Factors Influencing the Diagnosis of Chronic Fatigue Syndrome

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**Background:** Most of what is believed about chronic fatigue syndrome (CFS) is based on clinic-based studies. These studies may not reflect CFS cases in the population.

**Methods:** We used data from a population-based study of CFS to identify factors associated with receiving a CFS diagnosis. Wichita, Kan, residents were screened by random-digit dialing. Eligible individuals completed a telephone interview. Respondents meeting CFS criteria were invited for a clinical evaluation to confirm CFS. We analyzed all persons with confirmed CFS. The main outcomes of this study, prevalence and incidence of CFS, are published elsewhere. Herein, we present an exploratory analysis with previous CFS diagnosis as the outcome, predicted by demographic and symptom characteristics.

**Results:** We confirmed CFS in 90 subjects; 14 (16%) had been previously diagnosed as having CFS. Persons in the middle- vs the higher-income group were more likely to have been diagnosed as having CFS (9 [29%] of 31 subjects vs 3 [8%] of 39 subjects; P = .03), as were those with sudden vs gradual fatigue onset (7 [41%] of 17 subjects vs 4 [6%] of 64 subjects; P < .01), those reporting tender lymph nodes (7 [33%] of 21 subjects vs 7 [10%] of 69 subjects; P = .02), and those reporting a sore throat (6 [35%] of 17 subjects vs 8 [11%] of 73 subjects; P = .02). Only 17 (21%) of 81 subjects had sudden fatigue onset, and tender lymph nodes (reported in 21 [23%] of 90 subjects) and a sore throat (reported in 17 [19%] of 90 subjects) were the least common symptoms.

**Conclusion:** Most cases of CFS in the population are unrecognized by the medical community; persons diagnosed as having CFS may be different from persons with CFS in the general population.

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**CHRONIC FATIGUE SYNDROME (CFS) is defined by severe fatigue of at least 6 months’ duration that interferes substantially with occupational, educational, social, or personal activities; is not alleviated by rest; and cannot be explained by another medical or psychiatric condition. This otherwise unexplained disabling fatigue must be accompanied by at least 4 of 8 specified symptoms (unusual postexertional fatigue lasting at least 24 hours, significantly impaired memory or concentration, unrefreshing sleep, sore throat, tender lymph nodes, muscle pain, joint pain, or headaches).**

Fatigue and the accompanying symptoms are quite common in the general population and are not unique to persons with CFS. In addition, CFS has no characteristic physical signs or accompanying laboratory abnormalities. Thus, CFS poses a diagnostic and management challenge for health care providers.

Chronic fatigue syndrome imposes a significant burden on society and on those living with the illness. Two recent population-based studies in Wichita, Kan,2 and Chicago, Ill,3 have documented that between 142 and 560 per 100000 adults have CFS. Extending these rates to the United States, between half a million and a million adults have the illness. In one study,2 more than 50% of persons identified with CFS had been ill for at least 5 years, while in the other,3 the median duration of illness was 2.5 years. About a quarter of the subjects were unemployed or receiving disability income.1,5 Several clinic-based studies have found CFS patients to have substantial functional impairment compared with healthy control subjects and other patient groups with chronic illnesses.6-8 Other clinical studies have described patients with CFS as more severely impaired than persons with untreated hyperthyroidism,8 end-stage renal disease,10 heart disease,11 or multiple sclerosis.8
Despite the protracted chronic nature of CFS and the severity of the associated impairment and disability, only 16% of the persons from the Wichita population classified as having CFS reported ever being diagnosed as having the illness by a physician, and only 52% identified with CFS from the Chicago population were seeing a physician for their illness. Clearly, CFS is not adequately recognized, diagnosed, or managed by health care providers. This may reflect a lack of access to health care by those with the illness or inadequate knowledge by those who provide services.

The public perception of CFS as a problem of middle-aged, professional, white women is based on studies using clinic-based samples. However, because many persons with CFS are not clinically recognized and would, therefore, not be referred to a clinic-based study, such studies may not be representative of the general population. Indeed, recent population-based studies of CFS have suggested that the prevalence of CFS might also be high in minority groups. In the population-based study of CFS in Chicago, Jason et al found that white persons, compared with other racial/ethnic groups, had the lowest prevalence of CFS. Similar results were found in the Wichita study, in which the prevalence was highest in nonwhite persons. However, neither of these results was statistically significant.

