ELSEVIER

Journal of Psychosomatic Research 56 (2004) 217–229

Journal of Psychosomatic Research

Illness and disability in Danish Chronic Fatigue Syndrome patients at diagnosis and 5-year follow-up☆

M.M. Andersen[a], H. Permin[a,*], F. Albrecht[b]

[a] Department of Infectious Diseases M5132, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
[b] Regional Mid-Shore Mental Health Services, 17 S. Washington Street, Easton, MD 21601, USA

Received 25 June 2001; accepted 3 March 2003

Abstract

Objective: Evaluation of the life impact of Chronic Fatigue Syndrome (CFS) over 5 years. **Methods:** Thirty-three adult patients meeting 1988 and 1994 CDC case criteria answered identical questionnaires at diagnosis and 5 years later, when a retrospective questionnaire was also completed. **Results:** Work disability was very high and increased further, social isolation remained high, emotional adjustment improved. There were increased problems with reading and with allergies. Two measures of improvement were used: The relation between these measures was weak. Length of illness, extent of disability and emotional adjustment were poorly related to measures of improvement. Average illness scores were unchanged, but most individuals improved in some ways while worsening or remaining the same in others. Only one participant (3%) neared recovery, one other was substantially better but still severely disabled. **Conclusion:** CFS patients exhibit severe, long-term functional impairment. Substantial improvement is uncommon, less than 6%. Allergies and aspects of cognition may worsen, emotional adjustment often improves.

Keywords: Chronic Fatigue Syndrome; Cognitive disabilities; Neuropsychological problems; Repeated Measure; Social isolation; Five-year follow-up

Introduction

Studies of the natural course of Chronic Fatigue Syndrome (CFS) have produced inconsistent results, some showing significant proportions of patients improving or recovering, others contradicting these findings. Reasons cited for this variation include heterogeneity due to type of onset, differing types of sample (primary care, specialized clinic, population) and use of different case definitions. Three CFS case definitions have been in use over a period of 10–15 years: two CDC-defined definitions, Holmes et al. [1] and Fukuda et al. [2], and also a more lenient set of criteria, which does not require eight or more minor symptoms, Sharpe et al. [3]. The latter is often referred to as the "Oxford" definition. Other factors contributing to inconsistent results have been the lack of strict diagnostic work-up, problems with instruments, low response rates, reliance on overly simplified self-reports of improvement and the apparent heterogeneity of the illness itself. Another important reason for the inconsistency is that follow-up periods vary considerably.

Joyce et al. [4] performed a systematic review in 1997 of all studies of recovery from CFS. Length of follow-up varied from a few months to 3 years. In studies of subjects meeting operational CFS definitions, <10% returned to premorbid levels of functioning. In the remaining studies of patients in primary care, where less stringent criteria were used, at least 40% of patients improved. Hill et al. [5] followed severely ill patients for up to 4 years (average 3.4 years) and found that only 4% recovered. van der Werf et al. [6] found that complete recovery occurred only in patients with symptom duration of less than 15 month. Levine et al. [7] followed patients with epidemic neuromyasthenia for 10 years (New Zealand), and Strickland et al. [8] did a 10-year follow-up of an outbreak (Lake Tahoo) with very heterogeneous fatigue patients. Both studies found recovery rates of great variation depending on the measure used.

Tiersky et al. [9] studied neuropsychological functioning and employment status in CFS patients in a specialized clinic. The patients were reevaluated after a mean period of 3 years and 7 months following their initial visit. Results indicated that objective and subjective attention abilities,

☆ Conducted at the Department of Infectious Diseases, Rigshospitalet, Copenhagen.

* Corresponding author. Tel.: +45-35451492; fax : +45-35456648
E-mail address: rh01813@rh.dk (H. Permin).

0022-3999/04/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/S0022-3999(03)00065-5

mood, level of fatigue and disability improve over time. However, overall, the prognosis for CFS appears to be poor, as the majority of participants remained functionally impaired over time and were unemployed at follow-up, despite the noted improvements.

Jason et al. [10] reviewed four studies on community-based subtypes of CFS. They found variations in socio-demographics, illness onset, illness duration, symptom frequency, comorbidity and stressful precipitating events affected outcome measures of fatigue, symptom severity, functional ability and psychiatric comorbidity.

DeBecker et al. [11] performed a definition-based analysis of symptoms in a large cohort of patients with CFS to assess the Holmes and Fukuda definitions compared with idiopathic chronic fatigue patients not meeting either CFS case definition. They found patients meeting the Holmes criteria had both more symptoms and the most severe symptoms. Jason et al. [12] compared the Fukuda definition with the "Oxford" and concluded that using the latter case definition probably produces more heterogeneous patients groups, including some patients with purely psychiatric disorders.

Hickie et al. [13] studied temporal stability of chronic fatigue patients in primary care over 1 year and found that chronic fatigue is a persistent diagnosis over time. Bell et al. [14] followed pediatric cases from his practice for up to 13 years and found 80% of patients with "satisfactory outcome," but with mild to moderate persisting symptoms.

One conclusion supported by all studies is that CFS patients who fulfill strict diagnostic criteria [1,2] have worse prognosis compared to patients fulfilling lenient criteria.

Functional impairment in CFS is well documented, starting in 1995 with Wessely [15]. Schweitzer et al. [16] studied the impact of CFS on social and family relationships, work and recreational activities. They found significantly impaired quality of life (QOL), especially in areas of social functioning. Anderson and Ferrans [17] found the overall scores on their QOL index to be significantly lower in CFS than in other chronic illness groups. Buchwald et al. [18] used the Short-Form General Health Survey (SF-36) in patients with CFS and chronic fatigue seen in a university-based referral clinic. Among the factors found to be associated with functional limitations, increasing fatigue appeared to have the greatest effect. Hardt et al. [19] studied profiles of impairments in patients from three different countries using the SF-36. Patients scored below normal on all subscales. They concluded that health-related QOL is poor in CFS patients from all three countries. All in all, these findings unambiguously suggest that QOL is particularly and uniquely disrupted in CFS.

