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Postinfectious and Chronic Fatigue Syndromes: Clinical Experience from a Tertiary-referral Centre in Norway

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Abstract. *Background: We aimed to compare patients reporting acute infection with those reporting no infection at onset of chronic fatigue syndrome (CFS). Patients and Methods: This study includes 873 patients with CFS referred to a tertiary centre on average 4.8 years after symptom onset. Assessment was by both observer query and self-reports. Antibody analyses against infectious agents including Epstein-Barr virus and enterovirus were performed in a majority of patients. Results: Females comprised 75.3% of the patient group, and the mean age was 33 years. Initial infection was reported by 77%. There was no difference as to antibody analyses. Logistic regression showed that initial infection was independently associated with acute onset of fatigue, improvement of fatigue at referral, and the following symptoms at referral: fever, tender lymph nodes, and myalgia. Conclusion: CFS patients with initial infection as a precipitating factor more often report acute onset of fatigue, more frequent accompanying symptoms, and more frequent improvement on referral than do patients without initial infection.*

Chronic fatigue syndrome (CFS) is a complex incapacitating illness of unknown etiology (1, 2). The prevalence of CFS in the general population ranges between 0.23% and 0.56% in different studies (3-6). CFS is characterized by disabling fatigue of at least 6 months' duration accompanied by at least four of eight specific symptoms including post-exertional malaise lasting more than 24 hours; unrefreshing sleep; impaired short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social or personal activities; headache of a new type, pattern or severity; muscle pain; multi-joint pain without swelling or redness; sore throat; and tender cervical/ axillary lymph nodes (1, 7). CFS is more frequent among females (6). CFS is commonly reported to develop after an acute infectious illness (2, 8, 9). However, an infectious illness is not uniformly present, and CFS may be associated with stressful life events in the year preceding onset (2, 10). Most cases of CFS are sporadic. There are, however, several reported outbreaks of epidemic fatigue most likely associated with infectious disease (11, 12). Current research priorities include investigation of possible abnormalities in gene regulation and possible molecular pathogenesis in CFS (13). CFS patients have been reported to have evidence of immune activation (14-17) and hypoactivity of the hypothalamus–pituitary–adrenal axis (18).

Previous studies have identified subtypes of CFS based on a symptom-based approach (19, 20). We present the clinical spectrum of 873 patients with CFS. We aimed to compare patients reporting acute infection at clinical onset and patients reporting no infection at onset. We hypothesized that there are important clinical differences such as clinical course and spectrum of symptoms between these two subgroups of patients with CFS thus representing different sybtypes of CFS.

Patients and Methods

Patients. This study is based on consecutive patients with chronic fatigue referred to the Outpatient Clinic of the Neurological Department, Haukeland University Hospital, Bergen, Norway during 1996-2006. The patients were referred from all over Norway, and all were examined and interviewed by HIN and ES. All patients underwent extensive medical evaluation to disclose any somatic or psychiatric illnesses. Only patients meeting the Centers for Disease Control and Prevention (CDC) definition of CFS were included in the present study (1).

All patients completed a questionnaire at referral that included questions about symptoms at onset, initial time course of fatigue, symptoms at the time of referral, and factors influencing the level of fatigue as detailed below.

Initial infection was defined as reported fever, upper respiratory tract infection, flu-like illness, or gastroenteritis at onset of fatigue. Symptoms at onset comprised the presence or not of enlarged lymph nodes, rash, dizziness, nausea, tinnitus and myalgia. Time from onset to debilitating fatigue was defined as acute (days), taking weeks, or months. The level of fatigue at referral was defined as improved, unchanged or worsened. The symptoms at referral comprised the presence or not of throat pain, enlarged or tender lymph nodes, myalgia, muscle weakness, arthralgia, dyspepsia, weight change, nausea,

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frequent micturition, photophobia, slurred vision, dizziness, tinnitus, sleep disturbances, depression, unstable mood, problems with concentration, memory problems, palpitations, increased sweating, headache, and fever. Activities (including physical activity, psychic strain, work needing concentration, reading, driving, watching TV, and sexual activity) with possible influence on the level of fatigue at referral were graded as improving, no effect, some worsening, much worsening.

Fatigue was assessed by the Fatigue Severity Scale (FSS) (21). This is a 9-item questionnaire that assesses the effect of fatigue on daily living. Each item is a statement on fatigue that the subject rates from 1, "completely disagree" to 7, "completely agree". Examples of the items in the questionnaire are: "My motivation is lower when I am fatigued", "Exercise brings on my fatigue" and "I am easily fatigued". The average score of the 9 items represents the FSS score (minimum score is 1 and maximum score is 7). FSS was chosen because it has been shown to be a reliable scale distinguishing patients from controls (21).

