# Critical Life Events, Infections, and Symptoms During the Year Preceding Chronic Fatigue Syndrome (CFS): An Examination of CFS Patients and Subjects With a Nonspecific Life Crisis

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**Objective:** The purpose of this study was to describe the sequence of psychosocial events and infections preceding the onset of chronic fatigue syndrome (CFS). This information was related to the temporal development of crucial symptoms in relation to the onset of, namely, fatigue, sadness, irritability, pain, and feeling of fever. **Methods:** A personal interview was conducted in 46 patients (mean age, 39.5 years; SD, 9 years) who fulfilled international CFS criteria. These patients were matched with regard to age and gender to 46 carefully matched control subjects. Twenty-three percent of the study subjects were men, and 77% were women. The patient at first identified the month that coincided with the onset of CFS. Similarly, each control subject was asked to identify a "very difficult period" within approximately the same period as the patient with whom the control subject was matched. A list of 14 different life events was perused. Participants were asked to identify for each month whether each of the listed events had occurred. Furthermore, they were asked to rate the importance of the events they had experienced. In addition, for each of the cardinal symptoms (fatigue, sadness, irritability, pain, and feeling of fever) and for each month, the subjects were asked to rate, on a visual analogue scale, the symptom intensity. Also, the number of infections was noted. **Results:** A statistically significant group difference in fatigue intensity existed during the period 4 to 10 months before the onset of CFS. During the 3 months preceding the diagnosis for the CFS patients or the peak of the crisis for the control group, there was a dramatic rise in fatigue in both groups. The CFS group reached a much higher fatigue level, which leveled off somewhat during the first year of follow-up but still remained very high in comparison with the control group, which reached precrisis levels 4 months after the peak. Similar patterns were observed for fever and pain. With regard to sadness and irritability, no group difference was observed during the period preceding the crisis. In the patient group, the level stayed high throughout the whole first year of follow-up, whereas a slow return started in the control group; precrisis levels were reached after 1 year in this group. The prevalence ratio (CFS patients/control subjects) for negative events was around 1.0 for the periods 4 to 12 months preceding CFS but 1.9 during the quarter year preceding the onset. For infections, the prevalence ratio increased successively during the four quarters preceding CFS (from 1.4 to 2.3). **Conclusions:** According to the retrospective self-reports, there were differences between the groups in fatigue, pain, and feeling of fever during the months preceding the crisis. With regard to depressive and irritable feelings, no preillness differences were reported between the groups. There was a reported excess prevalence of both infections and negative life events during the quarter year preceding the onset of CFS or crisis. Potential sources of error are discussed. These findings must be replicated in longitudinal studies. **Key words:** chronic fatigue syndrome, critical life changes, infectious disease, sadness, irritability.

CFS = chronic fatigue syndrome; HPA = hypothalamo-pituitary-adrenal system; VAS = visual analogue scale.

## INTRODUCTION

CFS has existed as a diagnostic entity since 1988 with a later modification of criteria (1). It is characterized by extreme unexplained fatigue as well as somatic symptoms, such as tenderness in lymph glands, mild myalgia, arthralgia, recurrent sore throat, and headache. Unrefreshing sleep is frequently reported, as are impairment of short-term memory and capacity to concentrate. Physical exercise can exacerbate the illness. Intermittent fever or feeling of fever (1, 2) is also frequently described. The point prevalence in the population has been estimated to be 2.6%. The prevalence falls to 0.5% if persons with comorbid psychological disorders are excluded (3). The pathogenesis of CFS is poorly understood. It has been assumed that infections may be important, although the crucial microorganism has not been detected. Several studies have indicated that long-lasting psychosocial strain may be also be important in the pathogenesis. In particular, adverse critical life events have been implicated. Nonetheless, the studies that have been published regarding the role of negative events in CFS have shown divergent findings (4, 5).

