

## Monozygotic twins discordant for chronic fatigue syndrome Objective measures of sleep

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### Abstract

**Purpose:** Chronic fatigue syndrome (CFS) is characterized by profound fatigue accompanied by disturbances of sleep, cognition, mood, and other symptoms. Our objective was to describe sleep architecture in CFS-discordant twin pairs. **Methods:** We conducted a co-twin control study of 22 pairs of monozygotic twins where one twin met criteria for CFS and the co-twin was healthy. Twins underwent two nights of polysomnography. **Results:** The percentage of Stage 3 and REM sleep was greater among the CFS twins than their healthy co-twins ( $P \leq .05$  for both), but no other differences in sleep architecture including

sleep latency, REM latency, and total sleep time were observed. Compared to their co-twins, CFS twins had higher values for the apnea–hypopnea index and apnea–hypopnea arousal index ( $P \leq .05$  for both). **Conclusion:** These results do not provide strong evidence for a major role for abnormalities in sleep architecture in CFS. Respiration appears impaired in CFS, but these clinical abnormalities cannot alone account for the prominence of sleep complaints in this illness. The co-twin control methodology highlights the importance of selecting well-matched control subjects.

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### Introduction

Chronic fatigue syndrome (CFS) is an illness characterized by profound fatigue lasting at least 6 months accompanied by disturbances of sleep, cognition, mood, musculoskeletal pain, and other symptoms [1]. Sleep symptoms such as difficulties initiating and maintaining sleep are among the most common and disabling [2–6]. Investigators have sought to better characterize these complaints by using more objective and standardized measures such as overnight polysomnography (PSG), sleep diaries, and questionnaire-based assessments of sleep. Results from clinic-based studies have found that patients with CFS often have poor sleep efficiency [6,8–13], as well as intrinsic sleep disorders such as obstructive sleep apnea [2,6–9]. However, findings on

PSG have been mixed and abnormalities modest in comparison to the severity of patients' complaints. Furthermore, previous studies of sleep in CFS have suffered from numerous methodological deficiencies, including the absence of comparison groups [6,7,9,12], failure to perform PSG [5,14], use of in-home PSG [11,15], reporting only on presence of sleep disorders and not sleep architecture [2], and obtaining PSG data from a single night [2,6,7,9,11,13].

In this investigation we used a co-twin control methodology in monozygotic twins discordant for CFS. This approach controls for genetic differences and numerous environmental factors not considered in typical studies of CFS [16]. This research design offers a powerful alternative to traditional approaches that compare CFS patients to healthy, depressed, or sedentary control subjects. It is particularly valuable in studies of sleep since the number of data points generated is large, the range of values observed in normal individuals is relatively wide, and because genetic factors contribute substantially to sleep architecture [17]. In our study, the primary question of interest was “Do twins

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with CFS demonstrate more objective findings on PSG compared with their unaffected co-twin?"

## Materials and methods

### Participant recruitment

A total of 600 twins were mailed an intake questionnaire; 426 (71%) were returned, and complete data were available for both members of 193 twin pairs. Twins were recruited through patient support group newsletters (58%), practitioners/researchers familiar with CFS (11%), electronic bulletin board notices for CFS (15%), twin organization and researchers (6%), relatives and friends (3%), and other sources (8%). Each twin completed a mailed questionnaire that collected extensive data on demographics, zygosity, life style and habits, psychiatric and physical health conditions, and a section on the nature, extent, and consequences of fatigue along with a checklist of the symptoms of CFS [1]. The questionnaire contained a section for fatigued twins and another for nonfatigued twins; a screening question on fatigue directed respondents to the appropriate section. For the nonfatigued twin, the control version of questions did not reference fatigue. A more comprehensive description of the CFS twin registry can be found elsewhere [18]. Written, informed consent was obtained from all twins in accordance with regulations of our institutional Human Subjects Office.

### Psychiatric disorders

To determine psychiatric diagnoses, the Diagnostic Interview Schedule Version III-A [19] was administered via telephone interview by a trained research assistant to Registry participants. This instrument, which assigns diagnoses based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Version III-Revised* [20], included modules on major depression, dysthymia, generalized anxiety, panic, agoraphobia, posttraumatic stress disorder, mania, bipolar illness, schizophrenia, eating disorders, somatization, and substance abuse/dependence.

### Chronic fatigue syndrome

Responses to the CFS symptom checklist and the diagnoses generated by the DIS were used to determine whether the Centers for Disease Control research criteria for CFS were met [1]. To meet criteria, debilitating fatigue must be present for at least 6 months, 4 of 8 symptoms must be endorsed, and certain medical and psychiatric conditions cannot be present. The same inclusion and exclusion criteria (e.g., body mass index, certain psychiatric conditions) and review processes were applied to the fatigued and healthy twin. The twins' medical records for the last 5 years were reviewed by a physician knowledgeable about CFS for

potentially exclusionary medical conditions, including sleep disorders diagnosed by PSG. A psychologist and an infectious disease specialist also independently reviewed each twin's medical chart to verify health status and approve their participation. Prior to the scheduled visit, we confirmed that the ill twin still met CFS criteria and that the control twin was healthy and not fatigued.

### Participant selection

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 (one twin met the Centers for Disease Control and Prevention CFS criteria at the time of evaluation and the unaffected twin was healthy); (4) discontinue alcohol, caffeine, and all medications known to effect fatigue, cognition, and sleep at least 2 weeks before the evaluation; and (5) travel to the study site together.

Of 193 twin pairs, 119 (62%) were discordant for at least 6 months of fatigue; 67 (56%) of these were monozygotic by self-report and had complete data available. Among these 67 monozygotic, chronic fatigue discordant pairs, 14 were excluded for psychiatric illness, 4 for medical disorders, and 1 for a body mass index over 45. In an additional 9 pairs, the fatigued twin did not meet CFS symptom criteria, 4 pairs were not included because the nonfatigued twin had an exclusionary condition, and 6 pairs were excluded for other reasons (e.g., recent death of the co-twin, inadequate English, pregnancy). This process left 29 eligible twins pairs in which the ill twin met strict criteria for CFS and their co-twin was healthy and denied chronic fatigue. Of these, 22 (76%) completed the study, 1 (3%) refused, 2 (7%) could not be scheduled, and 4 (14%) were unable to discontinue potentially interfering medications.

### Zygosity

Monozygosity was initially determined using previously validated self-report methods [21,22], then confirmed with analysis of restriction fragment length polymorphisms. DNA samples were extracted and digested with the restriction endonuclease *HaeIII*. The restriction fragments were separated by molecular size in agarose gel, Southern blotted onto nylon membrane, and hybridized with a variable number of tandem repeat probes. Following six probes, the probability of monozygosity can be ascertained with 99.9% certainty [23].

### Overnight polysomnography

Sleep PSG data were collected over 2 consecutive nights at a certified sleep disorders laboratory; a clinical sleep history also was obtained. Twins arrived at the sleep laboratory approximately 2 h before bedtime for electrode

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