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Research

A population-based study of the clinical course of chronic fatigue syndrome

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Abstract

Background: Chronic fatigue syndrome (CFS) presents a challenge for patients, health care providers, and health insurance groups because of its incapacitating nature, unknown cause, and poorly understood prognosis. We conducted a longitudinal population-based study to characterize the clinical course of CFS.

Methods: Sixty-five CFS subjects were identified from a random-digit-dialing survey of Wichita, Kansas residents and followed for up to 3 years. We evaluated changes in CFS classification (partial or total remission, alternative medical or psychiatric diagnoses), CFS case-defining criteria, wellness scores, hours of activities and sleep, and treatments used to reduce fatigue. Associations between risk factors and outcomes were determined by use of logistic regression and generalized estimating equations models.

Results: Only 20%-33% of the subjects were classified as having CFS at follow-up, 56.9% ever experienced partial or total remission, 10% sustained total remission, and 23.1% received alternative diagnoses, of which 20% were sleep disorders. Higher fatigue severity scores and total number of symptoms were negatively associated with ever remitting. Duration of illness ≤ 2 years was positively associated with sustained remission. Unrefreshing sleep persisted in at least 79% of the subjects across all periods but, as with most of the CFS symptoms, tended to be less frequent over time. The number of activities affected by fatigue decreased over time, while wellness scores increased. At any follow-up, more than 35% of subjects reporting reduced fatigue used complementary and alternative medicine therapies, and of those subjects, at least 50% thought these therapies were responsible for reducing their fatigue.

Conclusions: The clinical course of CFS was characterized by an intermittent pattern of relapse and remission. Remission rates documented by our population-based study were similar to those reported in clinical studies. Shorter illness duration was a significant predictor of sustained remission, and thus early detection of CFS is of utmost importance. The persistence of sleep complaints and identification of sleep disorders suggest that CFS subjects be evaluated for sleep disturbances, which could be treated.

Background

Chronic fatigue syndrome (CFS) is a debilitating illness that causes substantial reduction in previous levels of professional, recreational, social, or educational activities [1]. CFS presents a challenge for patients, health care providers, and health insurance groups because of its incapaci-

tating nature, unknown cause, and poorly understood clinical course. A systematic review [2] of prospective studies found that 0%-37% (median = 6%) of adult CFS patients recovered, and 6%-63% (median = 35%) improved over time. Patients who recovered or improved were younger, did not have a co-morbid psychiatric disorder, and did not believe that the illness was due to a physical cause. More recent estimates of recovery and improvement are similar [3–6] (Table 1 [see Additional file: 1]). Short duration predicted a higher likelihood of recovery among patients enrolled in a surveillance system [4] but was not associated with recovery in severely ill patients selected from a CFS clinic [5] or from a CFS research registry [6]. All of these studies were conducted in clinical settings and thus involved people who were sick enough and had sufficient resources to seek and obtain medical care. In addition, most of the studies involved patients from specialty clinics at tertiary care medical centers who have been triaged or whose diagnosis was continuously supported by the health care system.

The objective of our study was to characterize the clinical course of CFS in the general population. We identified and followed CFS subjects from Wichita, Kansas for up to 3 years. We evaluated changes in CFS classification, case-defining criteria [1], wellness scores, hours of activities and sleep, and treatment use. We also determined associations between these changes and demographic and clinical factors.