The purpose of this study is to illustrate in more detail than previously the impact on patients' lives of severe CFS (meeting both Holmes and Fukuda case criteria). Daily activities, social isolation, cognitive difficulties and neuropsychological problems were studied over a 5-year period, using two kinds of self-report measure. Focusing on groups of patients functionally improved, worsened or remained unchanged over this period, we present a detailed and complex picture of the natural course of this illness over 5 years in a carefully diagnosed, culturally and ethnically homogeneous sample.

Methods

Data acquisition and scoring

In March of 1994 (Time One) a questionnaire was sent to the first 37 patients who had been diagnosed with CFS using the 1988 criteria [1] at the Department of Infectious Diseases, Rigshospitalet, Copenhagen. The same physician saw all patients. Work-up included physical history and examination, psychiatric examination and laboratory tests including blood cell count, immunoglobulins, C-reactive protein, electrolyte panel, renal, hepatic and thyroid function, and rheumatological and virological screening. Further tests were used when indicated. When the 1994 case criteria [2] became available, each patient was seen again by the same physician, resulting in one exclusion for obesity and a changed (non-CFS) diagnosis. This left a sample of 35 consecutive cases meeting both case criteria. Over the following 5 years, the physician saw each of these patients at least five times in the hospital outpatient clinic. All 35 questionnaires were completed and returned.

Exactly 5 years later, in March 1999 (Time Two), two questionnaires were mailed to these patients. One, which was identical to the Time One questionnaire, called herein the Repeated Measure. The second, called herein the One-Time Measure, asked patients to rate symptoms and functional changes over the 5 years. Thirty-four of the 35 responded. One of these was excluded because she had in the interim been diagnosed with melancholic major depression and was symptom-free following ECT treatment. Another did not feel that she could respond meaningfully to the One-Time questionnaire because, in the interim, she had been treated for Addison's disease. Thus, 33 patients (94% of the original sample) completed identical questionnaires at Time One and Time Two, and 32 answered the second (One-Time Measure) questionnaire.

All patients were Caucasian, ethnically and culturally Danish, 28 females, 7 males. Female mean age was 41.1 years (range 25–56). Male mean age was 46.4 years (range 25–58). Median 1994 duration of illness was 4 years (range 1–33, mean 6.2). Prior to illness, 33 had been employed full time outside the home and one had been in charge of a large household with social duties. Occupations prior to illness onset ranged from manual labor (concrete worker, semi-skilled laborer) through a range of midlevel jobs (typist, bank clerk, nursery school teacher) to careers requiring extensive education (physician, dentist, editor-in-chief).

The Repeated Measure is a QOL questionnaire based on clinical experience. It concerns coping with daily living and

consists of three sections: Section 1 "Questions regarding your social life, work situation, etc.," Section 2 "Questions regarding your cognitive abilities, memory, etc." and Section 3 "Neuropsychological problems, allergies, etc." (see Appendix A). Most items ask for details of current functioning, but some are symptom-oriented. Most questions call for checked responses, but a few require numerical answers (e.g., hours slept at night) or to write a word or two (type of job held before illness, treatments, hobbies, etc.).

The One-Time Measure is a retrospective questionnaire asking "Questions regarding the difference between now and 5 years ago." It includes global questions about improvement ("Has your health improved in general during the last 5 years?") as well as functional questions (see Appendix B).

Questionnaires were constructed in Danish, and the number of questions was limited in order to secure a high return rate. A pilot experiment was performed with five volunteers receiving the Repeated Measure twice 2 weeks apart. For each volunteer, the second set of responses was 100% identical to the first.

Analysis of data

Scaleable responses to the Repeated Measure were scored on a three-point scale, with the lowest score indicating no CFS-related disability or (on symptom-related questions) improvement. The highest score represented maximum disability or that the symptoms were much worse.

Responses were summed across questions within years and were divided by the maximum possible score to obtain the percent of disability on the respective item. Changes in scores from Time One to Time Two were used as a measure of improvement or worsening. Sets of responses from individual patients were summed together (such as an entire section, or a coherent subset of a section).

Four Section 3 questions about mental health (3, 4, 5 and 6a) were scored together and used as a measure of depression/anxiety (D/A).

Patients were categorized as "Better" or "Worse," respectively, if their score improved or worsened with more than 4 points and with minimum 10%, from Time One to Time Two. Patients with lesser change in scores were categorized as "No change."

The One-Time Measure was scored +1 or −1 for answers indicating improving or worsening, and 0 for "No change" or "Don't know" responses. Patients were categorized as "Better" or "Worse," if their mean score on the questions regarding overall health (general health, severity and number of symptoms) was equal to or more than +1 or −1, respectively. Patients with lesser change in scores were categorized as "No change."

Statistical analysis

Scores at Time One and Time Two were correlated using Spearman Rank Order Correlation. Statistical analysis was used only to correlate section and total scores from Time One to Time Two. Factor analysis of all questions was considered and rejected as not be technically feasible. In the absence of such analysis the grouping of questions into sections for statistical purposes could not be validated. Section scores do have face validity and are reported, along with group responses to various individual questions, as a description of this sample's experience of CFS.

Results

Results for the Repeated Measure

Activities of daily life

In 1994, work disability was 77% (Table 1). Of the 35 patients, 25 had stopped working completely, 4 had various part-time works and only 6 patients had remained in previous jobs. In 1999, work disability had increased to 91%. One patient was in a part-time supported employment, two were part-time students and one was self-employed less than full time. None had full time or regular employment. Housework disability was 56% in 1994 and was almost unchanged in 1999.

Social impairment was high with all items tested: family contact, contact with friends, out-of-home activity. Disability for these items scored from 37% to 69%. Out-of-home entertainment had especially high scores. Only very small changes were seen in these scores from Time One to Time Two. Reading books and magazines showed increased disability (Table 1).

Cognitive abilities and memory

Three items in this group of questions showed increased disability from Time One to Time Two (Table 2). Difficulty in attention while reading increased from 58% to 70%, difficulty with learning new names from 40% to 54% and difficulty maintaining focus while performing an in-home activity in the presence of distraction increased from 46% to 61%.

