Results of Isoproterenol Tilt Table Testing in Monozygotic Twins Discordant for Chronic Fatigue Syndrome

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Background: The pathogenesis of chronic fatigue syndrome (CFS) is unknown. Neurally mediated hypotension (NMH) has been suggested as a common comorbid condition or a potential underlying cause.

Methods: We conducted a cotwin control study of 21 monozygotic twins who were discordant for CFS. One twin met the 1994 Centers for Disease Control and Prevention criteria for CFS, and the other twin was healthy and denied chronic fatigue. The twins were selected from a volunteer twin registry in which at least 1 member reported persistent fatigue. As part of a 7-day clinical evaluation, all 21 twin pairs were evaluated with a 3-stage tilt table test with isoproterenol hydrochloride for the assessment of NMH. The presence of NMH was defined as syncope or presyncope associated with a decrease of 25 mm Hg in blood pressure and no associated increase in heart rate.

Results: A positive tilt table test result was observed in 4 twins with CFS (19%) and in 4 healthy twins (19%). This difference was not statistically significant (matched-pair odds ratio, 1.0; 95% confidence interval, 0.2-5.4; P = .90). Compared with the healthy twins, the twins with CFS reported more severe symptoms of CFS and NMH both in the week before and during the tilt table test.

Conclusions: These results do not support a major role for NMH in CFS. They highlight the importance of selecting well-matched control subjects, as well as the unique value of the monozygotic cotwin control design in the study of this illness.

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Chronic Fatigue Syndrome (CFS) is an illness characterized by profound fatigue lasting at least 6 months accompanied by disturbances of sleep, neurocognition, mood, musculoskeletal pain, and other symptoms. It is a symptom-based diagnosis of exclusion without distinguishing findings on physical examination or routine laboratory testing. In both clinical and community settings, CFS is reported most frequently among females. Initially, the prominence of infectious, neurocognitive, and psychological symptoms suggested a viral illness or psychiatric disorder. Subsequently, a variety of findings related to sleep abnormalities and neuroendocrine and immunological dysfunction have been observed in subgroups of patients with CFS, although a unifying mechanism has yet to emerge. More recently, perturbations in autonomic function have been associated with CFS. Many symptoms experienced by patients with CFS, such as fatigue, postexercise exhaustion, dizziness, and nausea, are typical of neurally mediated hypotension (NMH). Neurally mediated hypotension can be demonstrated by tilt table testing and manifested by hypotension with bradycardia (vasovagal reaction) on vertical tilting. Although previous research has produced mixed results in terms of the frequency of NMH in CFS, anecdotal reports have noted that patients with CFS and symptoms or signs indicative of autonomic dysfunction often improve but generally do not recover entirely with fluid, salt, or fludrocortisone acetate therapy. An explanation for the inconclusive results of these investigations involves potential problems with the selection of appropriate control subjects, as well as subtle differences between patients with CFS and controls with respect to fluid status, food intake, and baseline exercise level. A further complication is the method of tilt table test administration, which has been highly variable across studies. Thus, at the present time, the precise nature and extent of autonomic system involvement in CFS remains to be determined.

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SUBJECTS AND METHODS

REGISTRY CONSTRUCTION AND SUBJECT RECRUITMENT

A total of 632 twins responded to a solicitation to participate in a volunteer twin registry and requested the registry intake questionnaire. Of these, 454 individuals (72%) returned the questionnaire. Of the 233 twin pairs identified in whom one or both members met the study inclusion criteria of chronic fatigue (fatigue ≥6 months), 59% were recruited through patient support group newsletters, 10% through clinicians or researchers who are familiar with CFS and fibromyalgia, 18% through notices placed on electronic bulletin boards, 6% through twin organizations and researchers, 3% through relatives and friends, 3% through other national and international contacts, and 6% through unknown sources. Complete data were available for both members of 204 twin pairs (88%), and 127 (62%) were discordant for at least 6 months of fatigue. Each twin completed a mailed questionnaire that collected extensive data on demographics, zygosity, habits, lifestyle, distress, and physical health conditions and included a section on the nature, extent, and consequences of fatigue as well as a checklist of the symptoms of CFS.1 For the nonfatigued twin, a control version of questions was used that did not reference fatigue. A more complete description of the twin registry can be found elsewhere.20