Methods

Design

This study adhered to human experimentation guidelines of the U.S. Department of Health and Human Services. All participants were volunteers who gave informed consent. In 1997, we conducted a random-digit-dialing survey to estimate the prevalence of CFS and other fatiguing illnesses in Wichita, Kansas [7]. Briefly, a screening telephone survey asked 56,154 residents the following question: "Are you currently suffering from severe fatigue, extreme tiredness, or exhaustion that has been present for a period of one month or longer?" A total of 3,528 fatigued and 3,654 non-fatigued subjects were asked to participate in a detailed telephone interview to assess CFS case-defining criteria and other characteristics. Persons fatigued for ≥ 6 months, not feeling better after rest, not reporting any fatigue-associated medical or psychiatric conditions, and reporting at least 4 of the 8 CFS symptoms were eligible to participate in a clinical evaluation. These individuals were mailed a self-administered questionnaire requesting additional information about fatigue, symptoms, and medical history. During the clinic visit, subjects had a standardized physical examination and laboratory tests of blood and urine samples administered, and were given the Diagnostic Interview Scheduling (DIS) for DSM-IV [8] to establish psychiatric diagnoses. A physician review committee evaluated the clinical data and classified subjects on the basis of 1994 CFS case-definition criteria [1] as having medical or psychiatric diagnoses that could explain fatigue (permanent exclusions), temporary medical conditions that required resolution prior to classification (e.g., abnormal laboratory results, pregnancy), insufficient fatigue severity or number of symptoms, or CFS. Subjects who did not have any permanent medical or psychiatric exclusion [7] were re-interviewed yearly (4,228 in 1998, 3,980 in 1999, and 3,474 in 2000). Newly eligible subjects were invited for an initial evaluation, and subjects who had previously come to the clinic were invited for a follow-up visit. The physician review committee again assessed CFS classification.

This study considered CFS subjects who were identified during any year of the study and who had at least one follow-up visit. Of note, none of the participants in the study were informed of their CFS classification.

Changes in CFS classification

Changes in CFS classification at follow-up occurred because case-defining criteria were no longer satisfied (i.e., subjects reporting absence of fatigue, less than 4 of 8 symptoms, rest made fatigue a lot better, or fatigue did not interfere a lot with work, educational, social/recreational, or personal activities). Identification of alternative diagnoses (permanent or temporary) also precluded CFS classification.

Total remission was defined as having none of the case-defining criteria (i.e., absence of fatigue, less than 4 symptoms, health did not interfere with activities). Partial remission was defined as having some but not all of the case-defining criteria. Total (partial) sustained remission was defined as having two consecutive follow-up visits with total (partial) remission.

Fatigue reduction between clinic visits

Although subjects might not have been in remission at the follow-up clinic visit, they might have experienced at least one episode of reduced fatigue between clinic visits. Subjects at follow-up were asked "Since your last clinic visit, has there ever been a time when you have felt less fatigued?" Subjects reporting reduced fatigue were queried as to how long the most recent episode had lasted, whether they used any treatment since their previous clinic visit, and whether they thought the treatment was responsible for reducing their fatigue. Subjects who did not report reduced fatigue were not asked questions about treatment use.

Fatigue Assessment Instrument

Fatigued subjects also completed the 29-item Fatigue Assessment Instrument [9] and scores were calculated for four fatigue subscales: overall fatigue severity, situation-specific fatigue (measuring fatigue sensitivity to particular circumstances, such as heat, cold, and stress), fatigue consequences (measuring loss of patience, motivation or ability to concentrate), and fatigue responsiveness to rest or sleep.

Wellness scores, hours spent on activities and sleep during the past month

Subjects were asked the following questions referring to their wellness and activities during the past month: "Where would you place yourself in terms of energy, wellness, and ability to complete your every day activities on a scale from 1 to 100?"; "On average, how many hours per week did you spend on work duties, including working from home and travel related to work; household chores, such as cleaning, grocery shopping, and caring for your family; activities such as hobbies, schooling, or volunteer work?"; "How many hours of sleep, per day, including naps, have you averaged during weekdays and on the weekends?".

Statistical analyses

χ^2, Fisher's exact and McNemar's tests were used to compare proportions, and *t*-test and Wilcoxon test to compare continuous variables. Repeated measures were analyzed using generalizing estimating equations (GEE) models [10] with the first-order autoregressive correlation structure. The association between the likelihood of reporting a symptom and variables at initial classification (i.e., age at initial classification, sex, race, education, income, fatigue severity, wellness score, illness duration, onset type, and age at onset) was determined by using the binomial distribution with the logit link. Symptoms were grouped as CFS symptoms (those in the CFS case definition [1]) or non-CFS symptoms (those not included in the case definition). Models for the number of CFS or non-CFS symptoms used the normal distribution with the identity link. Logistic regression models were used to determine predictors of remission. All tests were 2-sided and p-values were considered significant if they did not exceed 0.05. All analyses were conducted using SAS version 8.1 (SAS Inc., Cary, NC).