Table 1
Mean disability: activities of daily life[a]

Type of activity	1994 (%)	1999 (%)
Illness-related work disability	77	91
Illness-related housekeeping disability	56	53
Social impairment, family, in home	56	48
Social impairment, family, out of home	37	42
Social impairment, friends, in home	56	53
Social impairment, friends, out of home	54	52
Reduced out-of-home entertainment	69	68
Reduced in-home entertainment	14	12
Reduced reading: books	54	62
Reduced reading: magazines	13	33
Reduced time spent on former hobbies	75	59

[a] From Repeated Measure Questionnaire Section 1, Questions 3–11. Expressed as a percentage of highest possible disability (higher score = greater disability).

Table 2
Mean disability: cognitive abilities and memory[a]

Cognitive category	1994 (%)	1999 (%)
Attention deficit while reading	58	70
Absent mindedness	62	59
Driving-related cognition impairment	41	33
Immediate memory impairment	28	32
Difficulty learning names	40	54
Intolerance of interruption	54	58
Word-finding difficulty	46	45
Difficulty making decisions	50	51
Daydreaming	39	40
Forgetting names	58	62
Problems keeping focus	46	61
Tip-of-tongue problem	71	71

[a] From Repeated Measure Questionnaire Section 2, Questions 1–12. Expressed as a percentage of highest possible disability score (higher score = greater disability).

Almost no change was seen from 1994 to 1999 in the other items studied. These included immediate memory, word-finding ability and forgetting names. These items scored from 28% to 62%, respectively. Tip-of-the-tongue problems scored high both years, 71% (Table 2).

Driving a car was problematic for a large minority of patients, scoring 41% and 33% in the respective years. Many patients stated that they felt unable to cope with traffic, or that they could do only one thing at a time. Some did not have a car (five in 1994 and four in 1999). No information was provided on whether those without a car had disposed of one due to CFS-related illness.

Neuropsychological problems, allergies, etc.

Table 3 shows that problems with vision and hearing scored around 70% and remained the same from Time One to Time Two. Emotional problems tended to improve, including all aspects of the D/A score. Panic attacks scored 48% in 1994 and were reduced to 32% in 1999. Losing temper was reduced from 63% to 51%. Feeling depressed in general also moved downward from 66% to 54%. Similarly, thoughts of suicide were at 27% in 1994 and moved downward to 17% in 1999. Depressed feelings and hopelessness about the illness, however, scored high at both times, around 65%.

Sleep problems were massive in 1994, scoring 96%, slightly improving to 87% in 1999 (Table 3). Occurrence of nightmares improved from 50% to 43%. The score for nighttime urination was 66% in 1994 and remained almost unchanged in 1999.

Sexual activity showed very high disability scores at both times, around 80%. Patients attributed this problem less to lack of desire (55% in 1994 and 42% in 1999) than to lack of energy (92% and 91%, respectively). From the additional information given, it appeared that in 1994, only 2 of the 35 (6%) did not have a sexual partner. In 1999, 6 of the remaining 33 (18%) had no partner.

Physical stress caused worsening of CFS symptoms in most patients in both years, scoring 87% and 90%, respectively. Mental stress apparently caused less worsening at Time Two, the score improving from 76% to 63%. Most patients experienced fluctuation of symptoms at both times (85% and 84%, respectively).

Table 3
Mean disability: neuropsychological problems and allergies[a]

Type of problem	1994 (%)	1999 (%)
Problems with vision (light sensitivity, other)	75	76
Problems with hearing (tinnitus, etc.)	66	65
Irritability, arguing	73	70
Panic attacks	48	32
Losing temper	63	51
Feeling depressed in general	66	54
Depressed by illness, feeling hopeless	65	69
Thoughts of suicide	27	17
Sleep problems	96	87
Nightmares	50	43
Nighttime urination	66	69
Reduced sexual activity	79	81
If sexual activity is reduced, it is because of:		
(a) Reduced desire	55	42
(b) Lack of energy	92	91
Symptoms worsened by physical stress	87	90
Symptoms worsen by mental stress	76	63
Symptoms fluctuate	85	84
Allergies, chemical intolerance	75	84

[a] From Repeated Measure Questionnaire Section 3, Questions 1–14. Expressed as a percentage of worst possible score (higher score = greater problem).

Allergies, sensitivities and intolerances scored high initially, 75%, and increased to 84% in 1999.

Overall, these results show that this group of patients experienced no overall improvement in CFS-related impairment over the 5 years. Social isolation scores were very high in both years, and some cognitive impairment increased. However, mental health (D/A) scores improved from Time One to Time Two and a related question about increased symptoms following mental stress also showed improvement. In 1999, a number of patients reported in written comments that they now felt better adjusted to their illness or that they were now better able to manage their lives in spite of illness.

Individual results for the Repeated Measure

Table 4 shows the number of patients who had improved or worsened in the respective sections over the 5 years. On activities of daily life, 16 patients improved and 10 worsened.

Table 4
Individual patients: changes in section scores, 1994–1999[a]

Section[a]	Better	Worse	No change
Activities of daily life	16	10	7
Cognitive abilities, etc.	12	15	6
Neuropsychological problems, etc.	13	6	14

[a] From Repeated Measure Questionnaire Sections 1, 2 and 3. Number of patients = 33.

Table 5
One-Time Measure: the difference between now (1999) and 5 years ago[a]

Health	Health better/ symptoms fewer	Health worse/ symptoms more	No change/ don't know
General health	5	14	13
Severity of symptoms, better/worse	8	18	6
Number of symptoms	7	11	14
House work + social contact	**More**	**Less**	**No change/ don't know**
House work you can do	0	19	13
Seeing or visiting family	3	22	7
Seeing or visiting friends	2	25	5
Going out (cinema, theater, etc.)	3	20	9

[a] From One-Time Measure Questionnaire Section 4, Questions 2–7. Number of patients = 32.

On cognitive abilities, 12 improved and 15 worsened. On neuropsychological problems, 13 improved and 6 worsened.

Improvement or worsening was inconsistent across sections. A majority of patients (23) were better on at least one section, but almost as many (21) were worse on at least one section. Eleven of the 23 who were better on at least one section were worse on at least one other. Only 8 patients of the 23 were better on all three sections, whereas 5 patients were worse on all three.

On each section and all sections together patient's scores from Time One to Time Two were highly correlated (Rank Order correlation factor (r) higher than .7 and $P < .00002$ in all cases).