PSYCHIATRIC DISORDERS

To ascertain psychiatric conditions, the Diagnostic Interview Schedule: Version III-A,21 which assigns current and lifetime diagnoses, was administered by telephone to registry participants. The Diagnostic Interview Schedule is a structured interview that uses a computer-based algorithm to generate psychiatric diagnoses based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.22 A trained research assistant administered the sections on major depression, dysthymia, generalized anxiety, panic, agoraphobia, posttraumatic stress disorder, mania, bipolar disorders, schizophrenia, eating disorders, somatization, and substance abuse and dependence. Melancholia was scored without the symptoms attributable to CFS.

SELECTION OF THE CLINICAL SAMPLE

From the twin registry, 22 sets of twins were chosen for a week-long in-person intensive evaluation based on the intake questionnaire, the Diagnostic Interview Schedule, and additional telephone interviews and screening. Twins were required to (1) be at least 18 years of age; (2) be monozygotic; (3) have been reared together; (4) be discordant for CFS (ie, one twin met the Centers for Disease Control and Prevention criteria at the time of evaluation, and the other was healthy and had no history of chronic fatigue); (5) discontinue using alcohol, caffeine, and all medications at least 2 weeks before and during the evaluation; and (6) be able to travel to Seattle, Wash, at the same time. The twins were reimbursed for travel and expenses for participation.

The selected pairs were rigorously screened to ensure that the ill twin had a high probability of having CFS and that the cotwin was healthy. In fatigued twins, CFS criteria were initially assessed using a symptom checklist and diagnoses generated by the Diagnostic Interview Schedule. Of importance, the same inclusion and exclusion criteria (eg, body mass index [weight in kilograms divided by the height in meters squared] and medical and psychiatric illness) and review process were applied to the fatigued twin and the healthy twin. Thus, a healthy twin with melancholic depression would preclude the study of the twin pair, even if the twin with CFS met all our study eligibility criteria. Next, all medical records for the past 5 years were requested and reviewed by an internist (D.B.) for potentially exclusionary conditions. All questionable health issues were resolved by telephone, physician contact, or blood tests performed before the planned evaluation. A psychologist and an infectious disease specialist then independently reviewed the charts and approved the twins for participation. Just before the scheduled visit, CFS symptom screening was readministered to the ill twin to document that CFS criteria were still met and to the healthy twin to confirm the absence of chronic fatigue.

ZYGOSITY

Zygosity was initially determined using previously validated self-report methods23,24 and then confirmed with analysis of restriction fragment length polymorphisms. More specifically, DNA samples were extracted from mononuclear cells and digested with the restriction endonuclease HaeIII. The restriction fragments were separated by molecular size in an agarose gel, Southern blotted onto a nylon membrane, and hybridized with a variable number of tandem repeat probes. With the use of 6 of these probes, the probability of monozygosity can be stated with a certainty of .99 or more.

TILT TABLE TESTING

Testing was performed according to the Johns Hopkins tilt table protocol,13 except that the subjects were not transported by wheelchair to the laboratory. All investigators and clinical staff were blinded as to the clinical status of the twins. Both members of a set were studied within 3 hours of each other. During testing, movement and noise were restricted. The twins were fluid restricted for 12 hours. They were then brought to the electrophysiology laboratory at least 15 minutes before starting the procedure, and an intravenous line was inserted. Systolic (SBP) and diastolic (DBP) blood pressure (BP) were measured with an automated cuff, and the heart rate (HR) was monitored continuously. After the subject was supine for 15 minutes, the test was begun. Stage 1 involved an upright tilt to 70° for
up to 45 minutes. Symptoms, BP, and HR were recorded at 1 minute, every 5 minutes thereafter, and every minute if lightheadedness occurred. An abnormal response was defined as the presence of presyncope or syncope in association with a decrease in SBP of at least 25 mm Hg lasting 1 minute or more without an increase in HR.

