There has been growing interest in several conditions associated with persistent fatigue. These include chronic fatigue syndrome (CFS), an illness characterized by disabling fatigue, subjective fever, chills, sore throat, sleep difficulties, and neuropsychiatric disturbances [1], as well as unexplained chronic fatigue (CF) that does not meet strict criteria for CFS. Although their causes are unknown, the symptoms of these conditions are reminiscent of an infectious disease.

One striking feature of CFS is its sudden onset following a presumably viral illness and the recurrent “flulike” symptoms [1] that might directly or indirectly result from the presence of viruses and/or the production of cytokines. However, an extensive search has not yielded conclusive evidence of a link between microbial agents and CFS or CF [2-4]. Nonetheless, the assumption that postinfectious CFS is a distinct entity has persisted, and distinctions based on the onset of illness continue to be discussed in scientific meetings (e.g., at the National Institute of Allergy and Infectious Diseases in April 1995), to be used in medical publications [5], and to be features in case definitions of CSF [1, 6, 7].

Since little is known about postinfectious fatigue and patients’ workups often focus on the acute onset and infectious causes, our goals were to clarify the usefulness of this historical feature in evaluating patients with CF, to identify associated findings, and to examine these variables in patients who met the criteria for CFS.

**Methods**

We enrolled 717 consecutive adults with unexplained fatigue who initially were seen at a university clinic; the patients were self-referred or had been referred by their physician. Their evaluation consisted of a standardized medical and psychiatric history, a physical examination, and recommended routine laboratory studies [1]. Other studies were performed (see below) based on clinic protocols tested during the development of an appropriate laboratory workup for CFS/CF. Such tests were performed for subsets of consecutive patients and were not obtained on the basis of historical or clinical manifestations.

Although patients were not required to meet the Centers for Disease Control and Prevention (CDC) criteria for CFS in order to be seen, data were collected on each item in the case definition. Patients were classified with use of the 1994 CDC criteria, or laboratory studies [1]. Other studies were performed (see below) based on clinic protocols tested during the development of an appropriate laboratory workup for CFS/CF. Such tests were performed for subsets of consecutive patients and were not obtained on the basis of historical or clinical manifestations.

All patients completed measures of functional and psychosocial status. The Medical Outcomes Study Short-Form General Health Survey consists of eight subscales that assess functional level [9]. Higher scores indicate better health. Among our patients, the α coefficients are adequate for the individual subscales (range, 0.74–0.90). The General Health Questionnaire measures somatic and psychological distress on a four-point scale of 0-33.

Postinfectious Chronic Fatigue: A Distinct Syndrome?

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Chronic fatigue syndrome (CFS) is often preceded by a viral illness and has recurrent “flulike” symptoms. We compared demographic, clinical, and laboratory features (markers of inflammation and viral infection) among 717 patients with chronic fatigue (CF) with and without a self-reported postinfectious onset to identify associated clinical and biologic findings and to examine the subset of patients with CFS. Only subjective fever, chills, sore throat, lymphadenopathy, poorer functional status, and attribution of illness to a physical condition were significantly associated with a postinfectious onset. The features of patients with CFS were virtually identical to those of the broader category of patients with CF. We conclude that a postinfectious onset was not associated with a pattern of abnormalities across multiple psychosocial and biologic parameters.
scale. A cutting score of ≥12 has been found to correlate best with a psychiatric diagnosis [10]. The questionnaire's α coefficient for our patients is 0.92. The fatigue attribution scale inquires about an individual's perception of disease, in particular, physical (e.g., viral) vs. psychological etiologies [11]. Psychiatric diagnoses were determined with use of a structured diagnostic interview that assigns diagnoses based on the criteria of the revised third edition of the Diagnostic and Statistical Manual of Mental Disorders [12].

Assays for markers of inflammation were performed at the University of Washington's immunology laboratory on specimens from 278 consecutive patients from June 1991 to August 1995. Soluble IL-2 receptor (T-Cell Diagnostics, Cambridge, MA) and IL-6 (Genzyme Diagnostics, Cambridge, MA) were determined by ELISA on a microtiter plate reader with automated curve-fitting (Molecular Diagnostics, Menlo Park, CA). C-reactive protein was quantified by latex-enhanced immunonephelometry (Behring Diagnostics, Somerville, NJ). β2-Microglobulin was measured with use of an immunoenzymatic fluorometric immunoassay (Abbott Laboratories, North Chicago, IL). Neopterin specimens were wrapped in foil and then examined by radioimmunoassay (Polymedco, Cortland Manor, NY).

Although initially a comprehensive serological evaluation was performed, preliminary analyses indicated that the results of tests for herpes simplex virus type 1 and herpes simplex virus type 2, rubella, and adenovirus for patients with CF did not differ from those in healthy populations. Thereafter, only titers of antibodies to human herpesvirus 6, Epstein-Barr virus, cytomegalovirus, and coxsackieviruses B 1–6 were obtained.

Antibodies to herpes simplex virus were detected by western blot by determining the presence of antibodies to types 1 and/or 2 at a serum dilution of 1:40. Rubella antibodies were detected at a single dilution with use of a commercial ELISA (Abbott Laboratories, Chicago, IL). Antibodies to adenovirus were assayed by complement fixation with serial dilutions from 1:2 to 1:32. Antibodies to human herpesvirus 6 were assayed with use of an ELISA and twofold serum dilutions from 1:100 to 1:51,200.