In physiological studies, it has been shown that patients with CFS suffer from disturbances in regula-

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tory arousal mechanisms (6). In particular, the HPA system, or axis, has been shown to be nonresponsive to physiological stimuli. This may explain why patients with CFS are unable to respond to stressful situations emotionally and practically. It may also partly explain why these patients suffer from unrefreshing sleep. Thus, regardless of the pathogenesis of CFS, a prominent feature is an "exhausted" HPA axis. There is evidence in some studies that other systems, such as the catecholaminergic system, and immunological parameters, such as natural killer cells, show disturbed regulation as well (4). Some of these disturbances may be compensatory.

The primary aim of this study was to increase the understanding of CFS by describing the sequence of psychosocial events, infections, symptoms of infection, and stressful feelings related to the onset of CFS. The study was retrospective and was designed to shed light on the temporal relationships between negative life events and infections in the year preceding the onset of CFS. In addition, crucial somatic (tiredness, fever, and pain) and psychological symptoms (sadness and irritability) were described for each month preceding and succeeding the onset of CFS. A group of control subjects, matched with CFS patients in terms of occupation, gender, and age, who had a life crisis during approximately the same period but did not develop CFS was studied using the same research protocol for the same periods.

## METHODS

### Subjects and Procedure

Interviews focused on critical life events and infections. All interviews were conducted by one of the authors (V.B.) in a standardized manner, and all lasted for 45 to 60 minutes.

Forty-six of 53 consecutive patients attending the CFS outpatient clinic and fulfilling diagnostic criteria (1) who received their diagnosis at a clinic for infectious diseases at a university hospital in the Stockholm, Sweden, region from January 1996 to January 1997 agreed to participate in the study. They were contacted by mail from the hospital. Clinic staff then gave the patients' telephone numbers to the interviewer. Participants were contacted and asked to decide where they wished to be interviewed at home or close to home, at work, or at the hospital. Those who were interviewed by telephone were patients referred from other parts of the country. The information collected during the interviews was considered confidential. Forty-six control subjects were selected at two public sector work sites, a public insurance office and a geriatric clinic. Control subjects were matched to patients in terms of age, gender, family situation (marital status and number of children), and occupation.

Twenty-three percent of the study sample were men, and 77% were women. The mean age in both groups was 39.5 years, with a standard deviation of 9 years. For age, gender, and family situation, participants were matched individually as closely as possible between the two groups, and the distributions did not differ significantly. Forty percent were single, and 60% were cohabiting. Twenty-nine percent had no children; 20%, one child, 34%, two children; and 17%, three or four children. The matching procedure was performed in collaboration with the local regional office of employment. Among the employed as well as the unemployed, occupational matching took place in the following categories: adult students, academic teachers, other teachers, nurses, child nurses, nursery teachers, nurses' aides, self-employed, employees in the employment office, employees in the public insurance office, and drivers. Occupational matching was not perfect, but the distributions across categories did not differ significantly between groups. Among the participants, 46% with CFS and 61% of control subjects were working in care, and 41% of CFS patients and 28% of controls were working in administration; 4% of CFS patients and 7% of controls were unemployed. In addition, 9% of CFS patients were students, whereas 4% of the control subjects were students.

Contacts between potential participants and the research group were established through their respective office. A majority of the control subjects (84%) were interviewed at work. The remaining subjects were interviewed at their homes or by telephone.

At first, each patient was asked to identify the month during which he or she considered the onset of CFS to have occurred. Half of the subjects reported that the onset took place between 1994 and 1996, and the other half reported that onset occurred during 1983 to 1993, with an almost even distribution throughout these years. Control subjects were asked in a similar way to identify a "very difficult period" during approximately the same period as the patient to whom he or she was matched. It was possible to match this period to the patient's onset period because many control subjects had experienced two or more crisis periods. Accordingly, when CFS onset in the patient group had occurred during an early period, the matched patients' early crisis periods could be selected. The distribution of crisis periods in the control group was similar to that of onset periods in the CFS group, with approximately half (22 CFS patients and 24 controls) in the years 1994 to 1996 and half (24 CFS patients and 24 controls) in the years 1980 to 1993.