If stage 1 was tolerated, the subject was returned to the supine position and, for stage 2, 1 to 2 µg/min of isoproterenol hydrochloride was infused for 10 minutes, titrated to achieve a 20% increase in HR. The table was then brought to the upright 70° position for 15 minutes or until an abnormal response was recorded. If this stage was tolerated, the subject was again returned to the supine position for another 10 minutes, during which 3 to 4 µg/min of isoproterenol hydrochloride was infused (stage 3). The subject was then brought to upright tilt for a maximum of 10 minutes. At this point, the test was completed, and the subject was placed in a supine position.

The primary tilt table outcome, NMH, was defined as hypotension without a concomitant rise of HR during upright tilt. The baseline HR and BP values were calculated as the average of the 10- and 15-minute supine readings, then 25 mm Hg was subtracted from the SBP reading. If this target BP value was maintained for 1 minute and presyncope occurred, the test was stopped. The test was also terminated for an HR higher than 180/min for 2 minutes during the isoproterenol infusion or if hypotension occurred. No complications (eg, arrhythmias, cardiopulmonary arrest, prolonged hypotension requiring fluid resuscitation or pressor support, or thrombophlebitis) occurred.

SELF-REPORT MEASURES AND EXERCISE CAPACITY TESTING

Immediately after the tilt table testing procedure, a questionnaire that included 10 items on CFS-related symptoms (eg, fatigue, sore throat, sleep disturbance, depression, and anxiety) and 11 items on symptoms typical of NMH (eg, dizziness, lightheadedness, nausea, chest pain, and shortness of breath) was administered. The twins were asked about the occurrence of these symptoms in the past week as well as during the tilt table test. The severity of each symptom was rated on a 6-point scale that ranged from 0 (none) to 5 (severe). Information was also obtained on the subjects' usual salt intake and the average number of smoking, body mass index, V˙O2 max, and salt and caffeine consumption.

The mean severity of each CFS and NMH symptom was calculated for the twins with CFS and the healthy twins both in the week before and during the tilt test procedure. The intrapair mean differences were compared using a matched-pair t test and the Wilcoxon signed rank test when normality assumptions were violated. Initial baseline means for SBP, DBP, and HR obtained in the supine position were compared using matched-pair t tests. The minute-to-minute mean BP and HR across each of the 3 stages of the tilt table test were plotted for the CFS and healthy pairs.

A random-effects model25 was used to assess the effects of group (CFS vs healthy), time (in 5-minute increments starting with baseline), and group-by-time interactions on BP and HR during the first stage of the tilt table test. This model is especially well suited for the analysis of twin data since it accounts for both the paired and the repeated measurement structure of the data. The specific model we used included random effects for the pair and the repeated measures within an individual; with these random effects in the model, it is possible to obtain estimates of the intrapair correlation for the BP and HR data. We performed single-factor statistical adjustment for the effects of smoking, body mass index, salt and caffeine intake, and V˙O2 max as a measure of fitness. Formal statistical testing was based on separate F tests for the effects of group, time, and group-by-time interaction. We did not conduct a formal statistical analysis of the stage 2 and 3 hemodynamic data because all pairs were not entered into these stages.

Survival analysis methods were used to examine the effects of the tilt table testing on NMH. Simple Kaplan-Meier survival curves were derived for each stage of the tilt table test for twins with CFS and healthy twins; the outcome in each stage was the time until NMH as defined by the presence of presyncope or syncope associated with a decrease in SBP of at least 25 mm Hg lasting 1 minute or more without an increase in HR. The total proportion of twins with CFS and healthy twins with NMH was determined along with the exact 95% confidence intervals (CIs). A matched-pair Fisher exact test (2-tailed) was used to compare the difference in the proportion of twins with CFS and healthy twins with NMH for all 3 stages together. Odds ratios and exact 95% CIs were calculated to measure the magnitude of the association between CFS status and NMH. We also conducted a conditional logistic regression analysis that examined the association between CFS and NMH after single-factor adjustment for the effects of smoking, body mass index, V˙O2 max, and salt and caffeine consumption.