Analyses of baseline data from the Centers for Disease Control and Prevention’s population-based study of CFS in Wichita, reported by Reyes et al, show that while persons with CFS who were identified from a population-based sample are similar with respect to age and illness duration, persons reporting sudden fatigue onset were more likely to have been previously diagnosed as having CFS than were those with a gradual onset. In this report, we used data from all 4 years of the Wichita study to examine in more detail and with a larger sample the potential differences between people with CFS who had and had not been diagnosed as having the illness previously.

This study adhered to the human experimentation guidelines of the US Department of Health and Human Services. All participants were volunteers who gave informed consent.

STUDY DESIGN

Details of the longitudinal population-based study to estimate the prevalence and incidence of CFS in the adult population of Wichita have been published. In brief, we used a computer-assisted telephone interviewing system to screen approximately 90,000 Wichita residents. Respondents with severe fatigue for at least 1 month (n = 3528) and randomly selected nonfatigued respondents (n = 3634), ranging in age from 18 to 69 years, completed detailed telephone interviews concerning fatigue, other symptoms, and medical history to determine the presence or absence of CFS case-defining criteria. The initial survey was conducted in 1997, and the originally identified fatigued and nonfatigued respondents were again interviewed by telephone in 1998, 1999, and 2000.

Each year, respondents who, based on their telephone interviews, were suspected to have CFS (ie, they reported severe fatigue of at least 6 months’ duration that was not substantially relieved by rest, at least 4 of 8 core symptoms, and no medical or psychiatric conditions that could explain their symptom com-
plex and, thus, exclude a CFS diagnosis) were invited to participate in a clinical evaluation to confirm a diagnosis of CFS, as were those who had been clinically evaluated in a previous study year. The clinical evaluation included a thorough physical examination, a laboratory work-up, and a psychologic evaluation to rule out exclusionary medical or psychiatric conditions. During the clinic visit, subjects were also given a self-administered questionnaire to verify their symptoms and disease characteristics, and were asked to report whether they ever had been diagnosed as having or were treated for CFS by a physician. A review committee of physicians determined a final classification of CFS, based on the clinical information. Because the study was conducted over 4 years, new CFS subjects were identified throughout the follow-up period.

For this report, we restricted our analysis to only those participants who we classified as having CFS at any time during the study’s 4-year period. For each subject, we used data from the first clinic visit in which we had classified the subject as having CFS. Subjects who had been diagnosed as having CFS by a health care provider before we had classified them as such were considered to have been previously diagnosed as having CFS.

DEMOGRAPHIC AND CLINICAL VARIABLES

Demographic variables that were assessed were sex, age, race/ethnicity, body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters), educational level, and annual household income. Age was split into 10-year groups, with the lower extreme collapsed into younger than 30 years and the upper extreme collapsed into 50 years or older because of low numbers at either extreme. Race/ethnicity was analyzed as white vs nonwhite because there were only 7 nonwhite subjects in the sample and only 1 Hispanic subject. Body mass index was divided into 5 categories that were based on guidelines published by the National Institutes of Health.

Highest level of education completed was collapsed into 3 categories: high school graduate or lower, some education beyond high school but not a bachelor’s degree, and bachelor’s degree or higher. Household income was also grouped into 3 categories: low ($≤$15,000 per year), middle ($15,001–$40,000 per year), and high ($>40,000 per year). The income and education categories were broad to retain sufficient numbers for analysis. A variable to indicate whether the subject’s household fell below the poverty threshold was calculated using data from the US census for Wichita, reported household income, and number of people living in the household (determined in the telephone screening). Poverty thresholds are dollar amounts used by federal agencies to determine poverty status. They are official measurements based on the size of the family and ages of family members, and they are updated annually to reflect inflation. Families that fall below the poverty threshold for a family of their size are considered to be in poverty.

