A Cluster of Patients With a Chronic Mononucleosis-like Syndrome

Is Epstein-Barr Virus the Cause?

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A cluster of 134 patients who had undergone Epstein-Barr virus (EBV) serological testing because of suspected chronic EBV syndrome was investigated in Nevada. Fifteen case-patients were identified who had severe, persistent fatigue of undetermined etiology for more than two months. When compared with the remaining 119 patients who had less severe illnesses and with 30 age-, sex-, and race-matched control-persons, these 15 patients had significantly higher antibody titers against various components of EBV and against cytomegalovirus and herpes simplex and measles viruses. Epstein-Barr virus serology could not reliably differentiate individual case-patients from the others, and the reproducibility of the tests within and among laboratories was poor. As a group, the case-patients appear to have had a syndrome that is characterized by chronic fatigue, fever, sore throat, and lymphadenopathy. The relationship of this fatigue syndrome to EBV is unclear; further studies are needed to determine its etiology.

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SINCE the 1930s, several reports have described syndromes of chronic debilitating fatigue associated with low-grade fever, myalgias, arthralgias, sore throat, headaches, neurological complaints, and a variety of other symptoms.[1-10] Although these syndromes are remarkably similar, they have been described by several names, including Akureyri disease,[1,2] Iceland disease,[3] atypical poliomyelitis,[4] benign myalgic encephalomyelitis,[5] epidemic neuromyasthenia,[6-8] encephalomyelitis,[9] and postviral syndrome.[10] Despite intensive searches for the etiologic agents of these syndromes, all have remained idiopathic. Some reports, however, have described syndromes that were thought to represent recurrent acute infectious mononucleosis.[11-13]

See also pp 2303 and 2335.

In the past 15 years, Epstein-Barr virus (EBV) has been established as the cause of most cases of infectious mononucleosis,[14] and EBV serological tests have become commercially available. The suggestion that the fatigue syndrome might represent recurrent infectious mononucleosis has prompted recent attempts to link the syndromes with EBV. Several studies[15-18] have described a syndrome of chronic fatigue that is similar to those described earlier and that is associated with persistently elevated serum titers of antibody against the early antigen (EA), viral capsid antigen (VCA), and nuclear antigen (EBNA) of EBV. This syndrome has become known as *chronic mononucleosis* or, more specifically, *chronic EBV disease* (CEBV).

In September 1985, we investigated a cluster of mononucleosis-like illnesses, thought to represent CEBV, in Nevada. The results suggest that EBV serology is inadequate for diagnosing these illnesses and that the illnesses may not be caused by EBV. However, they also suggest that some patients with these illnesses have an abnormality of infectious and/or immunologic origin.

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BACKGROUND

Incline Village, Nev, is a resort community on the northeast shore of Lake Tahoe, with a resident population of 4000 to 5000. The population of the area is heavily weighted toward upper-middle to high socioeconomic status. On Aug 8, 1985, two internists in Incline Village reported to the Centers for Disease Control (CDC) 80 to 90 patients seen since October 1984 who had illnesses characterized by increased fatigue. In many of these patients, the fatigue was associated with lymphadenopathy, pharyngitis, and splenomegaly or hepatomegaly. Epstein-Barr virus serology panels had been performed by a commercial reference laboratory (laboratory 1) on each of the patients. These tests measure indirect fluorescent antibody (IFA) titers of IgM[19] and IgG[20] against VCA (VCA-IgM and VCA-IgG); IgG against EA, both the diffuse (EA-D-IgG) and restricted (EA-R-IgG) components[21]; and IgG against EBNA (EBNA-IgG).[22] Elevated titers of various antibodies to EBV were detected in many of the patients; the results had been interpreted as indicating that the cluster of illnesses was related to CEBV. An investigation was undertaken.

METHODS

Case Detection

The patients who had undergone EBV serological testing because of suspected CEBV were found to have many nonspecific symptoms, but fatigue was the most universal. To improve the likelihood that our study patients had the same illness, we attempted to identify those patients who had the most severe and prolonged fatigue. We interviewed by telephone 134 (96%) of the 139 patients who had undergone EBV serol-

Table 1.—Prevalence of Symptoms and Signs in Case- and Noncase-Patients, Incline Village, Nev

Symptoms and Signs	Case-Patients (n=15), %	Noncase-Patients (n=12),* %	P†
Symptoms			
Fever/sweats	27	42	NS
Headache	20	17	NS
Sore throat	60	50	NS
Signs			
Pharyngitis	47	75	NS
Lymphadenopathy	93	83	NS
Palpable splenomegaly	87	33	<.01
Palpable hepatomegaly	20	17	NS

*Information was obtained for 12 of the 18 noncase-patients who were ill for a month or more but had other possible explanations for their illnesses.
†Fisher's exact test; NS indicates not significant.

ogy testing between Jan 1 and Sept 15, 1985, without prior knowledge of their medical histories, physical findings, or EBV serology results (laboratory records before Jan 1 were incomplete). Respondents were asked if they had suffered from excessive fatigue since Jan 1, 1985, and if so, the duration of their fatigue, the extent to which their daily activities had been altered as a result of their fatigue, and the month of onset of fatigue.