A majority of the patients underwent antibody analyses in the blood at the time of referral against the following infectious agents: *Mycoplasma pneumonia, Chlamydia pneumonia*, toxoplasmosis, Borreliosis, parainfluenza, influenza A, influenza B, respiratory syncytial virus, adenovirus, Epstein-Barr, cytomegalovirus, and enterovirus. In addition, total immunoglobulin (Ig)G, total IgM , total IgA, C3 and C4 serum concentrations were measured.

Statistics. Student's *t*-test, Mann-Whitney *U*-test, Fisher's exact test and Pearson's chi-square were used when appropriate. Based on the results from the univariate analyses, logistic regression was performed to identify the independent effect of the variables studied on patients with or without initial infection. All analyses were performed with SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

A total of 873 patients with CFS were included in this study, 657 (75.3%) females and 216 (24.7%) males ($p<0.001$, binominal test). The mean age was 33 years (±SD 12.1 years), and the mean duration of illness was 4.8 years. Overall, the proportion of patients with onset during September to March (6 months) was 59.6% ($p<0.001$, binominal test). Initial infection was reported by 672 (77.0%) patients. Demography of patients with and without acute infection at CFS onset is shown in Table I. There was no difference as to sex, age, mean FSS score or duration of illness. Table II shows the frequency of initial symptoms among patients reporting infection at onset compared with those without initial infection. All symptoms were significantly more frequent among patients with initial infection (Table II).

Table III shows the frequency of symptoms at referral among patients with infection compared with those without infection at onset. Symptoms related to infections such as fever, throat pain and tender lymph nodes were significantly more frequent among patients with infection at onset of CFS. The frequency of reported symptoms of depression was identical in the two groups.

Acute onset of fatigue (days) was more frequent among those reporting infection (340; 54.3%) compared to those without infection (66; 44.3%) at onset. Consequently fewer patients among those with initial infection had prolonged onset (months) of fatigue (131; 20.9%) compared to those without acute infection (57; 38.3%) at onset (overall analysis, $p<0.001$, Pearson's chi-square). Improvement of fatigue was reported more frequent among patients with infection 183 (29.7%) compared to those without infection 36 (19.7%) at onset. A total of 165 (26.7%) were stable and 269 (43.6%) were worsening among those with infection compared to 50 (27.3%) and 97 (53.0%) respectively among those without infection at onset (overall analysis, $p=0.019$, Pearson's chi-square).

Table I. *Demography of patients with and without acute infection at onset of chronic fatigue syndrome.*

	Acute infection	No infection	*P*-value
Females, n (%)	508 (75.6)	148 (74.4)	0.709
Age (years, mean±SD)	32.7±12.3	34.4±11.4	0.121
Duration of CFS (months, mean±SD)	58.7±65.2	57.8±53.7	0.895
FSS score (mean±SD)	6.59±.60	6.58±.61	0.787
Onset September – February, n (%)	343 (60.1)	83 (57.6)	0.635

SD: Standard deviation; FSS: Fatigue Severity Scale.

There was no significant difference between patients with and without acute infection at onset as to the effect of physical activity, psychic strain, work needing concentration, reading, driving, watching TV, and sexual activity on the level of fatigue (all *p*-values >0.3, Pearson's chi-Square).

Antibody analyses for infectious agents at referral showed no difference between patients with and without acute infection at onset of CFS (all *p*-values >0.05).

Table IV shows the results of logistic regression analysis using the presence or not of infection at onset as the dependent variable.

Discussion

This study shows that a CFS patient sample derived from a tertiary-referral centre is heterogeneous (22). It is likely that tertiary centres have a filtering effect favouring patients with more chronicity and functional disability (22). The high proportion (77%) of patients that reported acute infection at onset of CFS was in accordance with other studies (2, 8) and supports the belief that CFS is triggered by an acute infection in the majority of patients with CFS. This was further supported by more frequent onset during winter than summer, when viral infection is most prevalent. Onset of CFS was more frequent in winter than summer irrespective of the presence of initial infection or not. This suggests that some patients not reporting initial infection may have had a subclinical infection triggering the CFS. Patients with infection at onset reported a higher frequency of initial

Table II. *Initial symptoms among patients with and without acute infection at onset of chronic fatigue syndrome.*

	Acute infection		No infection		
	n	%	n	%	*P*-value
Headache	423	62.9	86	42.8	<0.001
Enlarged lymph nodes	83	12.4	10	5.0	0.002
Rash	110	16.4	21	10.4	0.043
Dizziness	421	62.6	105	52.2	0.009
Nausea	291	43.3	58	28.9	<0.001
Tinnitus	172	25.6	37	18.4	0.038
Myalgia	411	61.2	80	39.8	<0.001

symptoms than did patients without infection at onset. It seems likely that patients with subclinical or no acute infection at onset report fewer initial symptoms than patients with acute infection at onset. However, there is much controversy as to the role of acute infection at onset of CFS (23). Some studies have found little association between acute infection and the development of CFS (24), while others found that a positive Monospot test at onset predicted fatigue 6 months later (25).

