td>86.4</td>
<td>9.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I have trouble getting to sleep at night</td>
<td>72.7</td>
<td>22.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I have been unable to sleep at all for several days</td>
<td>18.2</td>
<td>0.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>I feel that I have insomnia</td>
<td>31.8</td>
<td>4.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>I often have a poor nights sleep</td>
<td>86.4</td>
<td>27.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>I take a prescription drug to help me sleep</td>
<td>61.9</td>
<td>0.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Twins answering disagree or never or rarely were combined into a single “no” group; twins answering sometimes, usually, or true or always were combined into a single “yes” group. All statistical tests are signed-rank tests.

### Table 2—Objective measures of sleep obtained from polysomnography

<table>
<thead>
<tr>
<th>Measures</th>
<th>CFS Twins Mean (95% CI)</th>
<th>Healthy Twins Mean (95% CI)</th>
<th>Intraclass Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time (hours)</td>
<td>6.3 (5.9 - 6.7)</td>
<td>6.3 (6.0 - 6.8)</td>
<td>0.74</td>
</tr>
<tr>
<td>Arousal number</td>
<td>111.7 (84.3 - 139.0)</td>
<td>116.1 (88.7 - 143.4)</td>
<td>0.61</td>
</tr>
<tr>
<td>Arousal index (arousals/hour of sleep)</td>
<td>17.9 (13.6 - 22.3)</td>
<td>18.6 (14.2 - 22.9)</td>
<td>0.71</td>
</tr>
<tr>
<td>Hypnogram awakenings</td>
<td>25.9 (20.7 - 31.1)</td>
<td>27.1 (21.9 - 32.4)</td>
<td>0.63</td>
</tr>
<tr>
<td>% Stage 1</td>
<td>83.5 (54.3 - 113.3)</td>
<td>90.6 (61.1 - 121.7)</td>
<td>0.72</td>
</tr>
<tr>
<td>% Stage 2</td>
<td>44.9 (41.4 - 48.4)</td>
<td>49.0 (45.5 - 52.5)</td>
<td>0.21</td>
</tr>
<tr>
<td>% Stage 3-4</td>
<td>19.1 (15.4 - 22.9)</td>
<td>17.5 (13.7 - 21.3)</td>
<td>0.72</td>
</tr>
<tr>
<td>% Stage REM¹</td>
<td>27.3 (24.6 - 30.7)</td>
<td>24.4 (21.3 - 27.5)</td>
<td>0.65</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>88.3 (83.4 - 93.1)</td>
<td>88.6 (83.7 - 93.4)</td>
<td>0.69</td>
</tr>
<tr>
<td>REM sleep latency (min)</td>
<td>63.5 (41.1 - 86.0)</td>
<td>88.0 (65.5 - 110.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>13.6 (7.8 - 19.4)</td>
<td>10.6 (4.8 - 16.4)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

CFS, chronic fatigue syndrome; CI, confidence interval; REM, rapid eye movement

### Table 3—Selected measures from the postpolysomnography survey

<table>
<thead>
<tr>
<th>Measure</th>
<th>CFS Twins (CI)</th>
<th>Healthy Twins (CI)</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do you feel rested now?</td>
<td>68.0% (43.2 - 94.3)</td>
<td>15.0% (0 - 32.1)</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Do you feel you slept well?</td>
<td>42.1% (17.7 - 66.6)</td>
<td>15.0% (0 - 32.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>How many hours do you think you slept last night?</td>
<td>6.2% (5.7 - 6.7)</td>
<td>6.7% (6.2 - 7.2)</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>How many times did you wake up during the night?</td>
<td>2.3% (1.7 - 2.9)</td>
<td>1.9% (1.3 - 2.5)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

CFS, chronic fatigue syndrome; CI = 95% confidence interval; * % no response; 1mean

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**DISCUSSION**

A striking finding in this study was the propensity of the CFS twins to report diverse symptoms of poor sleep in the absence of objective sleep pathology. In particular, they had more complaints compatible with insomnia compared to their healthy co-twins despite a sleep latency that was both normal and similar to that of the healthy twins. Similarly, twins with CFS reported more nighttime awakenings and more disturbed, restless, abnormal, and poor sleep than did their healthy co-twins in spite of similar arousal indexes, sleep efficiencies, sleep architecture, and total sleep time. Finally, the CFS twins were more likely to take prescription drugs to help them fall asleep. These findings agree with previous studies indicating that CFS patients have poor subjective sleep but are inconsistent with reports of increased sleep latency, reduced total sleep time and sleep efficiency, and decreased stage REM sleep in patients with CFS. Our use of a control group that accounts for familial influences on sleep, the discontinuation of medications that interfere with sleep for at least 2 weeks, and the performance of the PSG under the same conditions on the same nights might explain why our findings differ from those of previous investigations.

