THE "CHRONIC, ACTIVE EPSTEIN-BARR VIRUS INFECTION" SYNDROME AND PRIMARY FIBROMYALGIA

DEDRA BUCHWALD, DON L. GOLDENBERG, JOHN L. SULLIVAN, and ANTHONY L. KOMAROFF

Fifty patients with primary fibromyalgia who had been followed in an academic rheumatology practice frequently reported symptoms thought to be typical of "chronic Epstein-Barr virus infection," but not of fibromyalgia: recurrent sore throat (54%), recurrent rash (47%), chronic cough (40%), recurrent adenopathy (33%), and recurrent low-grade fevers (28%). In 55% of the patients, illness had begun suddenly, with what seemed to be a viral syndrome. Antibody titers to Epstein-Barr virus in the patients with fibromyalgia, however, were not significantly different from those in age- and sex-matched "healthy" and "unhealthy" control subjects.

Fibromyalgia, or fibrositis, is a form of nonarticular rheumatism that is characterized by diffuse musculoskeletal pain, most commonly of the axial skeleton (1–5). The chronic pain is accompanied by stiffness, particularly in the morning, and increased tenderness at specific tender points. The disorder is frequently accompanied by poor sleep, headaches, irritable bowel syndrome, and major affective disorders. Patients with fibromyalgia also complain of fatigue. Indeed, Yunus et al have stated that "one may question the diagnosis of primary fibromyalgia in the absence of tiredness" (1).

The syndrome is considered primary when no known cause or associated medical condition is present and all laboratory and radiographic results are normal, and is considered secondary when the characteristic signs and symptoms are thought to be secondary to trauma, various rheumatic diseases, or nonrheumatic disorders, such as hypothyroidism. In most situations, however, there is no definite relationship between the fibromyalgia and the course and treatment of the associated condition (2).

Until recently, the syndrome of fibromyalgia has not been widely accepted as a specific medical condition, even though up to 5% of patients at a general medical clinic and 12% of new patients seen by rheumatologists may have fibromyalgia (1–3). Indeed, some rheumatologists believe that primary fibromyalgia is the most common rheumatologic condition seen in their practice, particularly in women less than 50 years of age (1–5).

The clinical presentation of primary fibromyalgia is similar, in some respects, to that of a recently described syndrome that is associated with serologic evidence of reactivated latent infection with Epstein-Barr virus (EBV): the "chronic EBV infection" syndrome (CEBV) or "chronic mononucleosis"

From the Division of General Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; the Department of Medicine, Multipurpose Arthritis Center, Boston University School of Medicine, Boston, Massachusetts; and the Department of Pediatrics, Molecular Genetics and Microbiology, University of Massachusetts, Worcester.

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Dedra Buchwald, MD: Division of General Medicine, Department of Medicine, Brigham and Women's Hospital, and Henry J. Kaiser Family Foundation Fellow in General Internal Medicine; Don L. Goldenberg, MD: Department of Medicine, Multipurpose Arthritis Center, Boston University School of Medicine; John L. Sullivan, MD: Department of Pediatrics, Molecular Genetics and Microbiology, University of Massachusetts, and Established Investigator of the American Heart Association; Anthony L. Komaroff, MD: Division of General Medicine, Department of Medicine, Brigham and Women's Hospital.

Address reprint requests to Anthony L. Komaroff, MD, Division of General Medicine, Department of Medicine, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

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syndrome (6–12). While the 2 syndromes share certain common features—especially fatigue, myalgias, and arthralgias—they also are dissimilar in some respects. For this reason, it seemed pertinent to ask whether some patients with primary fibromyalgia might be found to have symptoms of CEBV, if specifically questioned, and whether they might have the serologic evidence of reactivated EBV infection that is characteristic of the CEBV syndrome. While it has not been established that EBV is the cause of CEBV, and while no specific therapy has been demonstrated to be effective against EBV, establishing a relationship between these 2 disorders could set the stage for future therapeutic interventions.