Results

Characteristics at initial CFS classification

Among all fatigued subjects who came to the clinic over the study period, 90 were identified with CFS (43 of 300 in 1997, 15 of 270 in 1998, 22 of 291 in 1999, and 10 of 217 in 2000). Of these, 65 (72.2%) had at least one follow-up visit and thus were considered in this study. Tables 1,2,3,4 describe these subjects' characteristics at initial classification. More than three-quarters of our sample self-reported their onset as gradual and only 13.9% reported ever being diagnosed or treated for CFS (Table 2). A diagnosis of depression was self-reported by 30.8% of the subjects, but only 16.9% had lifetime major depression disorder according to the DIS. The most prevalent CFS symptom was unrefreshing sleep and the most prevalent non-CFS symptom was problems getting to sleep (Table 3). More than 60% were currently employed, and only 16.9% reported unemployment due to the fatiguing illness (Table 4). Approximately 20% reported short duration of fatigue (≤ 2 years). Compared with published data for CFS subjects [9], our sample had a significantly higher mean for the situation-specific fatigue subscale (*t*-test p-value = 0.0087) and a significantly lower mean for the subscale indicating fatigue responsiveness to rest or sleep (*t*-test p-value = 0.0167).

Follow-up visits

Of the 65 CFS subjects, 59 (90.8%), 39 (60%), and 24 (36.9%) were followed 1, 2, and 3 years, respectively, after initial classification. Reasons for missing visits included permanent exclusions in the previous visit, refusal to participate, cancellation of clinic appointment, or loss to fol-

Table 2: Demographic characteristics of CFS subjects at initial classification (N = 65)

Characteristic	Description
Female (%)	83.1
Current age in years (mean, standard deviation, range)	46 (9, 27–69)
Race (%)	
White	89.2
Black	3.1
American Indian	4.6
Other	3.1
Hispanic origin (any race) (%)	1.5
Education beyond high school (%)	63.1
Household income in previous year (%)	
<$20,000	23.1
$20,001–$40,000	23.1
>$40,000	44.6
Declined revealing	9.2
Median	$30,000–$40,000
Current or most recent job (%)	
Professional	20.3
Clerical work	20.3
Sales worker or representative	9.4
Homemaker	9.4
Owner/proprietor	9.4
Technician	9.4
Manager, official	7.8
Other	14.0
Current living situation (%)	
Alone	24.6
Couple with/without children	64.6
Single parent/living with family, friends	10.8

Table 3: Clinical characteristics of CFS subjects at initial classification (N = 65)

Characteristic	Description
Age at onset (mean, standard deviation, range) in years	37.1 (11.0, 5–57)
Median proportion of life with illness*	13.0
Self reported onset type (%)	
Gradual	76.9
Sudden	20.0
Don't know/declined reply	3.1
Body mass index (%)	
20–24: Normal	26.2
25–29: Overweight	33.8
≥ 30:Obese	40.0
Median (interquartile range)	27 (24–31)
Ever been diagnosed or treated by a physician (%)	
Fibrositis or fibromyalgia	32.3
Depression	30.8
Allergies confirmed by formal testing	21.5
Irritable bowel syndrome	18.5
Temporomandibular joint syndrome	16.9
CFS	13.9
Environmental sensitivity disease	1.5
Yeast infection (only females)	48.2
Diagnostic Interview Schedule (%)	
Current/Lifetime somatization	0
Lifetime major depression disorder	16.9

* Ratio between illness duration (in years) and age (in years)

low-up (respondent moved or could not be located). Subjects with follow-up visits had shorter duration of illness (median = 6 years vs. 9.1 years, Wilcoxon test p-value = 0.0378), fewer non-CFS symptoms (mean = 4.9 vs. 6.2, *t*-test p-value = 0.0419) and higher annual income (49.2% vs. 20% above $40,000, χ^2 test p-value = 0.0128) than those who were not followed. No differences were found with respect to age, sex, race, education, fatigue severity scores, wellness scores, or number of CFS symptoms.