The disease characteristics that were assessed included onset type (subjects were asked to describe the onset of their illness as sudden or gradual), duration of illness (in months), number of core CFS symptoms reported, and reported presence or absence of each of the 8 core symptoms (unusual fatigue lasting at least 24 hours following exertion, headaches, joint pain, tender lymph nodes, memory and/or concentration problems, muscle pain, unrefreshing sleep, and sore throat).

STATISTICAL ANALYSES

Statistical analyses were done using SAS statistical software, version 8.01 (SAS Institute Inc, Cary, NC). Comparisons were made using the Fisher exact test. Continuous variables were divided into categories, and comparisons were made to the referent group. Referent groups were selected based on results from the prevalence and incidence study of CFS in Wichita, which
showed that, in a population-based sample of persons in Wichita, persons with CFS are more likely to be older, to have not attended college, and to have annual household incomes greater than $40,000. Thus, these categories served as the referent groups. The prevalence and incidence study did not discuss BMI or illness duration, so we chose the normal weight BMI group (BMI, 19-24) and the group whose fatigue had lasted at least 48 months as referent groups.

All statistical tests were 2-tailed, and significance was determined at an α level of .05. While the intent to examine differences between persons with CFS who had been diagnosed as having the illness and those who had not was the result of exploratory analyses of existing data, the specific comparisons made in this study were determined before analysis. Thus, the significance levels presented are not adjusted for multiple comparisons.

RESULTS

During the 4-year study period, 604 persons identified with suspected CFS based on their telephone interview were evaluated clinically, and 90 (15%) were classified as having CFS; 43 of these were identified at baseline, 15 in 1998, 22 in 1999, and 10 in 2000. Most of the persons with suspected CFS either no longer acknowledged sufficient fatigue severity or symptoms when they were evaluated clinically (62 [70%]) or had a previously unreported or unidentified medical and/or psychiatric condition that excluded a CFS diagnosis (250 [41%]). Another 2 had missing data or inconclusive test results and could not be classified.

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE SAMPLE

The population of people with CFS in Wichita was mostly women (77 [86%] of 90 persons), at least aged 40 years (62 [69%] of 90 persons), white (83 [92%] of 90 persons), and overweight (BMI, ≥25) (62 [70%] of 89 persons). Only 16 (18%) of 90 subjects had graduates of a 4-year college, 39 (44%) of 88 subjects had a household income above $40,000 a year, and 14 (14%) of 88 subjects fell below the poverty line.

Most CFS subjects described the onset of their fatigue illness as gradual (64 [79%] of 81 subjects) and had been fatigued for at least 2 years (77 [86%] of 90 subjects). Few (11 [12%] of 90 subjects) reported more than 6 of the 8 core CFS symptoms. For each individual symptom, most of the 90 subjects with CFS reported unrefreshing sleep (88 [98%]), muscle pain (82 [91%]), postexertional fatigue (73 [81%]), joint pain (72 [80%]), memory or concentration problems (71 [79%]), and headaches (54 [60%]). Of the 90 subjects, only 21 (23%) reported tender lymph nodes and 17 (19%) reported a sore throat.

SUBJECTS WITH VS THOSE WITHOUT A PREVIOUS CFS DIAGNOSIS

Demographic characteristics for the study subjects are shown in Table 1. Of the 90 subjects classified as having CFS, 14 (16%) previously had been diagnosed as having CFS by a physician, and all were women. However, the probability of having been diagnosed as having CFS was not statistically different between men and women, so the following presentation of results includes both sexes, because a separate analysis excluding men had virtually identical findings.

Household income was the only demographic variable significantly associated with having a previous diagnosis of CFS by a physician. Somewhat surprisingly, people in the middle-income group were more likely to have been diagnosed as having CFS than people in the high-income group. No differences were apparent according to educational level, racial/ethnic group, age, BMI, or poverty status.

