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Frequency of 'Chronic Active Epstein-Barr Virus Infection' in a General Medical Practice

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Twenty-one percent of 500 unselected patients, aged 17 to 50 years, seeking primary care for any reason were found to be suffering from a chronic fatigue syndrome consistent with "chronic active Epstein-Barr virus (EBV) infection." They had been experiencing "severe" fatigue, usually cyclic, for a median of 16 months (range, six to 458 months), associated with sore throat, myalgias, or headaches; 45% of the patients were periodically bedridden; and 25% to 73% reported recurrent cervical adenopathy, paresthesias, arthralgias, and difficulty in concentrating or sleeping. The patients had no recognized chronic "physical" illness and were not receiving psychiatric care. While antibody titers to several EBV-specific antigens were higher in patients than in age- and sex-matched control subjects, the differences generally were not statistically significant. A chronic fatigue syndrome consistent with the chronic active EBV infection syndrome was prevalent in our primary care practice. However, our data offer no evidence that EBV is causally related to the syndrome. Indeed, we feel that among unselected patients seen in a general medical practice currently available EBV serologic test results must be interpreted with great caution.

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MOST human beings have been infected with the Epstein-Barr virus (EBV). The clinical manifestations of initial infection are variable; some patients are asymptomatic, others develop mild respiratory infection symptoms, and others develop the clinical, serologic, and hematologic features of infectious mononucleosis.¹⁻³ When there are symptoms associated with the initial infection, these usually resolve within a mat-

ter of weeks. However, the virus can be isolated from saliva for months or years thereafter, suggesting chronic infection of the nasopharyngeal epithelium and/or salivary glands.⁴ Also, a small fraction of B lymphocytes remain latently infected, apparently for the rest of the patient's life.⁵

See also pp 2297 and 2335.

On occasion, individuals with various forms of immunodeficiency will be unable to contain the population of EBV-infected B cells, and they will go on to develop polyclonal B-cell proliferation and monoclonal B-cell lymphomas.⁶⁻¹⁶

Several investigators have reported another kind of chronic illness associated with, and perhaps secondary to,

persistent EBV infection. The syndrome is called *chronic active EBV (CEBV) infection* or *chronic mononucleosis*, and it is characterized by varying degrees of chronic fatigue, fever, pharyngitis, myalgias, headache, arthralgias, paresthesias, depression, and cognitive deficits. While the full syndrome has been described only in recent years,¹⁷⁻²³ earlier reports that may have been reporting the same phenomenon exist in the literature.²⁴⁻³⁶ The onset of the syndrome typically seems to be in late adolescence or young adulthood,¹⁷⁻²³ although it may also occur in childhood.²² By definition, patients with this syndrome have been evaluated for a variety of chronic infectious, rheumatologic, endocrinologic, and malignant diseases, and no chronic disease is apparent.^{17,21-23} The diagnosis has been made about twice as often in women as in men.^{17,20-23} The illness may follow a documented episode of infectious mononucleosis, or an acute viral syndrome for which the patient has not sought medical attention, but also may appear spontaneously.^{17,21-23} For most patients, the illness takes the form of a chronic, recurring "flu-like" illness.²¹⁻²³ Virtually all patients perceive themselves to be impaired in some way. Some patients are completely disabled by the fatigue, muscular weakness, and pain.

The results of laboratory tests generally ordered in patients with chronic fatigue are typically unremarkable. However, three recent reports all state that patients with this chronic fatigue syndrome have significant elevation of IgG antibody to the EBV viral capsid

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antigen (VCA) and to EBV early antigens (EA-Ab), in contrast with "healthy" patients.²¹⁻²³ Also, one of these reports has suggested the possibility that levels of antibodies to EB nuclear antigen (EBNA-Ab) are low in a subset of patients.²² Case reports also have described patients with extraordinarily high titers of VCA-IgG and EA-Ab.^{19,37-39}

The high titers to VCA and EA typical of patients with the syndrome also can be seen in an occasional healthy patient.⁴⁰⁻⁴² Also, not all patients reported to have the syndrome have elevated titers.²¹⁻²³

Because fatigue is a common presenting complaint in general medical practices, the general physician would like to know how common CEBV infection is among patients seen in a general practice setting. To our knowledge, previous published reports have not systematically addressed this question but have described only patients who in some way have come to the attention of the investigators. The general physician also would like to know the utility of serologic testing for EBV in a primary care practice setting; the patients reported in the literature have been highly selected and may have different clinical and serologic characteristics.

To address these two questions, we conducted a prospective study in a primary care practice setting.