Symptoms

Using GEE models, it was determined that the mean number of CFS and non-CFS symptoms decreased over time compared with the number of symptoms at initial classification (Table 3). Although the prevalence of CFS symptoms also tended to decrease over time, the ranking of symptoms remained the same. At all time points, unrefreshing sleep, muscle pain, post-exertion fatigue, difficulty thinking or memory impairment, and joint pain were the 5 most prevalent symptoms; whereas headaches, tender lymph nodes, and sore throat were the least prevalent symptoms.

Wellness, activities and sleep

Pairwise comparisons between consecutive time periods indicated that wellness scores were higher at the first year compared with initial evaluation (paired t-test p-value = 0.0085) (Table 3). No other significant differences were detected.

At initial classification, the median number (interquartile range) of hours spent on work duties, household chores, recreational activities, and sleeping during the week and during the weekend was, respectively, 40 (15–60), 15 (7–20), 0 (0–5.5), 7 (6–8) and 8 (6–9). No significant changes over time were detected.

Fatigue characteristics

Only a few fatigued subjects reported that rest relieved fatigue at any follow-up period (Table 4). The proportion of subjects reporting that fatigue interfered with social, professional, or educational activities at 1-year follow-up was significantly smaller than at initial classification (McNemar's test p-values = 0.002, 0.0124, 0.0290, respectively). Fatigue severity scores and number of activities affected by fatigue were also significantly reduced at 1-year follow-up (paired t-test p-values = 0.0047, 0.0001, respectively). No other significant differences were detected.

Illness states over time

About one-third of CFS subjects retained the classification after 1 year of follow-up (Table 5). At 2 and 3 years follow-up, only 21% of the subjects were classified as having CFS. Most transitioned into a non-CFS state because of insufficient symptoms or fatigue severity, absence of fatigue, or identification of an exclusionary condition. Overall, 23.1% (15 of 65) were eventually diagnosed with permanent exclusions, of which the most common were sleep disorders (i.e. sleep apnea or narcolepsy) (3 of 15), major depressive disorder with melancholia (3 of 15) and inflammatory bowel disease (2 of 15). Female sex, income ≤ $40,000, older age at initial classification, and higher fatigue severity scores were positively associated with the eventual detection of an exclusionary condition (Fisher's exact test p-values = 0.0197, 0.0169, and *t*-test p-values = 0.0008, 0.0042, respectively). No deaths were observed in this study.

Table 6 illustrates the pattern of illness states over the 3-year follow-up period. Overall, 56.9% of the subjects (37 of 65) experienced partial or total remission by the end of the follow-up. Among 40 subjects who had 2 consecutive years of follow-up, 22.5% sustained partial remission and 10% sustained total remission. The 4 CFS subjects who sustained total remission had been ill between 0.7 and 19.8 years and ranged in age from 35 to 53 years. There were 3 individuals with gradual and 1 with sudden onset, 2 females, 3 whites, and 1 Hispanic. Only 3 (7.5%) of 40 subjects sustained the CFS classification over two consecutive follow-up visits.

Table 4: Symptoms and wellness scores for CFS subjects at initial classification and follow-up