PATIENTS AND METHODS

Study setting and patient population. All participating patients were under the care of one of us (DLG) in a rheumatology practice that is located in a large, academic teaching hospital (Boston University Medical Center). The study was conducted when all of these patients were attending an annual patient education meeting. All clinical and laboratory data were obtained on the same day from all patients. At the time the study data were collected (mid-1985), EBV titers had not previously been determined in any patient, and the diagnosis of "CEBV" had not been considered in any patient.

The diagnosis of primary fibromyalgia was made on the basis of clinical criteria modified from the report of Yunus and coworkers (1). Those criteria were: 1) diffuse aches or prominent stiffness involving 3 or more anatomic sites for at least 3 months, 2) at least 6 tender points, and 3) at least 3 of the following: modulation of symptoms by physical activity, weather, or stress; poor sleep; fatigue; anxiety; headaches; irritable bowel syndrome; or subjective swelling and numbness. Isolated findings such as Raynaud's phenomenon, sicca symptoms, or the presence of antinuclear antibodies (ANA) were not grounds for exclusion, provided the patient had no other clinical or laboratory evidence of a systemic rheumatic disease (4). Each patient had been diagnosed as having fibromyalgia and had been followed longitudinally by one of us (DLG) for a minimum of 6 months.

Clinical and laboratory data. *Clinical data.* After giving written consent, each patient completed a detailed questionnaire that inquired into the patient's medical history and current health status. The questionnaire was the same one used to study patients with suspected CEBV. Each patient's medical record was reviewed with reference to the presence of other medical conditions and, in particular, symptoms and laboratory evidence of systemic rheumatic disorders and history of psychiatric disease.

Standard laboratory data. At the same time that sera were obtained for EBV serologic studies, complete blood counts, erythrocyte sedimentation rates (ESR), and tests for ANA were obtained on all patients.

Virologic studies. From each patient, a single serum specimen was obtained. Titers of IgM and IgG antibodies to the viral capsid antigen (VCA) of EBV (VCA-IgM and VCA-IgG), as well as IgG antibodies to the early antigens (EA-Ab), were determined by indirect immunofluorescence (13). No attempt was made to distinguish the restricted and diffuse components of EA-Ab. Antibodies to Epstein-Barr nuclear antigen (EBNA-Ab) were detected by anticomplement immunofluorescence (14). Due to unreliability of titer measurements when antibodies are present in very low levels, titers were reported as "0" when VCA-IgG was present in a dilution of <1:20, when VCA-IgM was present in a dilution of <1:20, when EA-Ab was present in a dilution of <1:20, and when EBNA-Ab was present in a dilution of <1:5. All antibody titers were determined in a single laboratory by the same technician, who routinely performs approximately 1,000 EBV antibody profiles each year.

Control subjects. Two groups of control subjects were selected from ambulatory patients seen in another large academic teaching hospital (Brigham and Women's Hospital). The controls were matched for age (within 5 years) and sex to each of the study patients, and were identified by direct questions and by review of their medical records.

Typically, "healthy" control subjects (HCS) had been seen for routine screening examinations, for care of acute minor illness, or for chronic illnesses that were not expected to produce chronic fatigue: hypertension, diet-controlled diabetes mellitus, osteoarthritis, or mild anemia. None of the HCS was receiving any immunosuppressive drugs.

"Unhealthy" control subjects (UCS) were clinic patients with at least 1 chronic illness other than the above (e.g., systemic rheumatic diseases, congestive heart failure, or renal failure). We studied these UCS for 2 reasons. First, since fibromyalgia is a poorly understood, chronic syndrome, we wanted to determine if the presence of any chronic medical condition was associated with abnormal EBV serologies. Second, although the majority of the fibromyalgia patients were otherwise healthy, 24% did have at least 1 other associated medical condition, such as cardiovascular disease.