### Interview and Questionnaires

In the first part of the interview, a list of 14 different events (see Table 1) was perused. This list was a condensed version of the original life change list presented by Holmes and Rahe (7), which included only the most serious life changes. Subjects were asked to identify, for each of the 12 months before the onset of CFS or life crisis, whether any of the listed events had occurred. Because the time of the occurring events was crucial, the interviewer tried to differentiate clearly between events and long-term difficulties and to ensure that the events could be classified as events. Because there may be a tendency for interviewed subjects during the first month (the one preceding the onset of CFS by 12 months) to include events that may have occurred earlier during the preceding year, an effort was made to make sure that only events that had actually occurred during this period were included. After the first part of the interview regarding life events, subjects were asked to rate the events on a five-point scale ranging from very negative (=1, "disaster") to clearly negative (=2), to indifferent (=3), to clearly positive (=4), and finally to very positive (=5, "complete happiness"). This builds on information previously published in the literature related to the rating of the significance of life changes (8). The interview and differentiation between changes and long-term difficulties build partly on the assessment technique introduced by Brown and Harris (9).

In the second part of the interview, participants were asked about infections and symptoms of infections during the year before the onset of CFS or crisis. Then, they rated the intensity of cardinal symptoms (fatigue, sadness, irritability, pain, and feeling of fever)

**TABLE 1. Prevalences of Reported Life Events in the CFS Group, the Control Group, and in the Stockholm MUSIC Study (1991)**

| CFS | Reference | Population |
|---|---|---|
| Conflict with spouse | | |
| 0.22 | 0.29 | 0.41 |
| Conflict with close relative or friend | | |
| 0.15 | 0.15 | NC |
| Illness/accident in spouse | | |
| 0.07 | 0.11 | 0.14 |
| Death of spouse | | |
| 0.00 | 0.02 | NC |
| Death of close relative or friend | | |
| 0.09 | 0.13 | 0.24 |
| Deteriorated financial situation | | |
| 0.17 | 0.22 | 0.12 |
| Conflict at work | | |
| 0.24 | 0.15 | 0.24 |
| Marital separation | | |
| 0.24 | 0.15 | 0.05 |
| Started marital relationship | | |
| 0.04 | 0.07 | 0.16 |
| Residential move | | |
| 0.26 | 0.17 | 0.25 |
| New child (adoption or birth) | | |
| 0.11 | 0.04 | 0.12 |
| Change of job | | |
| 0.46 | 0.38 | 0.39 |
| Reduced responsibility at work | | |
| 0.13 | 0.09 | 0.07 |
| Increased responsibility at work | | |
| 0.63 | 0.54 | 0.26 |

NC, not calculated.

monthly during the year before and the year after onset of CFS or the crisis episode. Cardinal symptoms were rated using a VAS with the extremes 0 (not at all) and 100 (worst possible).

Because the recall periods were relatively distant for many participants, a special interview method was used to help them recall the timing of events and symptoms. Subjects were asked in advance to bring work calendars and private calendars to the interview. Private major events were identified around which memories could be recalled and structured. In addition, the CFS patients were asked to complete self-administered questionnaires about life events and medical history when they were admitted to the clinical program.

### General Population Comparison

A study of the general working population in Stockholm, Stockholm MUSIC (10), was also used for comparison. In this study, performed in 1990, participants (94 men and 89 women) were asked to recall whether they had gone through each of the events on the list during the 12-month period immediately preceding the interview and the period 12 to 24 months preceding it. The latter interval was used for the present comparison because all of the participants in our study were recalling a 12-month period preceding the onset of CFS or personal crisis that occurred more than 1 year before the interview. In the population sample, the prevalences presented were weighted with regard to the number of women and men to make them comparable to the results of the present study.