Characteristic	Initial classification (N = 65)	1-year follow-up (N = 59)	2-years follow-up (N = 39)	3-years follow-up (N = 24)
CFS symptoms lasting ≥ 6 months (%)				
Unrefreshing sleep	95.4	88.1	89.7	79.2*
Muscle aches or muscle pain	92.3	74.6*	74.4*	66.7*
Unusual fatigue post-exertion	78.5	50.9*	53.9*	33.3*
Difficulty thinking/concentrating or memory problems	76.9	71.2	59.0	62.5
Pain in joints	73.9	64.4	64.1	66.7
Severe headaches	58.5	35.6*	41.0	29.2*
Tender lymph nodes	16.9	20.3	12.8	4.2
Sore throat	12.3	6.8	5.3	0.0
Number of CFS symptoms (%)				
0	0.0	1.7	7.7	4.2
1–3	0.0	32.2	25.6	50.0
7–8	7.7	10.2	2.6	0.0
Mean number (standard deviation)	5 (1.1)	4.1 (1.7)*	4.0 (1.7)*	3.4 (1.5)*
Non-CFS symptoms lasting ≥ 6 months (%)‡				
Problems getting to sleep or waking up early in the morning	81.4	69.5	74.4	75.0
General weakness	80.0	61.0*	74.4	50.0*
Sinus or nasal problems	67.7	50.9*	53.9	58.3
Sensitivity to light	56.9	52.5	59.0	58.3
Depression	49.2	44.1	38.5	37.5
Numbness or tingling	35.9	44.8	30.8	58.3*
Shortness of breath	35.4	27.1	23.1	45.8
Stomach or abdominal pain	24.6	30.5	28.2	13.0
Diarrhea	20.0	20.3	20.5	4.2
Chills	18.8	13.6	5.1	4.2
Nausea	12.3	6.8	5.1	4.2
Fever	12.3	6.8	0.0	0.0
Mean number (standard deviation)	4.9 (2.0)	4.3 (2.2)*	4.1 (2.1)	4.1 (1.9)
Total CFS and non-CFS symptoms, mean (standard deviation)	10 (2.5)	8.4 (3.5)*	8.1 (3.5)*	7.5 (2.9)*
Wellness scores, mean (standard deviation)	41.2 (17.3)	48.5 (20.7)†	46.8 (20.5)	50.4 (17.6)

*$p < 0.05$ in GEE models compared with values at T0 † $p < 0.05$ in paired t-test ‡ Symptoms not included in CFS Case Definition

Reduced fatigue between visits and treatments used

Thirty-two (54.2%) of 59, 23 (59%) of 39 and 11 (45.8%) of 24 subjects followed at 1, 2, and 3 years, respectively, reported that they felt less fatigued since the last visit. More than half of the subjects reporting reduced fatigued experienced at least 6 periods (53.1%, 65.2%, and 63.6% at 1, 2, and 3 years, respectively) of reduced fatigue. The median duration of the most recent period was 8 days for years 1 and 2, and 30 days for year 3 of follow-up. Fatigue reduction was not significantly associated with remission at the follow-up visit.

Although traditional medicine was the most common treatment among subjects reporting reduced fatigue (100%, 91.7%, and 81.8% at 1, 2, and 3 years, respectively, Table 7), only 20% reported using it exclusively. Most subjects reported a combination of traditional medicine, self-help strategies, and complementary and alternative medicine therapies (84.4%, 73.9%, and 63.6% at 1, 2, and 3 years, respectively). More than 35% of the subjects reported use of any complementary and alternative medicine at any point in time and at least 50% of those who used it thought that it reduced their fatigue (Table 7). Remission was not associated with any particular treatment.

Predictors of remission and symptom changes

To determine predictors of remission and symptoms, we considered only the 50 subjects who never developed a permanent exclusion. Sixty-two percent of these subjects ever experienced a partial or total remission. There was no association between the report of ever being diagnosed or treated for CFS and remission (Fisher's exact test p-value = 1.0). Higher fatigue severity scores and larger total number of symptoms were negatively associated with ever experiencing remission. Odds ratios (OR) and 95% confidence intervals (CI) from a multivariate logistic regression model were, respectively, 0.389 (0.156–0.971) and 0.724 (0.533–0.985). Subjects who eventually remitted tended to have fewer symptoms at initial classification

Table 5: Illness characteristics among CFS subjects at initial classification and among fatigued subjects at follow-up