Results for the One-Time Measure

Table 5 shows that when asked to recollect the status of their 1994 health and compare it to their present health (1999), 5 (15%) claimed that they were better, 14 that they were worse and 13 that there was no change or that they did not know. Questions concerning severity and number of symptoms confirmed the pattern that only a minority of the patients felt they were better in 1999 than in 1994, while a majority felt they were worse.

Four of 32 patients indicated their fatigue was better in 1999 than 1994, seven that it was worse. The scoring of general health was correlated with the scoring of fatigue (Fig. 1).

No patient in 1999 thought that she could do more housework than in 1994, while 19 said that they could do less and 13 claimed that there was no change or did not know.

A majority of patients stated that their social isolation had increased, 22 seeing family less, 25 seeing friends less and 20 going out less (Table 5).

Results compared across measures

Improvement or worsening on 1999's One-Time Measure were not the same persons who showed improvement or worsening on the Repeated Measure (Table 6a–c). For instance, among the five patients whose general health improved on the One-Time Measure, only one showed improvement on the activities of daily life, and none on cognitive abilities. Only two of the five patients claiming improvement in 1999 showed improvement on neuropsychological problems.

Fig. 2 shows that those improved, unchanged and worsened on the One-Time Measure all showed improvement in mental health (D/A) score. It is noteworthy that patients seeing themselves as worse in 1999 had the highest D/A scores, but also showed the most improvement. In spite of this improvement, their D/A scores in 1999 remained worse than those of the other groups.

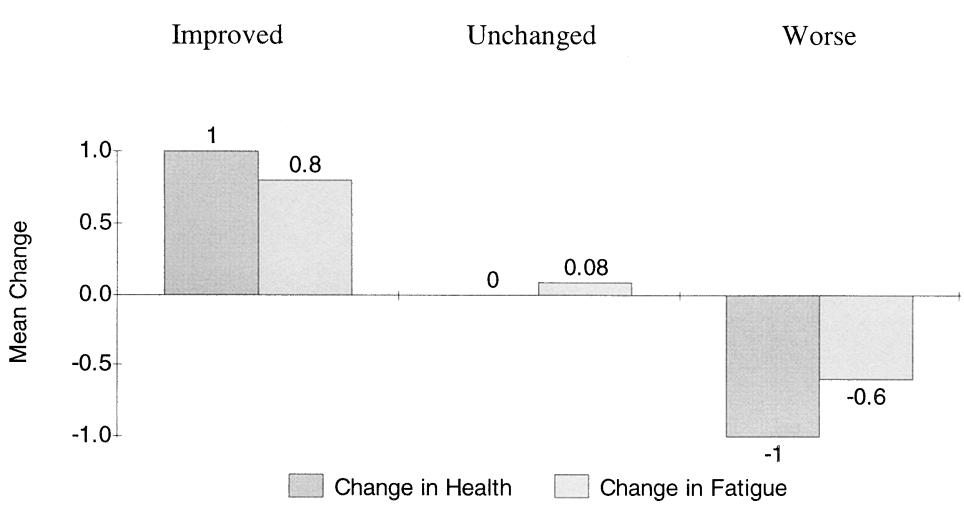

Fig. 1. CFS patients stating their overall health over the previous 5 years was improved, unchanged and worse, respectively, was compared to lessened, unchanged or worsened fatigue over the same period. Results from the One-Time Measure (1999).

Table 6

(a) Individual results compared across measures[a]

	One-Time Measure[b]		
Activities of daily life[a]	Better	No change	Worse
Better	1	3	8
No change	3	5	3
Worse	1	5	3

(b) Individual results compared across measures[c]

	One-Time Measure[b]		
Cognitive abilities[c]	Better	No change	Worse
Better	0	3	3
No change	2	6	4
Worse	3	4	7

(c) Individual results compared across measures[d]

	One-Time Measure[b]		
Neuropsychological problems[d]	Better	No change	Worse
Better	2	3	5
No change	1	8	9
Worse	2	2	0

[a] Based on scores for activities of daily life, Repeated Measure, Section 1.
[b] Based on scores for general health on One-Time Measure.
[c] Based on scores for cognitive abilities, etc., Repeated Measure, Section 2.
[d] Based on scores for neuropsychological problems, etc., Repeated Measure, Section 3.

In 1994, patients slept an average of 9.8 h and rested an average of 4.6 h, for a total sleep plus rest of 14.4 h. In 1999, they did slightly better with sleep of 9.6 h, rest of 3.9 and sleep plus rest of 13.5 h. This improvement in sleep and rest was mainly due to improvements made by the group of patients who stated their general health was better on the One-Time Measure (Fig. 3). Sleep/Rest was the only item studied that appeared to have a relationship between improvement by the Repeated Measure and improvement by the One-Time Measure.

A specific outcome difference between these two kinds of measure is that the Repeated Measure showed no increase in social isolation from family and friends, whereas the One-Time Measure indicates that isolation increased over the 5 years.

Other results

Repeated Measure noncoded questions asked about medications, treatment regimes, hobbies and other aspects of their lives. Patients indicated participating in a wide variety of regular and alternative treatment regimes. We were unable to find any correspondence between these responses and improvement or worsening as measured by our instruments. For instance, one patient reported at Time Two that removing mercury amalgams had produced significant improvement. However, she also reported sleeping or resting 14 h/day (down slightly from 15 h at Time One) and her social isolation score had increased. On repeated measures, she was better on one section, worse on another, overall unchanged.

We also correlated length of illness with 1999 scores, and with change in scores from 1994 to1999, but we found no difference.

Most patients (82% in 1999) reported fluctuation of symptoms, some daily, others weekly, monthly or seasonally. All patients reported what time of day they were most and least tired. We found no pattern to their responses.