## RESULTS

Figure 1, *a* through *e*, shows the results for the VAS ratings of fatigue, fever, pain, sadness, and irritability (hostility). A statistically significant group difference in fatigue intensity existed during the period 4 to 10 months before the onset or diagnosis of CFS. Analysis of variance (mixed model with analysis of repeated measures, group difference and group × time interaction) indicated highly significant differences between groups and observations as well as interaction between group and observations ($F$ group = 34.8, $p = .0001$; $F$ time = 16.9, $p = .0001$; $F$ interaction = 7.9, $p = .0001$). During the 3 months preceding the peak of the crisis, there was a dramatic rise in fatigue in both groups. The CFS group reached a much higher fatigue level, which leveled off somewhat during the first year of follow-up but still remained very high in comparison with the control group, which reached precrisis levels 4 months after the peak. Similar patterns were observed for fever ($F$ group = 94.0, $p = .0001$; $F$ time = 19.3, $p = .0001$; $F$ interaction = 21.7, $p = .0001$) and pain ($F$ group = 51.5, $p = .0001$; $F$ time = 9.3, $p = .0001$; $F$ interaction = 12.2, $p = .0001$). For the variables fatigue, fever, and pain, there were statistically significant group differences during the half-year 4 to 10 months before the onset of CFS ($F$ group fatigue = 4.9, $p = .03$; $F$ group fever = 12.1, $p = .001$; $F$ group pain = 4.1, $p = .05$).

With regard to sadness and irritability, no group difference was observed during the corresponding period preceding the crisis ($F$ group sadness = 0.002, $p = .96$; $F$ group irritability = 0.26, $p = .61$). In the patient group, the level stayed high throughout the whole first year of follow-up, whereas a slow return started in the control group; precrisis levels were reached after 1 year in this group. Because of the differences between the groups in the clinical course after onset, there were statistically significant interactions between group and time for the whole study period ($F$ group sadness = 1.3, $p = .26$; $F$ time = 8.2, $p = .0001$; $F$ interaction = 1.74, $p = .02$; $F$ group irritability = 1.9, $p = .17$; $F$ time = 2.20, $p = .001$; $F$ interaction = 1.8, $p = .01$).

With regard to negative life events, the results are described as the ratio of the prevalence of negative events in the CFS group to the prevalence of negative events in the control group. The proportion of subjects with at least one negative event was calculated for each quarter year preceding onset in both groups. This ratio is called the prevalence ratio for negative events in the text that follows. Results are shown in Figure 2. For the period 4 to 12 months before onset, the prevalence ratio is close to 1.0. During the period 1 to 3 months before onset, however, the ratio is 1.9.