None of the control subjects was pregnant. Each control subject was explicitly asked about, and each explicitly denied, the presence of persistent myalgias. Serum specimens obtained from each subject were tested for antibodies to EBV as described above. The technician did not know which serum specimens belonged to which control group or patient group.

Statistical analysis. Geometric mean titers in the patients were separately compared with those in both control groups, using a matched analysis. The comparisons were made for the entire group of patients and for the entire HCS and UCS groups. Comparisons were also made for each of several patient subgroups and their matched control subjects. Using parametric methods (Student's 2-tailed *t*-test), we first attempted to normalize the distribution: The value of each serologic result was log transformed (base 10). Patients with "0" antibody detected were given an arbitrary value of 1 instead of 0, so that geometric mean titers could be determined on the entire population, not just on seropositive patients.

Percentages of patients with a certain serologic finding were compared with the percentage of control subjects who were age- and sex-matched to that patient subgroup, using chi-square or Fisher's exact test (2-tailed).

RESULTS

Clinical findings. Fifty patients were enrolled in the study. Their mean age was 44 years; 46 were women (92%). These patients were compared with 50 healthy and 48 unhealthy control subjects. Table 1 summarizes the findings of the medical history and physical examination. The myalgias experienced by all of the patients were, at their worst, sufficient to cause 24 of 50 of the patients (48%) to stop all normal activity and to rest. Fatigue was reported by 48 of 50 patients (96%). Of the 48, 7 patients (15%) stated that the fatigue, at its worst, was sufficient to make them "bedridden: can do virtually nothing." Thirty-three of the 48 patients (69%) were never free of fatigue. Recurrent headaches were experienced by 45 of 50 of the patients (90%); in 20 of the 45 (47%), the headaches were sufficiently severe to force the patient to stop all normal activities and to rest. Fatigue plus headaches plus sore throat was reported by 26 of 50 patients (52%). A history of allergies was reported by 32 patients (64%).

Surprisingly, 27 of the 50 patients (54%) reported that they experienced recurrent pharyngitis; 23 reported recurrent rashes (47%); 19 reported recurrent cough (40%); 16 reported recurrent "swollen lymph glands" (32%), particularly in the neck; and 14 reported recurrent low-grade fevers (28%).

The majority of patients experienced concomitant sleep disorder, joint pain, anxiety, depression, difficulty concentrating, and diarrhea. Many patients had seen other physicians previously in an attempt to diagnose and treat the problem.

The mean duration (range) of the symptoms was as follows: myalgias 97 months (2–492); fatigue 94 months (6–492); headache 118 months (5–600); pharyngitis 40 months (1–384).

Standard laboratory data. The results of standard diagnostic tests were generally unremarkable. No patient tested had a hematocrit level <33%, 1 of 50 (2%) had a leukocyte count >10,000/mm^3, and 7 of 50 (14%) had a leukocyte count <5,000/mm^3. Twelve percent of the patients had an ESR >20 mm/hour, and 12% had an ESR <5 mm/hour; 6 of 50 patients tested had ANA titers >1:16, but only 1 had a titer >1:160. Each patient who had an abnormal laboratory value had been observed for >18 months, with no other clinical condition having been recognized (4). Most patients with isolated abnormal laboratory test results had normal results on serial evaluations. All patients had normal findings on liver function tests, thyroid function tests, and creatine phosphokinase determinations.

Table 1. Clinical findings in 50 patients (46 women, 4 men) with primary fibromyalgia