For disease characteristics (Table 2), 41% of the people whose fatigue was sudden had been diagnosed previously as having CFS, compared with 6% of those whose fatigue appeared gradually. Persons reporting all 8 of the core CFS symptoms were most likely to have been diagnosed pre-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subjects Not Previously Diagnosed as Having CFS*</th>
<th>Subjects Previously Diagnosed as Having CFS*</th>
<th>P Value†</th>
</tr>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n = 13)</td>
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<tr>
<td>Female (n = 77)</td>
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<td>14 (18)</td>
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</tr>
<tr>
<td>Age, y</td>
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<td></td>
<td></td>
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<tr>
<td>&lt;30 (n = 7)</td>
<td>6 (86)</td>
<td>1 (14)</td>
<td>&gt;.99</td>
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<td>30-39 (n = 21)</td>
<td>20 (95)</td>
<td>1 (5)</td>
<td>.12</td>
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<td>40-49 (n = 32)</td>
<td>27 (84)</td>
<td>5 (16)</td>
<td>.53</td>
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<td>≥50 (n = 30)</td>
<td>23 (77)</td>
<td>7 (23)</td>
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<td>BMI‡</td>
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<td>&lt;19 (underweight) (n = 2)</td>
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<td>1 (50)</td>
<td>.21</td>
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<td>23 (92)</td>
<td>2 (8)</td>
<td>Ref</td>
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<td>23 (85)</td>
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<td>7 (21)</td>
<td>.27</td>
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<td>40-44 (extremely obese) (n = 2)</td>
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<td>Ref</td>
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<td>Poverty status</td>
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<tr>
<td>Below the poverty line (n = 12)</td>
<td>11 (92)</td>
<td>1 (8)</td>
<td>.68</td>
</tr>
<tr>
<td>Above the poverty line (n = 76)</td>
<td>63 (83)</td>
<td>13 (17)</td>
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</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CFS, chronic fatigue syndrome; Ref, referent group.
*Data are given as number (percentage) of each group with each specific characteristic.
†Fisher exact test.
‡The study design excludes participants with a BMI of 45 or higher from a CFS diagnosis.
Previously as having CFS; previous CFS diagnoses ranged from 0% to 24% for persons with fewer than 8 symptoms, although this percentage does not consistently increase by number of symptoms, and only the comparisons of 4 vs 8 symptoms and 6 vs 8 symptoms reached statistical significance. Because of the few subjects in some of the strata, we were unable to assess a possible trend associated with the number of reported symptoms. There seemed to be a trend of previous CFS diagnosis associated with increasing duration of the fatiguing illness; however, comparisons between these groups were not significant.

Subjects were more likely to have been previously diagnosed as having CFS if they reported that their lymph nodes were tender vs not tender or the presence of a sore throat vs no sore throat. Comparisons of differences in subjects who had a previous CFS diagnosis vs those who did not, according to the presence of the other 6 symptoms, were not statistically significant (Table 3).

**COMMENT**

In summary, we clinically evaluated 90 people with CFS, of whom only 14 (16%) had ever previously been diagnosed as having CFS by a physician. All those who had received a previous diagnosis of CFS were women, and most had annual household incomes of less than $40000 and reported a sudden onset of their illness.

Because of recent reports from population-based research that reported a higher prevalence of CFS in minorities, we compared the demographic characteristics of persons with CFS who had been previously diagnosed as having CFS by a physician with those of persons who had not. We did not find any significant differences in demographic characteristics, except for income. People in the middle-income group were more likely to have a previous diagnosis of CFS than were people in the high-income group. A possible explanation for this may be that there are more people in the high-income group who work high-stress jobs or exceptionally long hours, and either they do not have time to see a physician or their fatigue is dismissed as a symptom of being “overworked.” It is also possible that people in the middle-income group who had been diagnosed as having CFS might have previously had higher incomes and that the increased diagnoses in the middle-income group may reflect higher-income people who can no longer sustain their previous employment.

Despite a lack of statistical significance, women, persons aged at least 50 years, and persons with more education were also more likely to be diagnosed as having CFS. All of these may be explained by differences in health-care-seeking behavior: women are more likely to go to a physician than are men; persons of a more advanced age generally have more health problems and, thus, more reasons to see a physician; and persons with more education are generally more trusting of the health care system.