Finally, our sample size of 21 pairs was based on the strong effects noted in previous research4; we estimated that for a matched-pair analysis with α = .05 and an expected tilt table positive rate of 96% in CFS twins and 29% in healthy cotwins, we had a power of more than 90%. Analyses were conducted using the following software programs: SPSS for Windows, version 6.1.4 (SPSS Inc, Chicago, Ill), SAS for Windows, version 6.12 (SAS Inc, Cary, NC), and PEPI PAIRS, version 3.0 (Rocky Mountain Center for Occupational and Environmental Health, University of Utah, Salt Lake City).

RESULTS

Of the 193 twin pairs, 119 (62%) were discordant for at least 6 months of fatigue; 67 (56%) were monozygotic pairs. Of these 67 monozygotic, chronic fatigue discordant pairs, 14 were excluded for psychiatric illness, 4 for medical disorders, and 1 for a body mass index of more than 45 kg/m². Among an additional 9 pairs, the fatigued twin did not meet CFS symptom criteria, and 10 pairs were excluded for a variety of other reasons (eg,
The mean severity of symptoms was graded on a scale of 0 (none) to 5 (severe). CFS indicates chronic fatigue syndrome; NMH, neurally mediated hypotension; and NA, not applicable.

**SYMPTOMS**

The table presents the self-reported symptoms of CFS and NMH in the week before tilt table testing and during the testing procedure. In the week before testing, the twins with CFS reported greater severity of all CFS symptoms (maximum, 5) compared with their healthy cotwins. For example, large differences were noted in the mean scores for fatigue (twin with CFS, 3.7; healthy twin, 0.7), concentration problems (twin with CFS, 2.9; healthy twin, 0.3), and sleep disturbance (twin with CFS, 3.4; healthy twin, 1.2). This same pattern was generally evident for symptoms present during the tilt table test, with the twins with CFS reporting more severe symptoms of fatigue, aching muscles, aching joints, concentration problems, and anxiety.

Although the severity of NMH symptoms during the week before the tilt table test was greater in the twins with CFS than in the healthy twins, the NMH symptoms were typically rated as less severe than the CFS symptoms. Notable differences in NMH symptom severity between the groups were noted for dizziness, lightheadedness, nausea, abdominal discomfort, sweating, chest pain, and shortness of breath. Similarly, symptoms of lightheadedness, abdominal discomfort, chest pain, and shortness of breath were increased in the twins with CFS during the tilt table procedure.

**HEMODYNAMIC MEASURES**

The mean supine SBP among the twins with CFS and the healthy twins did not differ (121 vs 120 mm Hg, *P* = .96). Similarly, no baseline differences were observed for the average DBP (twin with CFS, 74 mm Hg; healthy twin, 74 mm Hg; *P* = .81) or mean HR (twin with CFS, 76/min; healthy twin, 74/min; *P* = .48). Figures 1, 2, and 3 present the detailed minute-by-minute plot of the mean SBP, DBP, and HR for each stage of the tilt table test for twins with CFS and healthy twins. The overall pattern for each of the hemodynamic indicators was very similar for the twins with CFS and the healthy twins. As dictated by the testing protocol, the HR became elevated as the twins progressed from stage 1 to stage 3. The DBP decreased from stage 1 to stage 2 and then increased slightly from stage 2 to stage 3. The SBP demonstrated little variability across the different stages of the procedure.

The statistical analysis of the stage 1 hemodynamic data indicated that the SBP of the twins with CFS was higher than that of their cotwins (*P* = .01). There was also a significant downward trend over time in the SBP (*P* = .01)
during the course of the tilt table test, although the group-by-time interaction was not significant (P = .10). The random-effects model–estimated intrapair correlation for SBP was 0.50, after the repeated measures within an individual were accounted for. A difference was observed in the DBP between the twins with CFS and the healthy twins, with the twins with CFS having consistently higher readings (P = .004). Overall, the DBP significantly declined during the course of the 45-minute tilt table test (P < .001); (again, no group-by-time interaction was demonstrated (P = .45)). The intrapair correlation for DBP was 0.47. The HR showed no difference between the twins with CFS and the healthy twins (P = .98), although, as expected, there was a strong significant trend of increasing HR with time (P < .001). There was no group-by-time interaction for HR (P > .99). The intrapair correlation for HR was 0.49.