Findings (total no. reporting)	No. reporting (%)
Muscle aches, severity at its worst (50)	
Need to stop all normal activities and rest	24 (48)
Can continue normal activities but muscle aches make it hard	25 (50)
Not aware of muscle aches during normal activities, only at rest	1 (2)
Fatigue, severity at its worst (48)	
Bedridden, can do virtually nothing	7 (15)
Shut-in, cannot do even light housework or its equivalent	5 (10)
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	36 (75)
Frequency	
Constant fatigue that doesn't change	11 (23)
Always some fatigue that may get better but never goes away completely	22 (46)
The fatigue alternates with periods of feeling normal	15 (31)
Associated recurrent headaches, severity at their worst (43)	
Need to stop all normal activities and rest	20 (47)
Can continue normal activities but headaches make it hard	21 (49)
Not aware of headaches during normal activities, only at rest	2 (5)
Associated recurrent pharyngitis (50)	27 (54)
Associated recurrent swollen lymph glands (50)	16 (32)
Associated fevers at home (50)	14 (28)
Fatigue plus sore throat plus headaches (50)	26 (52)
Illness started with a viral syndrome (40)	22 (55)
Other associated symptoms (50)	
Waking up feeling unrested	47 (94)
Joint pain	46 (94)
Anxiety	43 (86)
Difficulty sleeping	39 (78)
Depression or unusual mood changes	36 (72)
Difficulty concentrating	36 (72)
Diarrhea	31 (62)
Intermittent swelling of the fingers	29 (59)
Odd sensations in the skin	29 (59)
Stomachache	28 (56)
Rash	23 (47)
Nausea	20 (40)
Cough	19 (40)
Loss of appetite	14 (28)
Weight loss	7 (14)
Vomiting	1 (2)
Medical history (50)	
Mononucleosis	11 (22)
Herpes	17 (34)
Allergies to foods or drugs, "hay fever"	32 (64)
Raynaud's phenomenon (36)	13 (36)
Sicca symptoms (36)	9 (25)
Other medical condition	13 (26)
Psychiatric diagnosis	17 (34)

Table 2. Comparisons of serologic results: various patient groups and their matched healthy control subjects (HCS) and unhealthy control subjects (UCS)*

Serologic study‡	All subjects	Subset of patients or controls†				
		Most severe myalgias	Fatigue, sore throat, headaches, and myalgias	Most severe fatigue	Cervical adenopathy or enlarged submandibular glands	History of mononucleosis
VCA-IgG						
Patients	131.8 ± 2.1 (50)	123.0 ± 1.8 (24)	131.8 ± 2.1 (26)	131.8 ± 1.7 (7)	134.9 ± 2.4 (16)	104.7 ± 2.0 (10)
HCS	120.2 ± 4.4 (50)	117.5 ± 5.4 (24)	102.3 ± 5.1 (26)	177.8 ± 2.8 (7)	117.5 ± 4.6 (16)	151.4 ± 2.3 (10)
UCS	199.5 ± 2.7 (48)§	218.8 ± 2.4 (24)§	218.8 ± 2.7 (24)	213.8 ± 2.6 (7)	151.4 ± 2.7 (14)	114.8 ± 2.4 (10)
EA-Ab						
Patients	9.02 ± 6.8 (49)	11.2 ± 6.8 (24)	9.18 ± 8.1 (23)	6.9 ± 6.5 (7)	10.2 ± 6.8 (16)	4.5 ± 5.7 (10)
HCS	8.9 ± 6.9 (50)	15.8 ± 6.4 (23)	7.7 ± 8.1 (23)	12.9 ± 6.6 (7)	7.4 ± 6.7 (16)	7.8 ± 5.3 (10)
UCS	13.5 ± 6.5 (48)	9.2 ± 8.2 (23)	9.8 ± 6.3 (23)	8.4 ± 8.1 (7)	9.0 ± 6.2 (14)	9.6 ± 5.0 (10)
EBNA-Ab						
Patients	14.5 ± 2.2 (50)	13.8 ± 2.3 (24)	12.3 ± 2.6 (26)	9.4 ± 3.0 (7)	13.5 ± 2.5 (16)	13.2 ± 2.6 (10)
HCS	10.5 ± 3.1 (50)	11.0 ± 3.1 (24)	9.4 ± 3.1 (26)	11.2 ± 2.1 (7)	8.0 ± 3.4 (16)	10.1 ± 2.7 (10)
UCS	16.2 ± 2.9 (48)	13.8 ± 3.1 (24)	18.2 ± 2.8 (24)	13.2 ± 1.6 (7)	20.0 ± 2.1 (14)	13.5 ± 3.4 (10)

* Values given are the geometric mean titer ± SD (n).
† See Results for details.
‡ VCA-IgG = IgG antibodies to the viral capsid antigen of Epstein-Barr virus; EA-Ab = IgG antibodies to the early antigens; EBNA-Ab = antibodies to Epstein-Barr nuclear antigen.
§ $P < 0.05$ versus patients.