An increased percentage of REM sleep and a clinical, though not statistically significant, shortening of REM latency was observed in the CFS group. This suggests that increased REM pressure is associated with CFS, either as a predisposing factor or a consequence of the illness. Of interest, previous twin studies have demonstrated that environmental, rather than genetic, influences contribute to REM-stage variability. Possible explanations for increased percentage stage REM in the ill twins include depression and primary sleep deprivation. Short REM latencies, increased REM-sleep density, and an increased percentage of REM sleep have been associated with depression, and depression is common in patients with CFS. Although we controlled for current mood with the PANAS in our analysis, this instrument does not provide diagnostic information. Thus, we cannot completely exclude comorbid major depression as contributing to the increase in REM sleep. These findings deserve further investigation.

Insomniacs tend to underestimate total sleep time and overestimate sleep-onset latency. Individuals with subjective insomnia despite objectively normal sleep are considered to have sleep-state misperception, the cause of which is unknown. The minimal criteria for the diagnosis of sleep-state misperception according to the International Classification of Sleep Disorders-Revised requires a complaint of insomnia despite normal sleep quality and duration. The CFS twins’ insomnia complaints were contrary to their normal sleep latencies, sleep efficiencies, and arousal indexes on PSG. Therefore, although there is not a misperception of sleep duration, as indicated by the CFS twins’ accurate estimation of total sleep time on their post-PSG survey, there is a misperception of sleep quality. As a result, we feel the CFS twins suffer from an element of sleep-state misperception.

Previous studies have suggested that sleep-state misperception may be a transitional state of sleep dysfunction between normal sleep and the disturbed pattern of objective insom-
nia30,32 and may also be associated with metabolic alterations.3 Others have observed that longer periods of wakefulness following sleep onset, greater self-perceived sleep impairment, and current psychopathology influence sleep-time estimation.33 Since beta and gamma activity, which is associated with cognitive processes, is enhanced in insomnia at sleep onset, a recent model of sleep-state misperception has proposed that insomniacs experience a level of information and memory processing that blurs the distinction between sleep and wakefulness and thereby influences perceptions of sleep initiation and duration.34 Taken together, these investigations suggest that psychobiologic abnormalities, sleep quality itself, and psychological factors may all affect the concordance of subjective and objective indexes of sleep.

One aspect of this study that deserves mention is our use of illness-discordant twins. Self-reported data have shown that hereditary factors are important in determining sleep patterns such as daytime napping, habitual bedtime, and sleep duration.3 A significant genetic contribution also has been found in the self-reported problems of trouble falling asleep, trouble staying asleep, waking often, and waking up tired.3 Likewise, twin studies have shown that sleep-onset latencies, awakening measures, sleep length, sleep-stage changes, stage 2 sleep, slow wave sleep (stages 3 and 4), and measures of REM sleep are all under genetic control.3,30,36 The striking similarity of sleep architecture between members of our twin pairs, as reflected by large intraclass correlation coefficients, is particularly noteworthy and likely reflects heritable influences on sleep. Because the co-twin design provides excellent control for background variation of electroencephalographic activity and, hence, maximizes the detection of abnormalities, our study provides strong evidence of sleep-state misperception in CFS.

This co-twin control study has several limitations. First, solicitation by advertisement resulted in a volunteer sample of twin pairs with the potential for ascertainment problems. However, the more desirable strategy of identifying twins from a population-based twin registry is not possible in the United States. Thus, how representative the twins in this study were of either twins in general or of persons with CFS is not known. Second, chronic sleep habits prior to the study or travel to the study site (eg, jet-lag) may have affected our data in unknown ways. Likewise, we cannot rule out differences between twin pairs in objective parameters of sleep that are subtle and unmeasured, yet important. Third, our ALICE 3™ digital scoring system lacked a verified algorithm to quantify alpha intrusion, a controversial measure of arousal observed not only in CFS,37,38 fibromyalgia39,40 and insomnia,40 but also in pregnant women41 and healthy individuals.3,38 Thus, it is possible that alpha intrusion may be related to the discordance between subjective and objective sleep in the CFS twins. Finally, although we can rule out confounding due to genetic factors, we cannot establish the temporal relationship between physiologic parameters of sleep, perceived insomnia, and CFS. In conclusion, twins with CFS had more complaints of insomnia than did their healthy co-twins despite remarkably similar objective measures of sleep. The higher percentage of REM sleep observed in the CFS twins may point to high REM pressure as a predisposing factor for, or consequence of, CFS. The mismatch between subjective and objective measures of sleep described here are consistent with an element of sleep-state misperception. A final caveat is that studies such as this one cannot address questions of mechanisms and etiology. Thus, the biologic and psychosocial underpinnings of the sensation of disrupted sleep in CFS remain to be elucidated.

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