Viral and bacterial antibody analyses were performed in a majority of the patients. These analyses did not show any differences between the patients with or without initial infection. This may indicate that the infectious agents chosen for antibody evaluation in our study are not associated with CFS. Another interpretation is that infectious agents trigger CFS both *via* clinical and subclinical infection, or that CFS is a host response to different infections rather than an effect of the pathogen itself (26). Viral and bacterial antibody analyses in a control group are required to evaluate these possibilities.

Logistic regression showed that myalgia, tender lymph nodes and fever at referral were associated with reported initial infection. These are symptoms often associated with viral disease and might suggest a more prolonged immunological response among the patients who reported initial infection. Furthermore, logistic regression showed that initial infection was independently associated with higher total IgM on referral. This also indicates that an elevated immune responsiveness is involved in some CFS patients. Elevated levels of circulating IgM complexes have been reported in a small study of CFS (16).

Patients reporting initial infection more often had acute onset of fatigue at CFS onset. Furthermore, patients with initial infection more often reported improvement at referral even though as a group they tended to report more symptoms. This may suggest different underlying pathophysiological mechanisms. Thus, our study adds evidence to the existence of different subtypes of CSF based on the presence or not of precipitating infectious illness.

Table III. *Symptoms on referral among patients with and without acute infection at onset of chronic fatigue syndrome.*

	Acute infection		No infection		
	n	%	n	%	*P*-value
Immune manifestations					
Fever	243	36.2	46	22.9	<0.001
Throat pain	377	56.1	89	44.3	0.004
Tender lymph nodes	264	39.3	55	27.4	0.002
Pain					
Headache	506	75.3	149	74.1	0.781
Myalgia	538	80.1	154	76.6	0.321
Arthralgia	428	63.7	111	55.2	0.032
Sleep dysfunction					
Sleep disturbances	518	77.1	142	70.6	0.075
Neurological manifestations					
Muscle weakness	525	78.1	150	74.6	0.293
Photophobia	348	51.8	101	50.2	0.748
Slurred vision	287	42.7	83	41.3	0.745
Dizziness	509	75.7	143	71.1	0.196
Tinnitus	255	37.9	66	32.8	0.211
Cognitive manifestations					
Concentration problems	616	91.7	178	88.6	0.206
Memory problems	559	83.2	156	77.6	0.076
Psychiatric manifestations					
Depression	242	36.0	72	35.8	1.000
Unstable mood	368	54.8	99	49.3	0.172
Autonomous manifestations					
Gastrointestinal disturbances	440	65.5	111	55.2	0.010
Nausea	375	55.8	91	45.3	0.010
Palpitations	317	47.2	94	46.8	0.936
Increased sweating	402	59.8	109	54.2	0.166
Frequent micturition	286	42.6	65	32.3	0.011

Table IV. *Logistic regression between patients with and without acute infection at onset of chronic fatigue syndrome (dependent variable).*

	OR	95% CI		*P*-value
IgM	0.797	0.673	0.943	0.008
Myalgia at referral	0.550	0.373	0.810	0.002
Fever at referral	0.503	0.315	0.804	0.004
Tender lymph nodes at referral	0.528	0.338	0.827	0.005
State of health at referral[1]	1.386	1.087	1.767	0.008
Time to debilitating fatigue[2]	1.405	1.123	1.756	0.003

OR: Odds ratio; CI: confidence interval; [1]improved, stable, or worsening; [2]days, weeks, or months.

It is possible that psychiatric disease may be the underlying cause of CFS among some patients. If psychiatric disease were a frequent cause, a probable consequence would be higher frequency of psychiatric symptoms among patients without initial infection. However, there were no significant differences in reported symptoms of depression, cognitive dysfunction, or sleep disturbances. This may indicate that psychiatric symptoms are a consequence rather than a cause of CFS.

One of the strengths of our study is the large number of patients with CFS, with age and gender distribution compatible to other studies. There are a number of weaknesses in the present study. The reporting of initial symptoms was based on patient recall and therefore prone to errors. However, this is a problem with most studies of CFS because the diagnosis cannot be made until 6 months after onset. Furthermore, the incidence of CFS is low which makes it difficult to perform large prospective studies. Another weakness of our study is that we did not register the prevalence of stressful events prior to CFS onset.

In conclusion, CFS patients with initial infections more often report acute onset of fatigue, more frequent accompanying symptoms both at onset and referral, and more frequent improvement on referral than do patients without initial infection.

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