Serologic findings. VCA-IgG was found at some level in all 50 patients (100%), 47 of 50 HCS (94%), and all 48 UCS (100%). VCA-IgM was detected in none of the patients, in 1 HCS, and in 3 UCS. EA-Ab was found at some level in 29 of 49 patients (59%), 29 of 50 HCS (58%), and 34 of 48 UCS (71%). EBNA-Ab was found in 48 of 50 patients (96%) and in 43 of 50 HCS (86%), compared with 45 of 48 UCS (94%).

Table 2 shows the geometric mean titers 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 none of the comparisons were the EBV antibody levels in patients significantly higher than in the matched control subjects; however, in 2 instances (all patients and those with the most severe myalgias), UCS had significantly higher ($P < 0.05$) levels of VCA-IgG than did the patients.

DISCUSSION

As the recently described "chronic Epstein-Barr virus infection" syndrome has gained increasing recognition (6–12), rheumatologists and other clinicians have noted that many features of the syndrome are similar to those of primary fibromyalgia (fibrositis). We sought to explore the similarity between these 2 syndromes.

Not surprisingly, we confirmed that 50 patients with fibromyalgia frequently reported symptoms consistent with either fibromyalgia or CEBV: myalgias, fatigue, arthralgias, recurrent headaches, and a chronic sleep disorder. Surprisingly, they also frequently reported symptoms typical of CEBV, but not of fibromyalgia: recurrent sore throat (54%), adenopathy (32%), low-grade fevers (28%), chronic cough (40%), and history of allergies (64%). In comparison, these findings have been reported in CEBV patients with the following frequency: recurrent sore throat 50–64%, adenopathy 43–59%, low-grade fevers 63–96%, chronic cough 38%, and history of allergies 53% (10–12,15). Thus, on clinical grounds alone, there appears to be considerable overlap between the 2 syndromes, and this raises the question of whether the same etiologic agent might be involved. We were particularly interested in a viral agent, and were impressed that 55% of patients stated that their fibromyalgia had started with a viral syndrome.

Although serologic evidence of reactivated latent EBV infection has been seen in many of the "CEBV" patients reported in recent literature, a minority of patients have not had such serologic profiles; indeed, some have been entirely seronegative for EBV (11,12). Also, we have found that patients who seek primary medical care for a clinical syndrome suggestive of CEBV do not have significantly different EBV antibody levels from those found in control subjects (15). Hence, there is reason to wonder if EBV

is the primary cause of the CEBV syndrome, let alone of fibromyalgia.

In this study, EBV serologies were not significantly different between the 50 patients with fibromyalgia and those in the 2 control groups. Control subjects have not been well described in previous studies of the CEBV syndrome; therefore, it has been difficult to judge what constitutes a "normal" EBV serologic value. We thought that control subjects should be chosen from age- and sex-matched patients seeking medical care, rather than from friends or coworkers of the investigator. In addition, all control subjects were explicitly asked about, and explicitly denied, having the primary symptom of fibromyalgia: chronic myalgias. Finally, we separated control subjects into 2 groups: those who were judged "healthy" (those with no illness that could produce chronic fatigue) and those judged "unhealthy" (those with a chronic illness that might have produced chronic fatigue). If anything, there was more evidence of reactivated EBV infection in the latter control group than in patients with fibromyalgia.