Of the 134 respondents, 50 described illnesses that resolved in less than one month. Many of these illnesses appeared to represent acute viral syndromes or other self-limited conditions. Fifty-one respondents had fatigue that lasted at least one month, but were either able to continue working (33 patients) or missed less than two weeks of work (18 patients). The remaining 33 patients had fatigue for one month or more; all 33 missed at least two weeks of work or reduced their daily activity by at least 50% as a result of their fatigue. Review of these patients' medical records disclosed other possible explanations for fatigue in 18 of the 33: fifth disease, depression, pregnancy, unspecified antinuclear antibody–positive disease, pneumococcal pneumonia, thyroiditis, chronic low-back pain with sciatica, Crohn's disease, unspecified colitis, chronic staphylococcal otitis media with metastatic abscesses, congestive heart failure, cirrhosis, iron deficiency anemia, and hypertension. These 18, along with the 101 patients who were ill for less than a month, will be referred to as *noncase-patients*.

The remaining 15 patients (*case-patients*) had illnesses that satisfied the following definition: persistently increased fatigue lasting at least one month that was sufficient to cause absence from work for two weeks or longer or reduction of daily activity by 50% or more, with no apparent explanation for the symptoms.

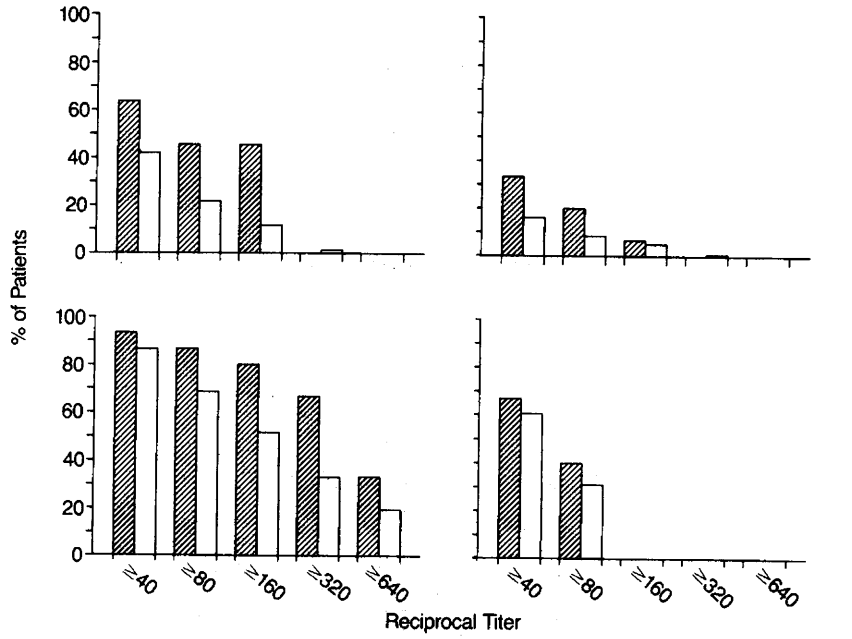

Fig 1.—Percentages of Epstein-Barr virus antibody titers at or above given threshold titers in case- (slashed bars) and noncase-patients (solid bars), Incline Village, Nev. Top left, IgG against early antigen, diffuse component. Results were available from 11 case- and 69 noncase-patients only. Top right, IgG against early antigen, restricted component. Bottom left, IgG against viral capsid antigen. Bottom right, IgG against Epstein-Barr nuclear antigen. All tests were performed at laboratory 1 between Oct 1, 1984, and Aug 1, 1985. Significant differences were noted for IgG against early antigen, diffuse component, 160 or greater ($P = .01$); and IgG against viral capsid antigen, 160 or greater ($P < .05$) and 320 or greater ($P = .01$).

Comparison of Case- and Noncase-Patients

During the telephone interviews we also obtained the following information from case- and noncase-patients: age, sex, race, town of residence, and history of acute infectious mononucleosis. Medical records of all 15 case-patients and 12 of the other 18 patients who were ill for at least one month were reviewed for history of headache, sore throat, and fever or sweats and findings of pharyngitis, lymphadenopathy, splenomegaly, and hepatomegaly. Statistical analysis of these data was performed using Fisher's exact test.