Eighteen patients indicated taking on new hobbies since becoming ill. These hobbies were predominantly sedentary (“listening to music,” “distance education,” and

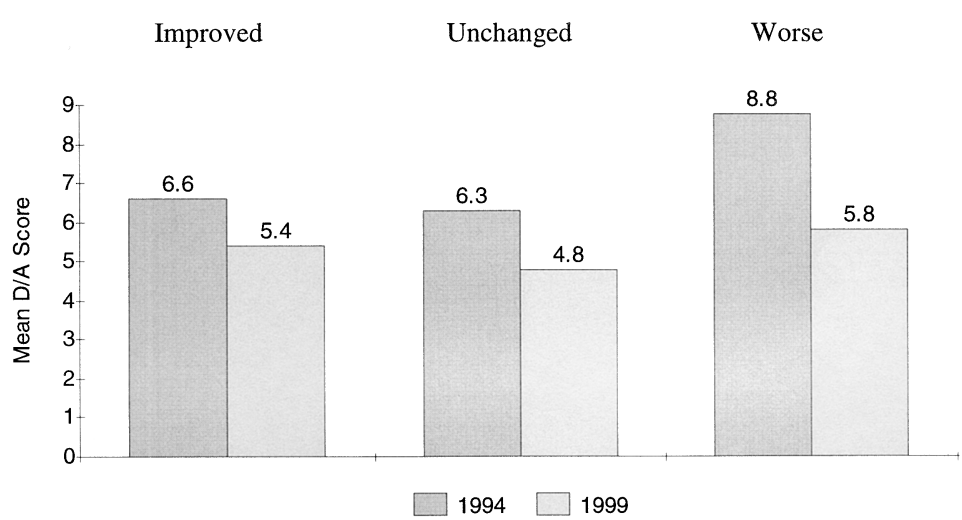

Fig. 2. Change in overall health (improved, unchanged, worse) and mental health in CFS patients in 1994 and 1999. Overall health was measured by the One-Time Measure, mental health (depression/anxiety) tracked by the Repeated Measure. Mental health improved regardless of change in overall health.

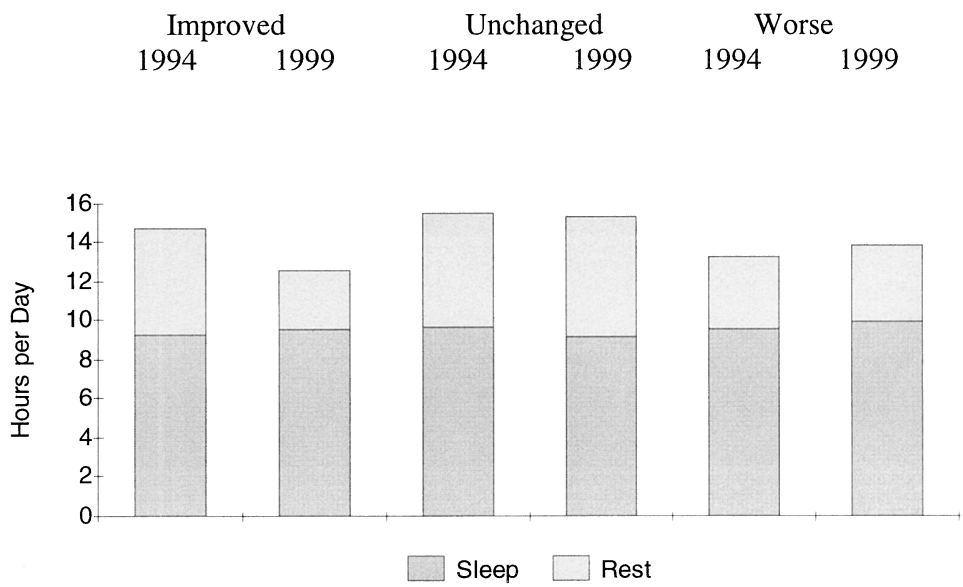

Fig. 3. Daily sleep and rest reported by CFS patients who stated on the One-Time Measure (1999) that over the previous 5 years, their overall health was improved, unchanged or worse. Only the improved group shows decreased hours for either sleeping or resting.

"embroidery"). Many new hobbies seemed illness-related, for instance, "spiritual development," "Yoga," "memory training" and "self-help groups."

Discussion

This 5-year follow-up of patients meeting both 1988 [1] and 1994 [2] CFS case definitions suggests that (1) recovery and substantial improvement are uncommon; (2) social isolation is severe and changes little over time; (3) some cognitive functions may decline over time; (4) emotional adjustment tends to improve over time but is unrelated to illness improvement or reduced disability; (5) some non-definitional symptoms, including reduced sexual function and increased allergy, may be common in CFS; (6) patients interpretation of general health is correlated to fatigue and to their need of sleep and rest; and (7) different ways of measuring improvement and worsening may produce inconsistent results. These conclusions are consistent with and add to many other findings.

Joyce et al. [4] summarized studies showing recovery rates from 3% to 19% over periods of 1.5–3 years, with improvement rates of from 35% to 63%. They noted worsened prognosis when the illness is defined stringently. Others confirm this pattern. The 10-year follow-up of the Lake Tahoe outbreak [8] shows that cases appearing to meet the 1994 criteria had a recovery rate of 15%, with only 3% of CFS patients returning to normal or near-normal activity. Hill et al. [5] studying "severe" CFS over a 3.4-year course found recovery in 1 of 23 (4%) and improvement in 9 (39%). Tiersky et al. [9] using both CDC criteria found only one instance of recovery (defined as no longer meeting case criteria) in 35 cases followed from 3 to 4 years. van der Werf et al. [6] studied 78 CFS patients finding that patients with a short duration of complaints had more favorable outcomes. After symptom duration of 15 months, there was no spontaneous recovery. This is in accordance with Russo et al. [20] who found that patients fulfilling strict CFS criteria twice, 2.5 years apart did not recover.

In the present study, we found improvement rates of 3–15%, depending on the criterion used. However, only one patient (3%) showed consistent improvement across all measures combined with a substantial reduction in illness-related disability. One other case showed improvement on all measures but remained very impaired (housebound, resting/sleeping 17 h/day). We conclude that 3–6% is a realistic estimate for significant improvement in our sample. From all of the above studies, including our own, it can be concluded that with CFS meeting strict criteria; the spontaneous recovery rate does not exceed 6%.

Almost all our patients reported symptom fluctuation, including daily, weekly or monthly periods. This, together with our other findings, suggests that symptoms often improve or worsen without altering the overall severity of the illness. Hill et al. [5] documented fluctuation of symptoms by rating illness severity at three points in time, and they found that among patients who at "time two" had improved, half were worse again at "time three." Jason et al. [21,22] have demonstrated four different phases of CFS illness by use of cluster analysis.