People who reported the sudden onset of fatigue, all 8 core CFS symptoms (as opposed to only 4 or 6), tender lymph nodes, or a sore throat were more likely than were those who reported none of these disease characteristics to have been previously diagnosed as having CFS. These factors may be more likely to inspire someone to seek medical care—a person whose fatigue onset is sudden may be more likely to notice that it is a problem and see a physician than someone whose fatigue appeared gradually.
Likewise, a person with 8 symptoms may also be more likely to seek medical attention because 8 symptoms are presumably more bothersome than 4. In this sample, persons reporting 5 symptoms were more likely to have been diagnosed as having CFS than those reporting 6, and none of those reporting 7 symptoms were diagnosed as having CFS; however, we do not believe that this is indicative of spurious associations for the other categories. Rather, we believe that this reflects the limitations one faces when performing analyses on small samples. Nevertheless, these results should be interpreted with caution.

Tender lymph nodes and a sore throat are symptoms common to many treatable infectious illnesses, and persons with these symptoms may again be more likely to see a physician. In addition, these factors may be more likely to be taken seriously by a physician than are other factors associated with CFS.

These differences in the disease characteristics among persons with and without a previous diagnosis are particularly interesting. Although only 17 (21%) of the overall 81 subjects with CFS had a sudden onset of fatigue, they composed half of the people who had previously been diagnosed as having CFS. Only 6 (7%) of the total 90 subjects reported all 8 of the core CFS symptoms, yet all 8 symptoms were reported in 4 (29%) of the 14 with a previous CFS diagnosis. Tender lymph nodes and a sore throat were relatively uncommon in the overall sample of persons with CFS (21 [23%] and 17 [19%] of the 90 subjects, respectively), but 7 (50%) of the 14 people with a previous diagnosis reported tender lymph nodes and 6 (43%) of the 14 reported a sore throat.

These results suggest that CFS patients reporting sudden fatigue onset, tender lymph nodes, or a sore throat are overrepresented in clinic-based samples. Indeed, we compared our data with data from the largest clinical surveillance study of CFS patients (data from representative physicians in Reno, Nev, Grand Rapids, Mich, and Atlanta), and found that sudden onset, swollen lymph nodes, and a sore throat were much more commonly reported in the clinic-based CFS sample than in our population-based study sample.

Perhaps of more interest, particularly from a policy or education standpoint, is why so few people receive a diagnosis of CFS. There are many reasons why a person with CFS might not be diagnosed as having the illness. For instance, it could be an issue of access to health care (eg, an inability to pay for health care or a lack of health insurance, living too far from a medical facility, or lack of transportation). It could also be an issue of health care use (ie, people do not see a physician about their symptoms because they are too busy, they do not perceive their symptoms as a “health problem,” or they do not think they will be taken seriously).

The lack of a CFS diagnosis could also be a result of a problem with the medical community. Perhaps people with CFS are seeing physicians, but their symptoms are dismissed or their physicians mistakenly diagnose them as having something else or diagnose something else for insurance purposes. Unfortunately, the participants in this study were not asked if they had seen a physician for their symptoms or other questions that would help to elucidate the reasons why persons who have CFS are not diagnosed as having the illness. The Centers for Disease Control and Prevention plans to include such questions in future CFS studies.

Despite a lack of established treatment recommendations, the diagnosis of CFS is important. Persons whose illness is recognized by a physician can, at least, try different therapies to relieve their physical symptoms. Clarke and James report that many persons with CFS go from physician to physician in search of a diagnosis and that a lack of acknowledgment of their illness by the medical community results in difficulties securing sick leave or receiving disability. Finally, they also suggest that having an illness that neither their physicians nor their friends and family think is real can cause emotional distress. Although this study was greatly limited by the few people with a previous CFS diagnosis, it sheds light on the problems associated with clinic-based studies of CFS. People diagnosed as having CFS by their physicians are clearly not representative of the population with CFS, and many of the perceptions about CFS—within the scientific community and in the general public—are based on studies in which participants are not drawn from a community sample. To gain a true understanding of this complex syndrome, the entire population with CFS, not just the small subset of persons who are diagnosed by a physician, must be studied.

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