In summary, a surprisingly large fraction of patients with fibromyalgia had symptoms commonly seen in CEBV, but not previously reported to be common in fibromyalgia. These recurrent symptoms (pharyngitis, cervical adenopathy, rash, and low-grade fever) suggest a chronic infection, although other noninfectious systemic diseases could produce a similar spectrum of symptoms. The majority of the patients stated that the fibromyalgia had begun suddenly, as an apparent "flu" or "virus" infection, and this was typically characterized by respiratory or gastrointestinal symptoms.

Despite these hints of a possibly viral etiology in many of the patients with fibromyalgia, there was no evidence that reactivation of latent EBV infection was associated with the patients' illness.

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REFERENCES

1. Yunus M, Masi AT, Calabro JJ, Miller KA, Feigenbaum SL: Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. Semin Arthritis Rheum 11:151–171, 1981
2. Goldenberg DL: Fibromyalgia syndrome: an emerging but controversial condition. JAMA 257:2782–2787, 1987
3. Wolfe F, Cathey MA, Kleinheksel SM: Fibrositis (fibromyalgia) in rheumatoid arthritis. J Rheumatol 11:814–818, 1984
4. Dinerman H, Goldenberg DL, Felson DT: A prospective evaluation of 118 patients with the fibromyalgia syndrome: prevalence of Raynaud's phenomenon, sicca symptoms, ANA, low complement, and Ig deposition at the dermal-epidermal junction. J Rheumatol 13:368–373, 1986
5. Felson DT, Goldenberg DL: The natural history of fibromyalgia. Arthritis Rheum 29:1522–1526, 1986
6. Tobi M, Morag A, Ravid Z, Chowers I, Feldman-Weiss V, Michaeli Y, Ben-Chetrit E, Shalit M, Knobler H: Prolonged atypical illness associated with serologic evidence of persistent Epstein-Barr virus infection. Lancet I:61–64, 1982
7. Ballow M, Seeley J, Purtilo DT, St. Onge S, Sakamoto K, Rickles FR: Familial chronic mononucleosis. Ann Intern Med 97:821–825, 1982
8. Edson CM, Cohen LK, Henle W, Strominger JL: An unusually high-titer human anti-Epstein Barr virus (EBV) serum and its use in the study of EBV-specific proteins synthesized in vitro and in vivo. J Immunol 130:919–924, 1983
9. Hamblin TJ, Hussain J, Akbar AN, Tang YC, Smith JL, Jones DB: Immunological reason for chronic ill health after infectious mononucleosis. Br Med J 287:85–88, 1983
10. DuBois RE, Seeley JK, Brus I, Sakamoto K, Ballow M, Harada S, Bechtold TA, Pearson G, Purtilo DT: Chronic mononucleosis syndrome. South Med J 77:1376–1382, 1984
11. Jones JF, Ray CG, Minnich LL, Hicks MJ, Kibler R, Lucas DO: Evidence for active Epstein-Barr virus infection in patients with persistent unexplained illnesses: elevated anti-early antigen antibodies. Ann Intern Med 102:1–7, 1985
12. Straus SE, Tosato G, Armstrong G, Lawley T, Preble OT, Henle W, Davey R, Pearson G, Epstein J, Brus I, Blaese RM: Persisting illness and fatigue in adults with evidence of Epstein-Barr virus infection. Ann Intern Med 102:7–16, 1985
13. Henle W, Henle G, Horowitz CA: Infectious mononucleosis and Epstein-Barr virus-associated malignancies, Diagnostic Procedures for Viral, Rickettsial and Chlamydial Infections. Fifth edition. Edited by EH Lennette. New York, American Public Health Association, 1979, pp 441–470
14. Reedman BM, Klein G: Cellular localization of an Epstein-Barr virus (EBV)-associated complement-fixing agent in producer and non-producer lymphoblastoid cell lines. Int J Cancer 11:499–520, 1973
15. Buchwald D, Sullivan JL, Komaroff AL: Frequency of "chronic active Epstein-Barr virus infection" in a general medical practice. JAMA 257:2303–2307, 1987