PATIENTS AND METHODS

Study Setting and Patient Population

The study was conducted over a six-month period in a large (30 000 visits per year) primary care general medical practice located in a large academic teaching hospital (Brigham and Women's Hospital, Boston). The practice was staffed by 12 faculty members, four fellows, 85 house officers, and four nurse practitioners. Prior to and during the time of the study, the interest of the authors in the CEBV infection syndrome was not widely known, and the practice was not being asked to see patients with CEBV infection in consultation.

The practice is divided into six areas, each with its own waiting room. Patients are scheduled to each area during 9 four-hour sessions per week. During a four-month period, research assistants were assigned to interview patients in a particular waiting room, during a particular session. They were asked to interview as many patients between the ages of 17 and 50 years during each session as time would allow. The waiting rooms and sessions were rotated during the four months of the study as to be representative of the entire practice.

During each interview session, patients were asked, prior to seeing their physician, the following question: "Have you had severe loss of energy or easy fatigability either constantly or recurrently for at least the past six months?" Patients who answered affirmatively were then asked: "Since you've been tired, have you had any of the following symptoms more than once: sore throat, muscle aches, or headaches?" The patients were also asked if they were pregnant, if they were taking corticosteroids or azathioprine, or if they had any of the following chronic diseases: diabetes, chronic lung disease, cancer, heart disease, anemia, kidney disease, liver disease, thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, or other autoimmune disorders. Each patient's medical record was reviewed in detail with reference to each of the above questions, and to determine whether they were under psychiatric care at the time of the onset of their chronic fatigue syndrome.

Clinical and Laboratory Data Collected

Clinical Data.—We asked the following patients to participate in the study: patients who stated that they did have a severe loss of energy for at least the past six months; and who had either recurrent sore throat, myalgias, or headaches; and who were not pregnant, nor taking immunosuppressive drugs, nor suffering from any of the above chronic diseases. Each patient gave written informed consent. A detailed questionnaire was then completed that inquired into present and past medical history. The patient's physician was asked to record the presence or absence of various physical examination findings on a study protocol.

Laboratory Data.—From each patient, a single serum specimen was obtained at the index visit. Titers of IgM and IgG antibodies to VCA (VCA-IgM and VCA-IgG), as well as IgG antibodies to the early antigens (EA-Ab), were determined by indirect immunofluorescence.⁴³ No attempt was made to distinguish the restricted and diffuse components of EA-Ab. The EBNA-Ab were detected by anticomplement immunofluorescence.⁴⁴ Titers were reported as zero when VCA-IgG was present in a dilution of less than 1:20; when VCA-IgM was present in a dilution of less than 1:20; when EA-Ab was present in a dilution of less than 1:20; and when EBNA-Ab was present in a dilution of less than 1:5—due to unreliability of measurements at these low levels of antibody. All antibody titers

were performed in a single laboratory by a single technician who routinely performs about 1000 EBV antibody profiles per year.

Control Subjects.—From the ambulatory practices of the Brigham and Women's Hospital, a group of "control" subjects matched for age (within five years) and sex to each of the study patients was identified. Control subjects were selected from patients scheduled to have a venipuncture performed. Typically, they were attending the practice for routine screening examinations; each subject was explicitly asked about, and explicitly denied, the presence of severe, prolonged chronic fatigue. Also, through a detailed review of the medical record, each control patient was deemed to be not pregnant, free of the chronic diseases listed above, and not receiving immunosuppressive drugs. Serum specimens obtained from each subject were tested for antibodies to EBV as described above. The technician tested patient and control subject serum specimens simultaneously and was blinded to the patient or control status of the serum specimens.

Statistical Analysis

Calculation of Geometric Mean Titers (GMTs).—The GMTs in the patients were compared with those in the control subjects using both parametric and nonparametric methods. The comparisons were made for the entire group of patients and control subjects and for each of several patient subgroups and their matched control subjects. Using parametric methods (Student's paired *t* test, two tailed), we first attempted to normalize the distribution; the value of each serologic result was log transformed (base 10). Patients with "zero" antibody detected were given an arbitrary value of 1 instead of 0, so that GMTs could be determined on the entire population, not just on patients with seropositivity. We also compared antibody levels in patients and control subjects by use of the nonparametric paired Wilcoxon rank-sum test.

Percentages.—Percentages of patients with a certain serologic finding were compared with the percentage of control subjects with that finding, using the χ^2 or Fisher's exact test (two tailed).