Nonparametric analysis of variance for repeated

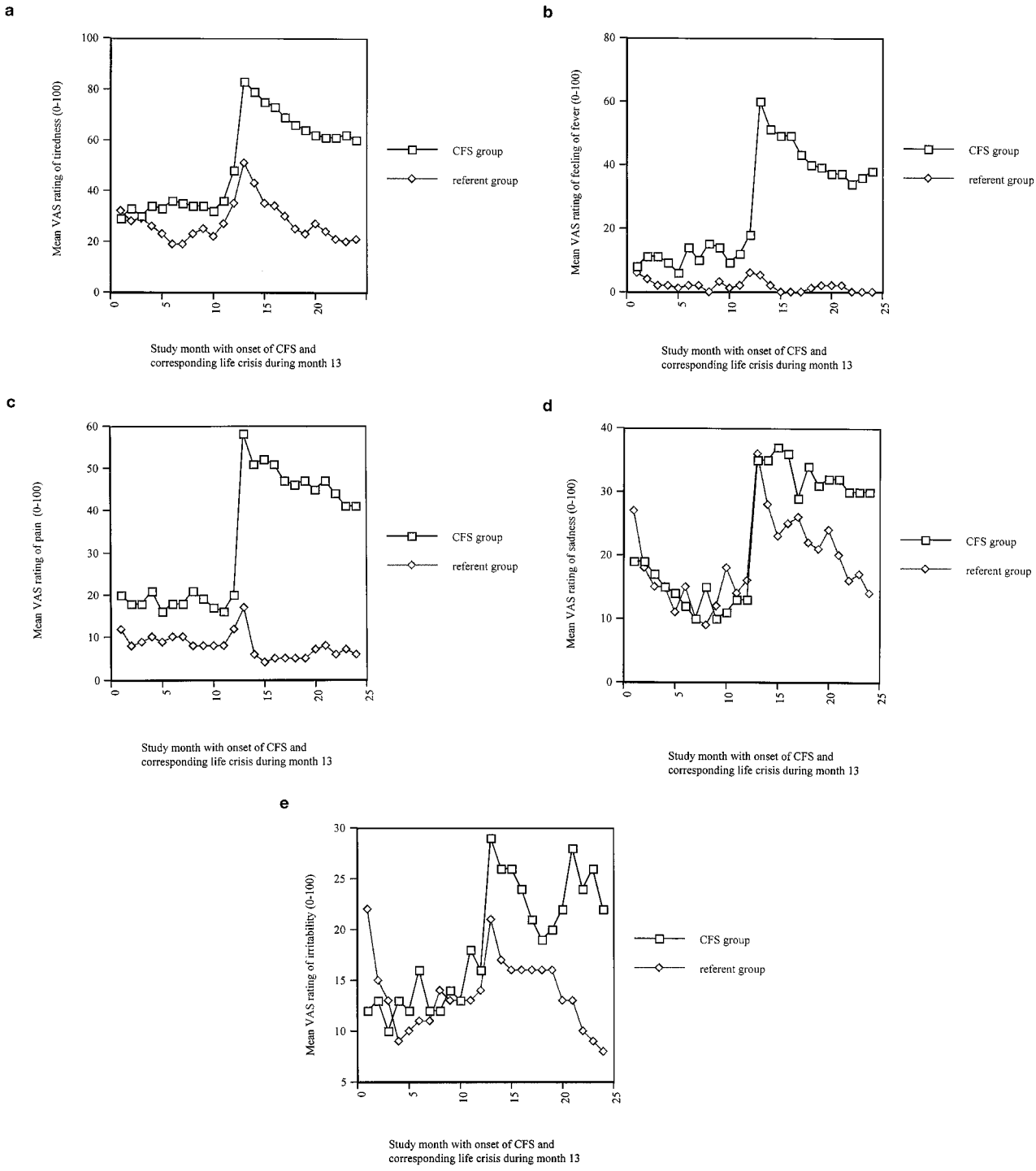


Fig. 1. Mean VAS ratings during the 12 months preceding (1–12) and 12 months succeeding (13–24) onset of CFS (*upper line*) and the corresponding crisis period in the control group (*lower line*) for (*a*) tiredness, (*b*) feeling of fever, (*c*) feeling of pain, (*d*) sadness, and (*e*) irritability.

measures according to Friedman indicated that there was a nonrandom distribution of the prevalence of negative events in the CFS group ($p = .001$, corrected for ties). No statistically significant differences between the periods were observed in the control group ($p = .16$, corrected for ties). High prevalences of negative events were observed during the 3 months during the quarter year preceding onset but also during the previous 12 months.

Infections were reported to have been more preva-

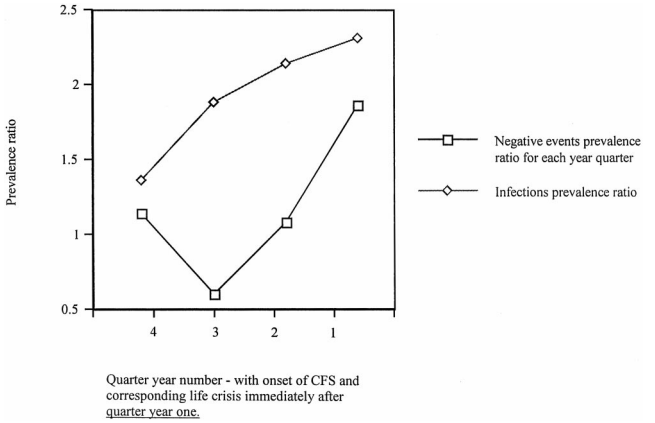


Fig. 2. Comparison of pre-CFS quarterly prevalence ratios; CFS/referents infections vs. negative life events. The specific life events have been introduced in Table 1, which also shows the 1 year prevalence (disregarding rating in negative, positive, or neutral) of each of them in the CFS group, the control group, and in the study of the general working population in Stockholm (10).

lent in the CFS group throughout the whole retrospectively studied period. The prevalence ratio, however, increased successively from 1.4 to 2.3. Thus, relatively speaking, infections became more common in the CFS group compared with the control group as the subjects approached CFS onset.