The results of the earliest EBV serology panels reported for each of the case-patients and noncase-patients were compared using two techniques. First, to determine if there were threshold titers that could effectively differentiate patients in the two groups, we compared the percentages of serum samples from case- and noncase-patients that had titers greater than or equal to reciprocal threshold values ranging from 40 to 640. Fisher's exact test was used for statistical analysis. Second, we determined geometric mean titers for case- and noncase-patients and analyzed the results using the t test, two tailed (assuming equal variances).

Case-Control Study

A case-control study was conducted using two control-persons, matched for age (plus or minus five years), sex, and race, for each of the 15 case-patients. Control-persons were selected from two groups—21 patients from the office practice who were scheduled for routine laboratory work unrelated to the study and nine office staff members within the medical building—none of whom had persistent fatigue or had been previously tested for EBV. Potential control-persons who had histories of chronic disease or long-term corticosteroid use were excluded. Informed consent was obtained from all participants after the purpose of the investigation had been fully explained.

Serum specimens were collected, refrigerated at 4°C, and transported to the CDC, where they were frozen at −70°C until testing. Specimens were tested for heterophil antibody, using an ox-cell hemolysin assay[23]; for EA-R-IgG by IFA, using slides prepared with NC37 cells[21]; for VCA-IgG by IFA, using a Burkitt's lymphoma cell line as the source of EBV-infected cells[20]; for VCA-IgM by IFA[19]; for EBNA-IgG by IFA[22]; for IgG against cytomegalovirus (CMV-IgG) by enzyme immunoassay (EIA), using a modification of the method of

Voller et al,[24] and by indirect hemagglutination assay (IHA)[25]; for IgG against herpes simplex virus types 1 and 2 (HSV-1-IgG and HSV-2-IgG) by IHA[26]; for IgG against measles virus (measles-IgG) by EIA using a modification of the method of Boteler et al[27]; and for total quantitative immunoglobulins (IgG, IgA, and IgM) with an automated clinical analyzer using a turbidimetric technique.

Aliquots of the serum samples were also forwarded to the reference laboratory used throughout by the two physicians (laboratory 1) for EBV testing and to a research laboratory at Georgetown University Medical Center, Washington, DC, for EIA tests for EA-IgG, VCA-IgM and -IgG, and EBNA-IgG, using monoclonal antibody–purified EBV antigens[28] (the EIA technique cannot differentiate EA-IgG into diffuse and restricted components).

Statistical analysis of the serological data was performed using two techniques. First, as for the case-noncase comparison, potential threshold titers ranging from 40 to 640 were tested and compared in unmatched form using Fisher's exact test. Second, matched data for each antibody type from each laboratory were analyzed using conditional logistic regression. To maintain the matched data sets for this analysis, we designated a titer one half that of the lowest reportable titer for each seronegative result (for example, for a titer <10, the value used for analysis was 5).

Comparability of EBV Serology Within and Between Laboratories

Laboratory 1 retested for EBV antibodies all serum samples that had been tested previously and were still available from the 15 case-patients and from a group of noncase-patients. A total of 19 samples from 12 case-patients and six from six noncase-patients were retested using the same techniques as before, and the paired results from the first and second tests were compared for significant (fourfold or greater) differences. Comparability of the EBV serological testing procedure between the two laboratories that used IFA tests (laboratory 1 and the CDC) was similarly studied using the 45 case-control serum samples.

RESULTS

Description of Case-Patients

The median age of the 15 case-patients was 40 years (range, 13 to 52 years). Thirteen of the patients (87%) were female, and all were white. Six (40%) resided in Incline Village, three (20%) in other communities on the north shore of the lake, and six (40%) in Truckee, Calif.