RESULTS

Study Population

Altogether, 500 patients were interviewed. They were representative of all patients between the ages of 17 and 50 years seen in our practice during the period of the study, as determined from a computerized patient registration and billing system: there were no significant

Table 1.—Clinical Findings

Findings	No. of Patients (% of Total)
History	
Chief complaint is the fatigue syndrome	12 (30)
Severity of the fatigue at its worst	
Bedridden: can do virtually nothing	11 (28)
Shut-in: cannot do even light housework or its equivalent	5 (13)
Can do all the things I usually do at home or work, but feel much more easily fatigued from it: no energy left for anything else	24 (60)
Description of the frequency of the fatigue	
Constant fatigue that does not change	6 (15)
Always some fatigue that may get better but never goes away completely	9 (23)
The fatigue alternates with periods of feeling normal	25 (63)
Associated recurrent pharyngitis	24 (60)
Associated recurrent muscle aches	32 (80)
Severity of muscle aches at their worst (N = 31)	
Need to stop all normal activities and rest	12 (39)
Can continue normal activities but muscle aches make it hard	7 (23)
Not aware of muscle aches during normal activities, only at rest	12 (39)
Associated recurrent headaches	33 (83)
Severity of headaches at their worst (N = 33)	
Need to stop all normal activities and rest	18 (55)
Can continue normal activities but headaches make it hard	11 (33)
Not aware of headaches during normal activities, only at rest	4 (12)
Fatigue plus sore throat, plus myalgias, plus headaches	18 (45)
Associated symptoms	
Depression or unusual mood changes	31 (78)
Difficulty in sleeping	29 (73)
Difficulty in concentrating	26 (65)
Anxiety	24 (60)
Nausea	22 (55)
Swollen lymph glands (N = 29)	17 (44)
Stomach ache	16 (40)
Diarrhea	15 (38)
Cough	15 (38)
Rash	14 (35)
Odd sensations in skin	13 (33)
Loss of appetite	12 (30)
Joint pain	12 (30)
Vomiting	10 (25)
Recurrent fevers at home	10 (25)
Intermittent swelling of fingers (N = 30)	6 (20)
Weight loss	6 (15)
Weight gain	2 (5)
Have seen a physician for this problem previously	22 (55)
Have seen more than one physician for this problem	10 (25)
The problem has caused problems or stress at home and at work	24 (60)
Patient has sometimes thought these symptoms "might just all be in my head"	23 (58)
Past history	
Mononucleosis (N = 39)	10 (26)
Oral herpes	15 (38)
Genital herpes	0 (0)
Herpes zoster ("shingles")	0 (0)
Allergies (to foods or drugs, or "hay fever")	21 (53)
Physical examination	
Tonsillar/pharyngeal exudate	0 (0)
Cervical adenopathy (enlarged or tender nodes)	
Anterior	6 (15)
Posterior	1 (3)
Submandibular gland, enlarged or tender (N = 38)	5 (13)
Hepatomegaly or splenomegaly	0 (0)
Temperature >37.5°C	0 (0)

differences between the 500-patient sample and the entire population with regard to age, sex, or medical insurance coverage.

Of these 500 patients, 185 stated that they had been experiencing severe fatigue for at least six months; of these 185 patients, 176 complained not only of fatigue but also of associated sore throat, muscle aches, or headaches. Of these 176 patients, 103 had no other known condition or illness that could explain the chronic fatigue and associated symptoms. Thus, 103 (21%) of 500 patients aged 17 to 50 years seeking primary care in our practice complained of symptoms suggestive of CEBV infection, ie, severe fatigue for at least the past six months, with associated symptoms of sore throat, myalgias, or head-

aches, and without any known chronic disease.

Of these 103 patients, 40 consented to participate in the study, and, thereby, to answer further questions about their symptoms, to undergo a physical examination, and to have serum obtained for serologic testing. The following reasons were given by 63 patients for declining to participate in the study: the patient was not interested in participating in any kind of research studies (n = 43); the patient felt that viral infection was unlikely and that there were "other reasons" (unspecified) to account for his or her fatigue (n = 11); and the patient did not want to have a phlebotomy (n = 9). Those patients participating in the study were not significantly different ($P > .05$) from those

eligible patients who declined to participate: mean age (34 vs 33 years); sex (70% vs 75% female); and severity of illness—percentage with fatigue and sore throat and myalgias and headache (29% vs 45%).

Clinical Findings

Table 1 summarizes the historical and physical examination findings. The full text of the historical questions asked of the patients is presented in Table 1. The patients described a syndrome of considerable severity; 28% stated that the fatigue at its worst was sufficient to make them "bedridden: can do virtually nothing." Nearly half of the patients reported "swollen lymph glands," particularly in the neck. Low-grade fevers were reported by 25% of patients; 14 patients recorded their temperatures in the morning and evening for one week following the index visit, and six of the 14 reported temperatures between 37.2°C and 37.5°C.