Characteristic	Initial classification (N = 65)	1-year follow-up (N = 49)	2-years follow-up (N = 29)	3-years follow-up (N = 18)
Fatigue duration in years (%)				
#2	18.5	2.0	0.0	0.0
2.1–5	23.1	20.4	27.6	11.1
5.1–10	30.8	34.7	31.0	44.4
>10	27.7	42.9	41.4	44.4
Median (interquartile range)	6 (3.6–10.8)	7.5 (5.3–13.2)	8.0 (4.8–12.9)	9.4 (7.2–13.9)
Rest did not relieve fatigue a lot (%)	100	95.2	96.6	94.4
Since fatiguing illness began, it interfered a lot with (%)				
Social activities	76.9	51.0*	62.1	44.4
Personal activities	76.9	69.4	58.6	55.6
Work activities	66.2	42.9*	55.2	33.3
Educational activities	40	28.6*	27.6	27.8
Median number of activities affected by fatigue	3	2†	3	1.5
Currently employed (%)	63.1	61.2	55.2	55.6
Unemployed because of fatiguing illness (%)	16.9	18.4	13.8	16.7
Fatigue Assessment Instrument subscales, mean (standard deviation)				
Severity	5.9 (0.9)	5.6 (0.8) †	5.8 (0.8)	5.4 (1.0)
Situation Specific	4.3 (1.3) ‡	4.3 (1.5)	4.5 (1.4)	3.8 (1.4)
Psychological consequences	6.0 (1.0)	6.0 (1.1)	6.2 (0.7)	5.8 (0.9)
Responds to rest/sleep	3.8 (1.8) ‡	3.3 (1.7)	3.8 (2.0)	3.4 (1.9)

* $p < 0.05$ in McNemar's test † $p < 0.01$ in paired t-test ‡ $p < 0.05$ in t-test, compared with published data

Table 6: Changes in CFS classification (%)

Classification	1-year follow-up (N = 59)	2-years follow-up (N = 39)	3-years follow-up (N = 24)
CFS	32.2	20.5	20.8
Insufficient symptoms or fatigue severity	30.5	30.8	37.5
Not fatigued	15.3	18.0	20.8
Exclusionary conditions			
Permanent medical or psychiatric*	8.5	15.4	16.7
Temporary medical†	13.6	15.4	4.2

*Permanent exclusions include bulimia, bipolar disease, chronic hepatitis, body mass index = 47, Sjögren's syndrome, diabetes with complications, multiple sclerosis, inflammatory bowel disease (2 subjects), sleep apnea or narcolepsy (3 subjects) and major depressive disorder with melancholia (3 subjects) † Temporary exclusions include abnormal urinalysis, beta-blocker medication, results for positive Romberg's test, rheumatoid factor, abnormal liver function, hypertension, breast mass, multiple myeloma, and thyroid disease.

but this trend was not statistically significant. Among the 32 subjects with at least two visits, 25% sustained partial remission and 12.5% total remission. By using categories of illness duration of ≤ 2 years, 2.1–10 years, and >10 years, it was found that subjects ill for 2.1–10 years were less likely to sustain remission than subjects ill for ≤ 2 years (OR = 0.107, 95% CI = 0.013–0.88). Subjects ill for >10 years were also less likely to sustain remission than those with shorter duration of illness, but this trend was not statistically significant (OR = 0.625, 95% CI = 0.073–5.350). No other variables were associated with sustained remission.

Few variables at initial classification were univariately associated with the likelihood of reporting individual symptoms (data available from the authors). Unrefreshing sleep was associated with female sex, being white, having higher fatigue severity scores, and being ill for 2.1–10 years when compared with 2 years or less. In a multivariate GEE model for unrefreshing sleep including these variables, being white, fatigue severity, and illness duration remained significant (p-values = 0.0005, 0.0003, 0.0058, respectively). The number of CFS symptoms was positively associated with higher fatigue severity scores (p-value = 0.0043), but the number of non-CFS symptoms was not associated with any variable.