We found, as did Schweitzer et al. [16] and Anderson and Ferrans [17], that reduced social contact, strained relationships and loss of friends are typical experiences of CFS

patients. Out-of-home social activity and entertainment were especially reduced in our study. Patients typically needed to rest or sleep 14 h of each 24, greatly reducing the time available for social/entertainment activities, especially those occurring away from home.

Several studies have found increasing work disability to be the norm in CFS [5,9,23]. In our study, work disability was high initially, perhaps because at Time One, the average duration of illness was 4 years. Work disability nevertheless increased, approaching 100% at Time Two. We believe that most, if not all, of the observed work disability resulted from the combined impact of severe fatigue and reduced cognitive capacity.

Being unable to drive and loss of sexual intimacy are also isolating factors. We found both. Sexual problems have also been documented by Friedberg et al. [24] and Jason et al. [25]. In our study, patients report both fatigue and loss of a partner as reducing sexual activity. Problems driving have not previously been noted, as far as we are aware. Because some patients specifically stated that they have difficulty coping with traffic, or that they could do only one thing at a time, we suspect that they may have problems processing multiple stimuli or maintaining attention in situations with rapidly shifting demands. This finding is in accordance with Ross et al. [26] who found divided attention deficits in patients with CFS. These authors concluded that it is probable that CFS patients will report more cognitive difficulties in real-life situations that cause them to divide their effort or rapidly reallocate cognitive resources between two response channels (such as vision and audition).

The authors noted above [24,25] also found increased cognitive problems in "long duration" (>10 years) as opposed to "short duration" (<7 years) CFS. Most of our patients fall into the "long duration" category (mean illness duration at Time Two was 9 years). Cognitive problems relating to maintaining attention while reading were noticeable in 1994 and worsened by 1999. This is consistent with another finding; that patients reported devoting less time to reading (both books and magazines) in 1999 than previously. Investigations of cognitive abilities in CFS have produced mixed results [9,24,27]. Short et al. [28] were unable to document them by a series of standard measures. Because only a few very delimited cognitive problems may be intrinsic to CFS, we suggest that testers use instruments focused on real life activities (such as reading a book or testing in a traffic simulator). Such testing should include pre- and posttest assessment of fatigue.

Schmaling et al. [29] compared SPECT scans among patients with CFS and healthy persons while performing a test of attention and working memory (PASAT). They found no group differences for performance on the PASAT despite CFS subjects' perceptions of exerting more mental effort to perform the task. Inspection of the scans, however, suggested a pattern of diffuse regional cerebral blood flow among subjects with CFS in comparison with the more focal pattern seen among healthy subjects. The authors hypothesized that this reflected the need for recruitment of additional brain regions in CFS patients during tasks. This finding, if confirmed might account for CFS patients' perception of having to expend greater effort at a task, even when actual performance is comparable to controls'.

It has been seen in many studies, including Ray et al. [30], that good mental health does not predict improvement. Our findings are similar. We found that patients with poor mental health (D/A) scores usually improved in this way over the 5 years, regardless of whether or not they reported improvement in overall health. Our findings support Tiersky et al. [9] that mood improves over time. It also agrees with studies using the Fennell Phase Inventory [21,22] showing emotional integration and coping skills improving over time in spite of relapses or lack of physical recovery. The findings by Buchwald et al. [31] that psychological distress was associated with shorter duration of illness are also consistent with our results.

One aspect of CFS symptomatology, which has received relatively little attention, is that of allergies and hypersensitivities. Friedberg et al. [24] found evidence of hypersensitivity, a finding consistent with our data showing a high incidence of these problems at Time One and a trend toward even greater allergies after 5 years. This aspect of CFS deserves attention, together with the other aspects of immunology and neurobiology, which are now being recognized as factors in CFS pathophysiology.

Our finding that different measures of improvement may contradict each other is not unique. Bell et al. [14] contacted CFS patients seen 13 years earlier, finding a rather weak relationship between self-rated improvement and visual analog (VAS) scores of symptom severity. Some patients who claimed complete recovery had VAS scores indicating continuing illness. A majority responding that they felt "well" had such scores. A similar discrepancy is seen in the Lake Tahoe [8] finding that 15% of CFS cases claimed "recovery," but only 3% claimed return to normal or near-normal activity.

Discrepancies in self-report may have a number of causes, including adaptation level [32], recency effects [33] and other response biases, as well as poorly framed questions and faulty memory. In addition, the words used in a question may not have the same meaning for all respondents. Symptom fluctuation also helps explain our data. Patients can get better in one way worse in another — and then reverse that at a later time.

It is remarkable that patients' responses to questions about their general health consistently reflected their level of fatigue. The only other factor that is related to responses about general health was the amount of sleep plus rest (Fig. 2). This contrasts with responses to many other questions posed concerning social life, cognitive skills and neuropsychological problems where no such relation was found. For instance, our patient 22 reported on the

One-Time Measure (1999) that she had, on the whole, improved since 1994. She was housebound in both 1994 and 1999, and her overall score on the Repeated Measure was unchanged, though she worsened on Section 2, cognitive abilities. She, however, reported reduced fatigue, and that she now slept/rested only 17 h/day, instead of 21 as previously.

This study included careful diagnostics, thorough medical follow-up and a very low dropout rate. Our unstandardized, self-report questionnaires showed a high test–retest correlation in a small pilot study and also between administrations in 1994 and 1999. The results also show considerable internal consistency. We thus feel encouraged to view our findings as a valid reflection of these patients' experience of CFS, and we continue to follow these patients in further studies.

References

[1] Holmes G, Kaplan J, Gantz NM, Komaroff AL, Schonberger LB, Strauss SE, Jones JF, Dubois RE, Cunningham-Rundles C, Pahwa S, Tosato G, Zegans LS, Purtilo DT, Brown N, Schooley RT, Brus I. Chronic fatigue syndrome: a working case definition. Ann Int Med 1988;108:387–9.

[2] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A, The International Chronic Fatigue Syndrome Study Group. The chronic fatigue syndrome: a comprehensive approach to its definition and study. Ann Intern Med 1994;121:953–9.