The median duration of the symptoms was as follows: fatigue, 16 months (six to 458 months); pharyngitis, 13 months (0.5 to 96 months); headache, 13 months (0.5 to 144 months); and myalgias, 17 months (one to 84 months). The patients were asked explicitly if they had suffered from these associated symptoms since the onset of the severe fatigue. A detailed history of past experience with pharyngitis, headache, and myalgias was not obtained. The patients reported an average of six sick days in the preceding six months (range, zero to 40 days per patient).

A majority of patients had seen a physician previously in an attempt to diagnose and treat the problem, and 25% had seen more than one physician. Sixty percent of the patients stated that the chronic fatigue syndrome had created substantial stress both at home and in the workplace.

Physical examination findings were benign. None of the patients had a fever at the time of examination. Fifteen percent had anterior cervical adenopathy, and 13% had enlarged submandibular glands.

Serologic Findings

The VCA-IgG was found in 39/40 (98%) of patients and 36/40 (90%) of control subjects ($P = NS$). The EA-Ab was found in 30/40 (75%) of patients and 24/40 (60%) of control subjects ($P = NS$). The EBNA-Ab was found in 39/40 (98%) of patients and 34/40 (85%) of control subjects ($P = NS$). The VCA-IgM was detected in 4/40 (10%) of patients and in none of 40 control subjects ($P = NS$). In the four patients with VCA-IgM, the values of EA-Ab were 1:20, 1:40, 1:40,

Table 2.—Comparisons of Serologic Results, Different Patient Groups, and Their Matched Control Subjects*

	GMTs ± SD					
	VCA-IgG		EA-Ab		EBNA-Ab	
	Patients	Controls	Patients	Controls	Patients	Controls
All patients (N = 40)	134.9 ± 3	81.2 ± 5	18.2 ± 6	10.0 ± 7	13.2 ± 2	8.5 ± 3
Patients with chief complaint of chronic fatigue (n = 12)	151.3 ± 2	38.0 ± 10	11.8 ± 7	12.3 ± 10	12.9 ± 2	6.0 ± 3
Patients with fatigue plus sore throat plus headaches plus myalgias (n = 18)	117.5 ± 2	52.5 ± 8	13.8 ± 6	6.0 ± 8	10.7 ± 2	6.8 ± 4
Patients with most severe fatigue (intermittently bedridden/homebound) (n = 16)	147.9 ± 2	102.3 ± 5	16.2 ± 6	15.9 ± 7	11.5 ± 2	9.6 ± 3
Patients with cervical adenopathy or enlarged submandibular glands (n = 12)	123.0 ± 2	50.1 ± 9	28.2 ± 3	10.5 ± 8	10.5 ± 2	7.4 ± 4
Patients with history of mononucleosis (n = 10)	162.2 ± 2†	93.3 ± 1†	16.2 ± 7	6.3 ± 7	15.1 ± 2	8.1 ± 2

*GMTs indicates geometric mean titers; VCA-IgG, IgG antibodies to viral capsid antigen; EA-Ab, antibodies to Epstein-Barr virus early antigens; and EBNA-Ab, antibodies to Epstein-Barr virus nuclear antigen.

†P = .015. All other differences not statistically significant.

and 1:160, respectively; the values of EBNA-Ab were 1:5, 1:10, 1:40, and 1:10, respectively.

The VCA-IgG levels were 1:320 or greater in 12/40 (30%) of patients and 8/40 (20%) of control subjects ($P = NS$); EA-Ab levels were 1:40 or greater in 22/40 (55%) of patients and 17/40 (43%) of control subjects ($P = NS$); these levels had been regarded as "abnormal" in our laboratory. In the patient group, 11/40 (28%) of patients and 6/40 (15%) of control subjects ($P = NS$) had both VCA-IgG levels of 1:320 or greater and EA-Ab levels of 1:40 or greater.

Table 2 displays the GMTs of VCA-IgG, EA-Ab, and EBNA-Ab in all patients and all matched control subjects, and in specific patient subsets (with their matched control subjects). In all but one of the 43 comparisons reported in the above paragraphs and in Table 2, the EBV antibody levels in patients were higher than in the matched control subjects. However, in only one instance was the difference between patients and control subjects statistically significant ($P = .015$) (the subset of patients with a history of mononucleosis). Given the relatively small cell sizes in the various paired comparisons, the power of the study to recognize real numerical differences of the magnitude shown in Table 2 was weak, ranging from 3% to 69% and averaging 28%. The only comparison in which the power was greater than 50%—VCA-IgG levels in patients with a history of mononucleosis, compared with their age- and sex-matched controls—was the only instance in which a significant difference was found.