Table 7: Illness states for CFS subjects at follow-up

No. of subjects	1-year follow-up (N = 59)	2-years follow-up (N = 39)	3-years follow-up (N = 24)
10	CFS	No visit	No visit
1	CFS	No visit	CFS
1	CFS	CFS	No visit
2	CFS	Partial Remission	No visit
1	CFS	Partial Remission	No visit
1	CFS	Partial Remission	CFS
1	CFS	Temporary exclusion	Partial Remission
1	CFS	Permanent exclusion	-
1	CFS	Permanent exclusion	-
3	Partial Remission	No visit	No visit
3	Partial Remission	CFS	No visit
1	Partial Remission	CFS	CFS
1	Partial Remission	CFS	Partial Remission
1	Partial Remission	CFS	Temporary exclusion
2	Partial Remission	Partial Remission	No visit
1	Partial Remission	Partial Remission	CFS
2	Partial Remission	Partial Remission	Partial Remission
1	Partial Remission	Partial Remission	Partial Remission
1	Partial Remission	Partial Remission	Permanent exclusion
2	Partial Remission	Temporary exclusion	Partial Remission
1	Partial Remission	Temporary exclusion	Permanent exclusion
3	Partial Remission	Total Remission	Total Remission
1	Total Remission	No visit	Partial Remission
1	Total Remission	Permanent exclusion	-
2	Total Remission	Permanent exclusion	-
1	Total Remission	Total Remission	No visit
5	Temporary exclusion	No visit	No visit
1	Temporary exclusion	Partial Remission	No visit
1	Temporary exclusion	Temporary exclusion	No visit
1	Temporary exclusion	Temporary exclusion	Partial Remission
3	Permanent exclusion	-	-
1	Permanent exclusion	-	-
1	Permanent exclusion	-	-
1	No visit	No visit	Permanent exclusion
1	No visit	CFS	CFS
1	No visit	Partial Remission	Partial Remission
1	No visit	Partial Remission	Partial Remission
1	No visit	Partial Remission	Permanent exclusion
1	No visit	Permanent exclusion	-
% Partial remission	37.3	38.5	45.8
% Total remission	8.5	10.3	12.5

Discussion

Our data revealed a complex and intermittent pattern of illness over time, where persistent CFS was the exception and not the rule. We found that 20%-33% of the originally identified CFS subjects remained in the CFS state at any subsequent visit, and only 7.5% remained in the CFS state for two consecutive periods. Although 56.9% experienced remission at some point during follow-up, only 22.5% sustained partial and 10% sustained total remission for two consecutive periods. We believe the apparent discrepancy between the low proportion of subjects who consistently fulfilled CFS criteria over time and the similarly low proportion that sustained total remission may reflect characteristics of the study design. Persons were classified as CFS only if they satisfied all criteria at the time of their clinical evaluation. Thus, individuals who met criteria shortly before evaluation but had temporarily improved around the time of their appointment (i.e., reported insufficient symptoms or fatigue severity) were not classified as having CFS. Clinical diagnosis is probably less conservative and practitioners would have continued to endorse CFS in such persons over time.

Table 8: Treatment use and perception that the treatment was responsible for reduced fatigue at follow-up

Treatment	% reporting treatment use among subjects reporting reduced fatigue*			% believing treatment responsible for reduced fatigue among subjects reporting use		
	1-year	2-years	3-years	1-year	2-years	3-years
Any traditional medicine	100.0	91.7	81.8	84.4	54.6	77.8
Medical doctor, emergency room	71.9	73.9	63.6	34.8	23.5	57.1
Prescription medication	78.1	69.6	63.6	64.0	37.5	71.4
Over-the-counter medication	65.6	65.2	27.3	42.9	26.7	100.0
Psychotherapy, counseling	12.5	13.0	9.1	50.0	33.3	100.0
Vitamins	81.3	69.6	72.7	65.4	56.3	62.5
Any self-help strategy	78.1	73.9	54.6	68.0	41.2	83.3
Exercise	68.8	65.2	54.6	63.6	33.3	83.3
Changes in diet	53.1	34.8	27.3	58.8	50.0	66.7
Any complementary and alternative medicine therapy	37.5	39.1	36.4	50.0	77.8	100.0
Herbal remedies	34.4	30.4	27.3	45.5	71.4	100.0
Homeopathy	6.3	4.4	18.2	100.0	100.0	100.0
Behavior modification (biofeedback)	3.1	4.4	0.0	0.0	100.0	0.0
Acupuncture	15.6	4.4	18.2	60.0	0.0	50.0

* N = 32, 23, and 11 at 1, 2, and 3 years, respectively

Permanent exclusions were identified in 23.1% of the subjects by the end of follow-up. Sleep apnea or narcolepsy and major depression disorder with melancholia were the most prevalent (20%). This proportion was remarkably higher than clinic-based studies that report rates between 2% and 13% [2]. This discrepancy may be due to the different case ascertainment approaches in clinical and population-based settings. Clinic-based studies reflect subjects seen at referral clinics who have generally been triaged and well evaluated to rule out known exclusionary conditions. In contrast, persons in our study represented the occurrence of the illness in the Wichita population. Since only 13.9% had ever been treated or diagnosed with CFS, the majority had either not perceived their status as an illness or had not undergone evaluation for identifiable causes of fatigue. Thus, it is not surprising that by yearly examination of our participants, we identified a high proportion of medical or psychiatric exclusions. In any event, this highlights the importance of health care providers consistently following their patients over time so that diseases can be promptly recognized and treated.