[3] Sharpe MC, Archard LC, Banatvala JE, Borysiewicz LK, Clare AW, David A, Edwards RH, Hawton KE, Lambert HP, Lane RJ, McDonald EM, Mowbrag JF, Pearson DJ, Peto TEA, Preedy VR, Smith AP, Smith DG, Taylor DJ, Tyrell DAJ, Wessely S, White PD. A report — chronic fatigue syndrome: guidelines for research. J R Soc Med 1991;84:118–21.

[4] Joyce J, Hotopf M, Wessely S. The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review. Q J Med 1997;90: 223–33.

[5] Hill NF, Tiersky LA, Scavalla VR, Lavietes M, Natelson BH. Natural history of severe chronic fatigue syndrome. Arch Phys Med Rehabil 1999;80:1090–4.

[6] van der Werf SP, de Vree B, Alberts M, van der Meer JWM. Natural course and predicting self-reported improvement in patients with chronic fatigue syndrome with a relatively short illness duration. J Psychosom Res 2002;53:749–53.

[7] Levine PH, Snow PG, Ranum BA, Paul C, Holmes MJ. Epidemic neuromyasthenia and chronic fatigue syndrome in West Otago, New Zealand: a 10-year follow-up. Arch Intern Med 1997;157: 750–4.

[8] Strickland SS, Levine PH, Peterson DL, O'Brien I, Fears T. Neuromyasthenia and Chronic Fatigue Syndrome (CFS) in Northern Nevada/California: a ten-year follow-up of an outbreak. J Chronic Fatigue Syndr 2001;9:3–14.

[9] Tiersky LA, DeLuca J, Hill N, Dhar SK, Johnson SK, Lange G, Rappolt G, Natelson BH. Longitudinal assessment of neuropsychological functioning, psychiatric status, functional disability and employment status in chronic fatigue syndrome. Appl Neuropsychol 2001;8:41–50.

[10] Jason LA, Taylor RR, Kennedy CL, Harding ST, Song S, Johnson D, Chimata R. Subtypes of chronic fatigue syndrome: a review of finding. J Chronic Fatigue Syndr 2001;8:1–22.

[11] DeBecker P, McGregor N, DeMeirleir K. A definition based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome. J Intern Med 2001;250:234–40.

[12] Jason LA, Richman JA, Friedberg F, Wagner L, Taylor R, Jordan KM. Politics, science, and the emergence of a new disease. The case of chronic fatigue syndrome. Am Psychol 1997;52:973–83.

[13] Hickie I, Koschera A, Hadzi-Pavlovic D, Bennett B, Llyod A. The temporal stability and co-morbidity of prolonged fatigue: a longitudinal study in primary care. Psychol Med 1999;29:855–61.

[14] Bell DS, Jordan K, Robinson M. 13-Year follow-up of children and adolescents with chronic fatigue syndrome. Pediatrics 2001;107: 994–8.

[15] Wessely S. The epidemiology of chronic fatigue syndrome. Epidemiol Rev 1995;17:139–51.

[16] Schweitzer R, Kelly B, Foran A, Terry D. Quality of life in chronic fatigue syndrome. Soc Sci Med 1995;41:367–72.

[17] Anderson JS, Ferrans CE. The quality of life of persons with chronic fatigue syndrome. J Nerv Ment Dis 1997;185:359–67.

[18] Buchwald D, Pearlman T, Umali J, Schmaling K, Katon W. Functional status in chronic fatigue syndrome, other fatiguing illnesses, and healthy individuals. Am J Med 1996;101:364–70.

[19] Hardt J, Buchwald D, Wilks D, Sharpe M, Nix WE, Egle VT. Health-related quality of life in patients with chronic fatigue syndrome. An international study. J Psychosom Res 2001;51:431–2.

[20] Russo J, Katon W, Clark M, Kith P, Sintay M, Buchwald D. Longitudinal changes associated with improvement in chronic fatigue patients. J Psychosom Res 1998;45:67–76.

[21] Jason LA, Fennell PA, Taylor RR, Fricano G, Halpert JA. An empirical verification of the Fennell phases of CFS illness. J Chronic Fatigue Syndr 2000;6:47–56.

[22] Jason LA, Fricano G, Taylor RR, Halpert J, Fennell PA, Klein S, Levine S. Chronic fatigue syndrome: an examination of the phases. J Clin Psychol 2000;12:1497–508.

[23] Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Prognosis in chronic fatigue syndrome: a prospective study on the natural course. J Neurol Neurosurg Psychiatry 1996;60:489–94.

[24] Friedberg F, Dechene L, McKenzie MS, Fontanetta P. Symptom patterns in long-duration chronic fatigue syndrome. J Psychosom Res 2000;48:59–68.

[25] Jason LA, Torres-Harding SR, Carrico AW, Taylor RR. Symptom occurrence in persons with chronic fatigue syndrome. Biol Psychol 2002;59:15–27.

[26] Ross S, Fantie B, Straus SF, Grafman J. Divided attention deficits in patients with chronic fatigue syndrome. Appl Neuropsychol 2001;8: 4–11.

[27] Bastien C. Patterns of neuropsychological abnormalities and cognitive impairment in adults and children. In: Hyde B, Goldstein J, Levine P, editors. The clinical and scientific basis of myalgic encephalomyelitis (chronic fatigue syndrome). Ottawa: The Nightingale Foundation, 1992. p. 54.

[28] Short K, McCabe M, Tooley G. Cognitive functioning in chronic fatigue syndrome and the role of depression, anxiety, and fatigue. J Psychosom Res 2002;52:475–83.

[29] Schmaling KB, Lewis DH, Fiedelak JI, Mahurin R, Buchwald DS. Single-photon emission computerized tomography and neurocognitive function in patients with chronic fatigue syndrome. Psychosom Med 2003;65(1):129–36.

[30] Ray C, Jefferies S, Weir WRC. Coping and other predictors of outcome in chronic fatigue syndrome: a one year follow-up. J Psychosom Res 1997;43:405–15.

[31] Buchwald D, Pearlman T, Kith P, Katon W, Schmaling K. Screening for psychiatric disorders in chronic fatigue and chronic fatigue syndrome. J Psychosom Res 1997;42:87–94.