Figure 4 presents the survival curves for NMH in the twins with CFS and in the healthy twins for each stage of the tilt table procedure. Notably, the proportion of twins with and without CFS who tested positive for NMH did not differ (P > .99). Of the twins with CFS, 4 (19%; 95% CI, 6-42) tested positive for NMH, compared with 4 (19%; 95% CI, 6-42) of the healthy twins (odds ratio, 1.0; 95% CI, 0.2-5.4). No twins were concordant for the presence of NMH. During the first stage, 3 twins with CFS and 1 healthy twin manifested NMH. All the positive responses in stage 1 occurred at 14 to 28 minutes. During the second stage, 1 twin with CFS was positive for NMH at minute 8 and 1 healthy twin was positive at minute 4. In the last stage of the tilt table test, no twin with CFS and 2 healthy twins were positive for NMH (at 5 and 9 minutes). A matched-pair conditional logistic regression analysis of the full 3-stage tilt table protocol, after the effects of smoking, body mass index, VO₂ max, and salt and caffeine consumption were singly adjusted for, did not alter these results.

**COMMENT**

Literature on the nature, extent, and association of autonomic dysfunction in patients with CFS has been increasing over the last 5 years. This body of work has examined various measures of sympathetic and parasympathetic activity such as NMH, HR variability, and response to Valsalva maneuvers and deep breathing. Although NMH may play a major role in CFS, methodological differences in tilt table testing across studies temper this conclusion. In this regard, some investigators have used a single-stage tilt table procedure, while others have preferred a multistep approach, with isoproterenol infusion during stages 2 and 3. The duration and angle of the tilt itself have varied by study from 4014 to 4515 minutes and from 60°16 to 80°17. Also, the length of fasting before the test is performed has ranged from 217 to 413 hours. Few studies have accounted for the role of patient deconditioning or other health habits, such as salt and caffeine intake. Finally, patient and controls have been selected in idiosyncratic ways from study to study, greatly increasing the chances for selection bias.

A strong association between CFS and NMH was initially reported in adolescents and subsequently in adults. In the latter study, 22 (96%) of 23 adults with CFS, 43% of whom reported a history of syncope, developed hypotension associated with presyncope or syncope during upright tilt table testing. In an uncontrolled trial, 21 patients were treated with β-blockers, dietary salt loading, fludrocortisone, disopyramide, and midodrine; 16 experienced improvement in their illness. The investigators also observed that patients with CFS often purposely practiced salt restriction in an attempt to be health conscious. However, another group demonstrated an abnormal response in only 22 (28%) of 78 patients with CFS. Eleven of these 22 patients responded to increased dietary sodium chloride therapy and no longer had an abnormal tilt table test response. Of interest, some patients manifested an abnormal increase in HR associated with upright tilt and hypotension, a finding previously observed, suggesting...
gesting that some patients with CFS might be better described as having a postural orthostatic tachycardia syndrome. Finally, in a larger investigation of 75 unselected patients with CFS, 29 (39%) responded abnormally to upright tilt table testing, and 16 developed syncope; 7, exaggerated tachycardia; and 6, a combination of tachycardia and syncope. Factors associated with an abnormal test response included a shorter duration of disease and younger age.

In the most comprehensive evaluation of autonomic function, 20 patients with CFS were compared with age- and sex-matched controls. In addition to tilt table testing, data were collected on supine and sitting HR, SBP, DBP, expiratory-inspiratory ratio, Valsalva ratio, maximum HR minus minimum HR, BP response to isometric exercise, and a standardized measure of activity. Although only 4 (25%) of 16 patients who underwent the tilt procedure demonstrated hypotension, no control patient did (P<.01). Taken together, these investigations on autonomic function suggest that there appears to be a subgroup of patients with CFS who develop hypotension when subjected to tilt table testing.