Most studies that describe the clinical course of CFS are set in hospitals or specialty clinics and include chronically ill patients. These subjects usually experience a poor outcome. Some investigators have suggested that subjects from primary care clinics or the general population might have better prognosis [11]. Contrary to these expectations, our population-based remission rates were within the range of those published in the literature of clinical studies [2–6]. Illness duration was the only predictor of sustained remission and this effect could be detected only when we defined categories of duration. Subjects with shorter duration of illness (≤ 2 years) were more likely to sustain remission than subjects ill for a longer time. It thus seems important to consider the possibility that the effect on clinical course outcomes is not the same for each additional illness duration year. Failure to define clinically meaningful categories may explain inconsistent associations across studies. Finally, in agreement with other studies [2], no deaths occurred in our sample.

We found a steady decrease in the number of CFS symptoms over time. However, unrefreshing sleep, the most common and persistent symptom at all follow-up periods, was still reported by 79.2% of subjects at the end of follow-up. Unrefreshing sleep was also one of the most commonly reported symptoms (87.5%) in another population-based study [12]. Of interest, subjects reported sleeping a median of 7 hours on weekdays. Thus, although hours of sleep were within normal limits, subjects found their sleep non-restorative. This observation has also been noted in a study of sleep, using polysomnography, in CFS patients who slept an average of 7 hours per night but reported feeling unrefreshed on waking [13].

We found decreased fatigue severity scores at the 1-year follow-up, but these levels were still significantly higher than values for normal fatigued controls [9]; thus, from a practical standpoint, subjects remained severely fatigue throughout the follow-up period. Despite this observation, our sample was highly functional (e.g., approximately 60% remained currently employed and worked a

median of 40 hours per week) compared with other samples in published literature [3–6].

There is currently no standard treatment for CFS. A recent systematic review [14] concluded that cognitive behaviour therapy and graded exercise therapy have shown promising results in controlled trials that evaluated interventions in CFS subjects. These therapies, however, are not widely available to the general public. Although there is insufficient evidence that complementary and alternative medicine therapies are effective [14], they are definitely more accessible. In our study, almost 100% of our subjects who felt less fatigued between clinic visits used traditional medicine treatments, but more than 35% reported use of complementary and alternative medicine therapies, such as herbal remedies, homeopathy, biofeedback, and acupuncture. This figure is twice as high as the 1997 US national prevalence estimate of 17.5% [15]. These therapies might be more prevalent among CFS subjects than the general population because of patients' desire to improve their health status and their lack of success with traditional approaches.

Our findings are limited by reduced sample size over time, which was due to elimination of subjects with permanent exclusionary conditions, refusals, or loss to follow-up. These factors should be considered when estimating the size of future longitudinal studies. In addition, we did not have a standardized measure of improvement or recovery, nor did we ask subjects whether they considered themselves partially or fully recovered. We created a definition based on absence of CFS case-defining criteria. This definition did not assess any measurable change in physical or mental function that could objectively indicate meaningful recovery from a clinical standpoint. As with so many other CFS parameters, it is fundamental that standardized measures of recovery be developed so that ambiguities in the clinical course of CFS are resolved. Last, most of our subjects reported a gradual onset and long duration of illness. Given enough subjects with sudden onset and/or short duration of illness, prognosis might have been quite different.

Authors' contributions

RN performed the statistical analyses and wrote the paper. JFJ and ERU contributed to the study design and clinical aspects of the paper. MR and WCR conceived of the study and participated in its design and coordination. All authors provided critical input during manuscript preparation and read and approved the final manuscript.

Additional material

Additional file 1

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