[32] Daltroy LH, Larson MG, Eaton HM, Phillips CB, Liang MH. Discrepancies between self-reported and observed physical function in the elderly: the influence of response shift and other factors. Soc Sci Med 1999;11:1549–61.

[33] Suh E, Diener E, Fujita F. Events and subjective well-being: only recent events matter. J Pers Soc Psychol 1996;70:1091–102.

Appendix A.

The Danish CFS Questionnaire
Repeated Measure
(Translation)

I. Questions regarding your social life, work situation, etc.

1. Sex _____ Age _____

How many years have you suffered from CFS?_____

2. Did you have a paid job before you became ill? _____yes _____no

What was it ?_____

	More	The same	Less	Stopped
3. Did your work situation change after you became ill?				
If less work/shorter hours: a) 1/2 time or less _____ b) Changed to easier work _____ c) Fired due to illness _____ d) Stopped work by free will _____				
4. Do you work around the house to the same extent as before you became ill?				
5. Your family, those that are **not** living with you, do you see them as often as before ? a) at their place?				
b) at your place?				
6. Your friends and relatives, do you see them as often as before ? a) at their place?				
b) at your place?				
7. Cinema/Theater visits etc. 'going out' compared to before?				
8. Amount of TV and Video compared to before you became ill?				
9. Heavy literature (books), how much do you read compared to before you became ill?				
10. Light literature (Magazines) how much do you read compared to before you became ill?				
11. Your old hobbies and interests, how much time do you spend compared to before?				

12. What new hobbies or interests have you taken up since becoming ill with CFS?

_____

13. Number of hours *sleep* a day (24 hours) _____

14. Number of hours *resting* (besides sleep) on the couch/bed a day _____

15. When during the day are you *most tired* ? _____

16. When during the day are you *least tired* ? _____

II. Questions regarding your cognitive abilities, memory, etc.

	No change	Seldom or Never	On and off	Often/ always
1. When you read something, do you find afterwards that you had not paid enough attention and have to re-read it ?				
2. Do you go from one side of the house to the other, just to realize that you forgot what you went for ?				
3. Are you worried/unsure of yourself to drive a car ? (Maybe because you find you cannot do two things at the same time)				
4. When you have left the house, are you then uncertain or confused whether you remembered to turn off the light/gas and locked the door				
5. Do you have trouble learning people's names the first time you meet them ?				
6. If you are in the middle of something, do you not notice if someone speaks to you ?				
7. Do you have trouble finding the exact words or wonder if you used words in the correct context ?				
8. Do you have difficulty making up your mind ?				
9. Do you day dream (let you mind flow freely), while you ought to pay attention ?				
10. Do you forget peoples names ?				
11. Can you be up to doing something at home and then get distracted and find your self doing something different ?				
12. Do you have memory problems where it feels as if the word is on the tip of your tongue' ?				

III. Neuropsychological problems, allergies, etc.

	Yes	Maybe	Sometimes	No
1. Do you have sensitivity to light or other disturbances of eye sight? Which: _____				
2. Do you have problems with hearing such as ringing, buzzing or tinnitus?				
3. Are you now more irritable/edgy (having arguments with the family, not tolerating being criticized, finding 'the others' are the problem)				
4. Do you suffer from sudden attacks of panic (panic attacks) ?				
5. Do you lose control (make a big fuzz over small things that gave you no problems earlier) ?				
6. Are you periodically depressed ? a) generally much more depressed/ in low spirit than before				
b) Sad/ depressed for being ill, see no hope for the future				
c) Considering 'ending it all', having thoughts about suicide				
7. Do you have difficulties sleeping (either sleep much more than before, cannot fall asleep, wake up frequently) ?				
8. Do you have nightmares?				
9. Do you have to get up at night to urinate ?				

	Yes	No	No Lover
10. Are you having as much sex with your lover (wife, husband, partner) as before CFS ?			
IF NO - is it because of: a) You do not experience/feel any sexual desire ?			
b) You do feel desire, but you simply haven't the energy to 'do something about it'?			
c) Other reasons: which?: _____			

	Yes, all of them	Yes, some	Yes, a few	Not sure	No
11. Do your symptoms get worse after **physical** stress?					
12. Do your symptoms get worse after **mental** stress?					

	Yes	No	Don't Know
13. Do you experience fluctuations in your symptoms (for instance, daily, monthly, yearly)? Which _____			
14. Have you developed allergies, sensitivities or intolerancee since getting CFS? Which _____			

15. List Medicines you have used for CFS:

a. Painkillers over the counter (Aspirin etc.)
which _____
b. Sedatives (Stesolid etc.)
which _____
c. Antidepressives
which _____
d. Other medicines on prescription
which _____
e. 'Alternative' medicines
which _____
f. Vitamins/Magnesia and the like
which _____

16. Did you seek alternative treatment for CFS ? Zone therapy, healing, astrology ?
which kind(s)?_____

Comments:

Appendix B.

One-Time Measure

Questions regarding the difference between now and 5 years ago

1. If you work, has your position changed since 5 years ago? _____yes _____no ____don't know

In what way ?_____

Do you get disability pension ? _____

Which kind ?_____

	yes	no	Don't know
2. Has your health improved in general during the 5 last years ?			
a) Have some of the symptoms disappeared?			
b) Are some of the symptoms of a lighter nature ?			
c) Are there fewer symptoms all together?			
d) Would you say that you all in all are better now ?			
3. Has your health deteriorated in general during the 5 last years ?			
a) Have you encountered new symptoms ?			
b) Are some of the old symptoms worse now ?			
c) Are there more symptoms all together?			
d) Would you say that you all in all are worse now ?			
4. Do you work around the house the same as 5 years ago ?			
5. The part of your family you are not living with, do you see them as often?	XXX	XXX	XXX
a) More visits all together ?			
b) Less visits all together ?			
6. Friends and relatives, do you see them as often ?	XXX	XXX	XXX
a) More visits all together ?			
b) Less visits all together ?			
7. Cinema/theater/'out', do you go as much ?	XXX	XXX	XXX
a) Same as 5 years ago ?			
b) Less all together ?			
c) More all together ?			

8. Fatigue. Number of hours *resting* (besides sleep) on the couch/bed a day:
is it more or less than 5 years ago? _____