Because the two samples in the interview study are comparable with regard to the amount of reported life changes in general, it is the comparison between the CFS and control samples with regard to relative prevalence of kind of events that is most interesting. The prevalences are in general quite comparable. However, there were slightly more marital separations and conflicts at work reported during the study year in the CFS group.

Conflict with spouse, illness or accident involving spouse, and death of a close relative or friend were less frequently reported in the CFS group than in the general population. On the other hand, marital separation and changes in responsibility at work (reduced or increased) were reported more frequently by the CFS group than by the population group. The differences were particularly striking for marital separation and increased responsibility at work. These events were not confined to the last months before CFS onset but rather distributed during the months of the whole year preceding onset of CFS.

### Reliability

An indirect test of reliability of reporting was made by splitting the samples into those with a "short" recall period (CFS onset or crisis during 1994–1996) and those with a "long" recall period (1980–1993).

With regard to symptom development, the findings were the same in the two recall groups, but the levels were slightly lower in both groups for all the symptoms in the long recall groups (on average, 0.34 VAS units lower in the CFS group and 0.42 units lower in the control group).

In the CFS group, it was shown that the mean number of negative life events per quarter year preceding CFS onset or crisis was identical in the short and long recall groups (0.26). In the control group, on the other hand, the reported mean number of negative life events was lower in the long than in the short recall group (0.17 vs. 0.29). The temporal sequence was more clear in the short recall group, with the highest prevalence ratio (CFS/control group) in the quarter year closest to CFS onset (1.88, which is similar to the values of the total group and the long recall group, whose ratio during this quarter year was 1.79). In the long recall group, there was, however, also an excess CFS/control prevalence ratio in the quarter year 10 to 12 months before onset or crisis. In the short recall group, the ratios (negative life event prevalence in CFS group/negative life event prevalence in control group) were as follows for each quarter year from 10 to 12 months to 0 to 3 months preceding onset or crisis: 0.78, 0.17, 1.28. and 1.88.

With regard to infections, a clearly lower mean quarter year rate of infections was reported in the long vs. short recall CFS group (0.72 vs. 0.45), whereas more similar prevalences were observed in the two recall groups among the controls (0.35 in the short and 0.27 in the long recall group). In both groups, however, there was an increasing excess rate of infections in the CFS group during the latter part of the year preceding onset or crisis than during the earlier part.

## DISCUSSION

With regard to the selection of study group, it should be pointed out that the CFS patients had been referred to an infectious disease clinic. Thus, there is a bias in the population studied. A large group of "exhausted" subjects in the general population may not consult this department. It should also be pointed out that fatigue lasting for at least half a year is a necessary criterion of CFS; furthermore, headache, muscle pain, sore throat, and swollen lymph glands are included in possible CFS criteria. The diagnosis had been made after the period that the patient identified as the month of onset. This was an important part of the design; the study period should not be confounded by the illness itself. Accordingly, there is no a priori expectation that CFS patients should have had tiredness, pain, or fever during the months preceding onset.

It was possible to make comparisons between the CFS group and the normal population with regard to the reported prevalence of specific life changes. It should be cautioned, however, that the study was designed as a retrospective case-control study. The reports provide only information about the patients' perceptions, in retrospect, of the temporal sequence.

Despite the fact that the cases were confined to newly admitted ones, onset turned out to have occurred during a long retrospective period. Accordingly, the month of onset occurred between 12 months and 13 years before the interview. Despite this difficulty, the prevalence of negative life events during the year preceding onset of CFS seemed to be reliable because no difference was observed between those with long recall periods and those with short ones. It is possible that the CFS patients regarded the onset of CFS to have been so important that they could easily memorize important events and symptoms surrounding it despite the distance in time. It should be emphasized that the special interview technique may have been helpful and that only the most important life events were explored. In the control group, on the other hand, the prevalence of negative life events may have been less reliable.