IgM and IgG antibodies to Epstein-Barr virus viral capsid antigen and antibodies to the early antigens were determined by indirect immunofluorescence with use of serial twofold dilutions from 1:10 to 1:1,280 for viral capsid antigen IgG and early antigen antibodies. Anticomplement immunofluorescence was used to test for antibodies to nuclear antigens at a 1:2 dilution. Reactivity above the background signal obtained with Epstein-Barr virus cells that did not contain nuclear antigen was considered positive.

End point titers of antibodies to cytomegalovirus were determined by latex agglutination (Whitaker MA Bioproducts, Walkersville, MD) end point dilution using twofold dilutions from 1:20 to 1:1,024. Titers of antibody to coxsackieviruses B 1–6 were ascertained by microneutralization of infectivity for buffalo green monkey cells and twofold dilutions of sera from 1:8 to 1:512. Following confirmation of a normal distribution, geometric mean titers were calculated based on log_{10} transformed antibody titers. All assays were completed by the virology laboratory at the University of Washington.

Patients were divided into two groups on the basis of whether they met the CDC criteria for CFS and whether they had a self-reported onset of illness with an acute viral syndrome. This illness was defined as "starting suddenly with a 'flu," cold, or virus and characterized by two or more of the following complaints: fever, headache, muscle aches, earache, sore throat, congestion, runny nose, cough, diarrhea, or fatigue." Most (58%) patients without a postinfectious onset of CF described a gradual onset, although some reported their illness began acutely without an infection or following an operation or motor vehicle accident.

Statistical analysis was performed with the χ² test and the t test to compare group differences with use of dichotomous and continuous variables, respectively. Logistic regression analyses were performed with demographic features, clinical features (duration of fatigue, fever, chills, sore throat, lymphadenopathy, temperature of ≥37.5°C, concurrent fibromyalgia), laboratory features (nonspecific inflammatory markers, viral serologies), and psychosocial features as the independent variables and onset type as the dependent variable. On the basis of the number of comparisons, only P values of <.01 were considered significant.

Results

Among all patients, there were no differences by onset type in demographic features, duration of fatigue, proportion meeting the criteria for CFS or fibromyalgia, and the proportion reporting close or household contacts with CFS. The group with a postinfectious onset noted more frequent subjective fevers, chills, sore throats, and lymphadenopathy (P < .0001) but did not differ in reporting other CFS-associated symptoms, sinus infections, urinary infections, vaginal infections, and oral and genital herpetic infections and did not differ in the presence of documented fever, tender and/or enlarged lymph nodes, or pharyngitis.

With use of functional and psychosocial status assessments, it was determined that patients with a postinfectious onset of CF had worse physical (P < .01) and role functioning (P < .01), had greater body pain (P < .001), and attributed their illness more often to a physical condition (P < .001) than those who did not have a postinfectious onset. There were no differences in the distribution of individual current and lifetime psychiatric diagnoses by onset type. Likewise, the results of tests for detection of the 13 viruses and the nonspecific markers of infection were similar for the postinfectious and non-postinfectious illness groups.

Subsequent examination of the CFS subgroup found that, as in the broader category of CF patients, subjective fever initially and after 2 months (P < .001) was more frequent in the group...
with a postinfectious onset, as were chills, sore throat, and lymphadenopathy ($P < .01$). However, no statistically significant differences were observed in functional status or illness attribution among the CFS patients by onset type. The regression model predicted the type of onset in 70% of CF cases. A postinfectious onset was associated only with a physical attribution of illness ($P = .009$). Among patients with CFS, 73% were correctly classified using all independent variables, but no individual factor was associated with onset type.

Discussion

CFS/CF has been postulated to result, directly or indirectly, from infections and/or immune activation. One theory states that CFS/CF occurs in vulnerable individuals in whom depression, atopy, or viral infections have resulted in immune compromise. Subsequently, latent viruses are reactivated and contribute to morbidity by eliciting an ongoing immune response. Alternatively, a primary viral infection may lead to immune compromise and the persistent production of cytokines that cause symptoms. However, despite the attractiveness of this theory, previous studies have failed to confirm a direct role for viruses in CFS/CF [2–4], and the search for markers of inflammation and immune activation has yielded mixed results [13, 14]. If such a mechanism were present in patients with CFS/CF, one might expect to find such serum markers, especially in patients with a viral precipitant.

The present study has shown that CF patients with a postinfectious onset reported symptoms consistent with a “flulike” illness and attributed their condition to physical causes more often than did those without a postinfectious onset; however, these groups did not differ by objective measures such as laboratory examination findings, antibody concentrations, and markers of immune activation and inflammation. Thus, we do not recommend routinely obtaining the specific tests examined in this investigation in the evaluation of patients with CFS/CF, including those with a postinfectious onset. Nonetheless, although our findings argue against the presence of a persistent active infection and a postinfectious subtype of CFS/CF, they do not rule out infections as triggering events of CFS/CF.

In conclusion, despite its historical prominence, a subjective postinfectious onset of illness was not associated with a consistent pattern of abnormalities across multiple psychosocial and biologic parameters and did not identify a discrete population of patients with CFS/CF. Our findings may not be generalizable to other clinical settings since our patients were drawn from a referral clinic. In addition, although an antecedent viral syndrome was reported by most patients with CFS/CF, medical records containing clinical or serological evidence of such a precipitating infection were virtually never available. Thus, objective abnormalities could be present in a well-defined group of fatigued patients with a verified antecedent infection or among those studied more proximal to the precipitating event. Nonetheless, based on multiple factors examined in this study, it was not useful to classify CFS/CF patients on the basis of a self-reported postinfectious onset.

References