Our study did not show a difference in tilt table–provoked NMH between monozygotic twins who were discordant for CFS defined according to Centers for Disease Control and Prevention criteria. The overall proportion of twins with CFS who demonstrated an abnormal hemodynamic response to tilt table testing (approximately 20%) was similar to that observed in some, but not all, previous studies. In comparing the rate of hypotension during tilt table testing in our twins with rates in other studies, differences in eligibility criteria and protocol administration need to be evaluated. Most notably, our sample only included patients 18 years of age and older. This may have influenced our findings, since it is known that the rate of tilt table-generated hypotension is higher in adolescents than in adults. Also, 90% of our twins were female, while up to 49% of subjects were male in other studies. The requirement for travel and extensive testing may also have resulted in a less ill population. Finally, the end points for tilt table testing have varied considerably across studies and have included NMH, orthostatic intolerance, and postural orthostatic tachycardia syndrome, as well as symptoms in the absence of definitive vasomotor changes. In this study, we defined positivity as strictly meeting criteria for NMH. However, even when autonomic dysfunction in other investigations was defined only as NMH, the proportion of subjects with a positive tilt table test response in our study still differs from rates reported by several others using the same methodology.

Measures of BP and HR were also comparable between twins at baseline. During stage 1 of the tilt table test, we did observe a difference in SBP and DBP between the pairs, but there was no difference in HR. This finding is consistent with twin and family studies that have demonstrated moderate to strong heritable effects on HR. Interestingly, a common family environmental component to fainting has also been found in a twin study of middle-aged Australian twins. Nonetheless, compared with their cotwins, those with CFS reported increased severity of CFS, as well as the

Figure 4. Kaplan-Meier survival curves for neurally mediated hypotension (NMH) in twins with chronic fatigue syndrome (CFS) and healthy twins.
NMH symptoms of lightheadedness and shortness of breath, during the tilt table test. The observation that patients with CFS report a worsening of their CFS symptoms in the upright position has been noted by others.\textsuperscript{13,27}

Because tilt table testing can be influenced by a large number of personal factors, such as age, slight build, baseline BP, medications, exercise, familial tendencies, and diet, salt, and fluid intake,\textsuperscript{25-26} the selection of control subjects is particularly critical. In previous work, controls were either not recruited\textsuperscript{12,28} or described as normal, healthy volunteers, without adequate reference to the nature or extent of their physical activity, salt intake, or diet.\textsuperscript{13,15,26,27} In the current study, the healthy twin was, of course, identical in terms of age, sex, and genetics. Furthermore, even after the potential confounding influence of exercise capacity (\textsuperscript{VO_2 max}) and salt and caffeine consumption was adjusted for, the lack of a difference in NMH between the twins with CFS and the healthy twins remained. The tilt table test was also completed under strictly blinded conditions during the same day for both twins. Such methodological considerations are crucial, since changes in diet owing to illness and cardiovascular deconditioning are possible explanations for the NMH observed in some subjects with CFS.

This cotwin control study has several notable limitations. First, the method used to identify the sample was not ideal. Solicitation by advertisement resulted in a volunteer sample of twin pairs with the potential for ascertainment problems. However, the more desirable strategy of systematically identifying twins from a well-defined population-based twin registry is not readily accomplished in the United States. Thus, how representative the twins in this study were either of twins in general or of persons with CFS is not known. However, the demographic and clinical characteristics of our twins were similar to those previously described for referral populations of patients with CFS. A second limitation is related to the heterogeneity of CFS. While we applied the Centers for Disease Control and Prevention CFS inclusion and exclusion criteria in a systematic and rigorous fashion, it is still possible that CFS is not a single disorder. A third limitation is related to sample size. Although our study was similar to most prior investigations in terms of number of subjects, we believe that it is premature to make conclusive statements about the relationship of CFS to NMH. There may be a subset of patients with CFS and NMH; however, their characteristics await better definition. Finally, although highly selected in one respect, unlike most participants in previous investigations, the twins with CFS were not recruited from tertiary care referral centers and thus may be more representative of patients in the community.

In summary, this cotwin control study of 21 pairs monozygotic twins who were discordant for CFS does not support a major role for NMH in CFS. We found that individuals with CFS are no more likely to experience NMH than exceedingly well-matched, healthy, nonfatigued controls. Because twin studies are especially well suited to the study of illnesses for which the appropriate comparison groups are not clearly defined,\textsuperscript{19} they offer a unique approach to examine the strength of abnormalities, such as NMH, that are reported to be associated with CFS.

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