The strength of the design lies in the fact that the time course could be evaluated. A careful matching procedure made the study groups quite comparable in terms of age, gender, and social factors. Thus, it is of considerable interest that symptoms of depression and irritability were not more common among the CFS patients during the months preceding onset than they were in the control group. It is also of interest that the disappearance of sadness and irritability was more rapid in the CFS group than during a "normal crisis" situation, although the disappearance of sadness took longer than that of irritability in the control group.

It has been documented in previous studies (11) that important life changes are reliably stored in the memory for a long time, even for several years. The interviewer applied a specific interview technique to improve recall. Using this technique, Bildt Thorbjörnsson et al. (12) were able to show that working conditions could be described retrospectively, even decades later, in a way that was found to be reliable when indirect information was compared with self-ratings.

In the comparison between the normal population and the CFS group, the period to be recalled was more than 1 year earlier in the two groups, with very long recall periods for some participants. In a previous study (5), the amount of time between interview and recall period was also a methodological problem, because the healthy comparison group had been asked about the year preceding the interview and the CFS group had been asked about the year preceding illness onset. In the present study, the recall period was more distant in time in the study group than it was in the population group. In the CFS group, it made no difference to the estimation of the prevalence of negative life events whether subjects had a long or short recall period. However, it did in the control group, which had a much lower mean of quarter year negative life events in the long than in the short recall group (0.17 vs. 0.29). Accordingly, the prevalence of specific as well as general negative life events in the control group may be underestimated.

The CFS and population groups in the present study were approached differently: the CFS group participated in an interview, whereas the population group completed a self-administered questionnaire. This could have increased the CFS group's prevalence of life changes in a relative manner. On the other hand, the interview allowed the research group to exclude some life changes that could have occurred more than 1 year preceding the onset of CFS. The only specific life change prevalence that was markedly affected by this, however, was the prevalence of conflicts at work, which diminished from 39 to 24% as a result of this correction. Thus, on balance, the differences in methodology might have produced relatively higher prevalences in the CFS group. Despite this, the prevalences were remarkably similar for most events. For two of them, however, markedly higher prevalences were observed in the CFS group than in the population group, marital separation (24 and 5%, respectively) and increased job responsibility (63 and 26%, respectively).

VASs have been applied in many studies, such as studies of depression (13, 14), pain (15), and fatigue (16). For all these outcomes, VASs have been considered to provide valid measures that correlate with established questionnaire measures. The two additional outcomes measured by means of VASs in the present study, fever and irritability, on the other hand, have not been established in previous research.

Although the weaknesses of a retrospective study warrant caution, the tentative conclusion from the present study is that CFS patients have not had an excess prevalence of negative life events compared with the general working population during the year preceding onset of CFS. However, for two specific areas, increased work responsibility and marital separation, they tended to report an excess prevalence. As expected, the CFS patients have had approximately the same intensity of negative life event experiences during the year preceding onset compared with those of a normal crisis group, but there was a buildup of negative events in the CFS group compared with the

normal crisis group during the 3-month period preceding onset.

The association between psychosocial adverse stress and incidence of infections is now established (17). In the two study groups, the occurrence of psychosocial adverse stress differs with more negative life events occurring during the last quarter preceding the onset of CFS. However, the number of infections had increased among CFS patients during the months preceding this last quarter year. This observation may suggest that infections could have sensitized the patients; that is, when the final negative life events occur during the last quarter year preceding CFS onset, vulnerability to CFS increases. In the present study, the CFS patients reported more fatigue and symptoms of infections during the year before CFS than subjects in the control group. However, we do not know whether this was due to repeated infections or other factors. With regard to psychological symptoms, no differences were observed between the groups. The cause of the predisposition, whether genetic or resulting from environmental influence of some kind, remains to be elucidated.

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