COMMENT

Chronic active EBV infection is a controversial clinical entity. There seems to be little doubt that some pa-

tients with extraordinarily high titers of EBV antibodies (particularly VCA-IgG and EA-Ab) really are suffering from a syndrome associated with reactivation of EBV.^{19,37-39}

Several recent reports have described patients with less dramatic elevations of EBV antibody titers.²¹⁻²³ These reports involved highly selected patients who were referred to investigators known to have an interest in CEBV infection. No attempt was made by these investigators to ascertain the prevalence of the condition. Levels of EBV antibodies (VCA-IgG and EA-Ab) were significantly higher in these patients than in control subjects, suggesting that measurement of antibodies to EBV has diagnostic value in highly selected patients.

These recent reports²¹⁻²³ provide further evidence of a chronic fatigue syndrome associated with serologic evidence of reactivated, latent EBV infection. However, as the authors acknowledge, the demonstration of such an association does not prove that reactivation of EBV is the cause of the fatigue and associated symptoms seen in these patients. Indeed, the elevated EBV antibody titers may represent only an epiphenomenon; some other primary pathogenetic event (such as infection with another lymphotropic virus) could have caused the patients' illness and also reactivated a latent EBV infection.

In this study, we attempted to assess the prevalence of a syndrome suggestive of the CEBV infection syndrome in an unselected population of patients seeking primary medical care. We found that a clinical syndrome suggestive of CEBV infection or chronic mononucleosis was present in a surprisingly high fraction (21%) of patients aged 17 to 50

years, coming to our primary care practice; none of these patients were felt by their physicians to have evidence of other preexisting "organic" or psychiatric illnesses that could account for their symptoms. On the other hand, while these patients tended to have higher levels of antibody to EBV (particularly VCA-IgG and EA-Ab) than did age- and sex-matched control subjects who did not have a chronic fatigue syndrome, the differences between patients and control subjects almost never were statistically significant.

In contrast with several previous studies, we obtained control subjects from among patients (not laboratory technicians or employees) attending the same practice. The control subjects were matched for both age and sex, were asked specifically whether they had been experiencing chronic fatigue, and explicitly denied having chronic fatigue; the "normality" of the control subjects was not assumed. Finally, the antibody determinations in control subjects were performed blindly by the same technician who performed the determinations on patients.

It seems likely that our patients were less sick than patients in the several other recently reported studies.²¹⁻²³ None of the 40 patients in our study had been fully disabled by his or her illness, in contrast with some patients in the previous studies, and the patients had relatively few days when they could not work. Also, the VCA-IgG and EA-Ab levels in our patients were lower than in these previous studies (although the fact that our serologic studies were performed in a different laboratory makes such comparisons hazardous). We expected any patients we detected with a syndrome suggestive of CEBV infection to be less sick than previously described patients, since we were seeing patients seeking primary care for any reason; we were not seeing patients referred for evaluation of chronic fatigue.

At the same time, the patients reported in this study had been experiencing considerable morbidity from their syndrome (Table 1), for a median duration of 16 months (range, six to 458 months). Sixty percent reported that the syndrome had caused substantial stress at home and at work. The majority stated that the fatigue became so severe that they were periodically bedridden; the associated myalgias and headaches became so severe at times that the patients had to stop all normal activities and rest. Twenty-five percent of the patients stated that they had sought help for the problem from multiple physicians, to no avail.

Many of the symptoms associated with the CEBV infection syndrome—particularly the chronic fatigue, myalgias, and headache—are also manifestations of chronic depression and anxiety. Therefore, it is possible that some of these patients were suffering from a psychoneurosis, even though none of them were being treated for a psychoneurosis at the time that their chronic fatigue syndrome started. At the same time, depression and anxiety do not so easily explain the recurrent

pharyngitis, adenopathy, paresthesias, arthralgias, or fevers reported by many patients.

The results of this study indicate that a chronic fatigue syndrome suggestive of a mild form of the CEBV infection syndrome may be surprisingly common in a primary care practice. However, our study offers no proof that EBV plays a causal role in the pathogenesis of this syndrome. Furthermore, our study emphasizes the difficulties of diagnosing this syndrome using currently avail-

able serologic techniques, at least with patients seen in a general medicine primary care practice.

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