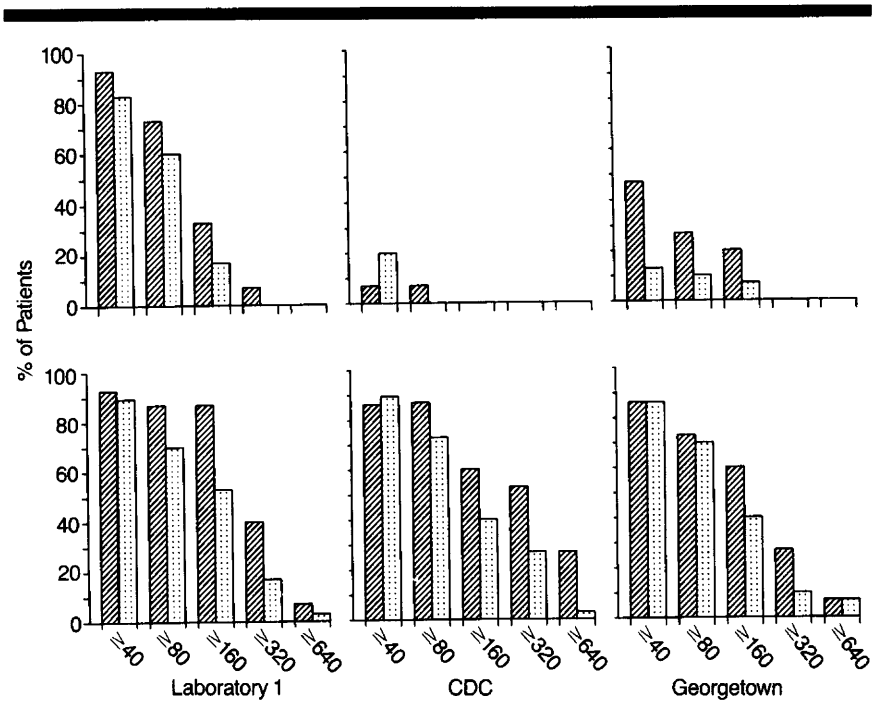

Fig 2.—Percentages of Epstein-Barr virus antibody titers at or above given threshold titers in 15 case-patients (slashed bars) and 30 age-, sex-, and race-matched control-persons (dotted bars), Incline Village, Nev. Top, IgG against early antigen, restricted component (IgG against early antigen in the Georgetown laboratory). Bottom, IgG against viral capsid antigen. CDC indicates Centers for Disease Control (Atlanta); Georgetown, Georgetown University Medical Center (Washington, DC). Significant differences were noted for IgG against early antigen (Georgetown), 40 or greater ($P<.05$); IgG against viral capsid antigen (Laboratory 1), 160 or greater ($P<.05$); and IgG against viral capsid antigen (CDC), 640 or greater ($P<.05$).

The months of onset of fatigue in the 15 case-patients ranged from January 1985 to August 1985. Eight patients (53%) described onset in May. Ten (67%) of the 15 case-patients were ill at the time of our telephone survey, with a median duration of illness of four months (range, two to ten months). The other five patients stated that they had recovered at the time of the survey, with a median duration of illness of three months (range, two to four months).

Fourteen months after completion of the telephone survey, the status of the ten case-patients who had symptoms at the time of the investigation was as follows: five were still unable to work, four had improved sufficiently to resume work, and one had recovered. Of the five case-patients who stated that they had recovered at the time of our investigation, three had suffered relapses of their illnesses after the investigation but had subsequently improved, one was still well, and one was unavailable for follow-up.

A history of infectious mononucleosis was reported by three case-patients (20%). In each of the three, the illness had occurred more than nine years earlier and had completely resolved. No attempts were made to confirm the accuracy of these diagnoses.

Comparison of Case- and Noncase-Patients

The case and noncase groups were similar, or not significantly different ($P<.05$), with regard to age (median, 40 vs 36 years, respectively), sex (87% female vs 66% female), race (all white), and history of infectious mononucleosis (20% vs 11%). Case-patients were significantly more likely than noncase-patients to reside outside Incline Village (nine of 15 vs 36 of 119, $P<.05$) and to reside in Truckee (six of 15 vs 18 of 119, $P<.05$).

Case-patients were more likely to have had splenomegaly recorded in their medical records ($P<.01$) (Table 1); otherwise, there were no statistically significant differences in the prevalence of symptoms or physical findings between the two groups.

Analysis of the original EBV serology test results performed by laboratory 1 on each case- and noncase-patient (Fig 1) indicated that higher percentages of case-patients than of noncase-patients had titers greater than or equal to almost every threshold value tested for EA-D-IgG, EA-R-IgG, VCA-IgG, and EBNA-IgG. These differences were statistically significant in three instances—EA-D-IgG, 160 or greater ($P=.01$); VCA-IgG, 160 or greater ($P<.05$); and VCA-IgG, 320 or greater

Table 2.—Reciprocal Geometric Mean Antibody Titers and Matched Analyses of Case-Patients (n = 15) and Control-Persons (n = 30) in Three Laboratories

	Geometric Mean Titers								
	Laboratory 1			Centers for Disease Control			Georgetown University Medical Center‡		
Antibody*	Case-Patients	Control-Persons	P†	Case-Patients	Control-Persons	P	Case-Patients	Control-Persons	P
Heterophil	. . .§	. . .	. . .	11	12	NS	. . .	. . .	. . .
EA-D-IgG (IFA)	18	14	NS	. . .	. . .	. . .	. . .	. . .	. . .
EA-R-IgG (IFA)	84	55	NS	12	11	NS	. . .	. . .	. . .
EA-IgG‖ (EIA)	. . .	. . .	. . .	. . .	. . .	. . .	22	9	<.05
VCA-IgG (IFA)	160	88	NS	180	107	NS	168	143	NS
EBNA-IgG (IFA)	33	21	NS	15	14	NS	112	75	NS
CMV-IgG (IHA)	. . .	. . .	. . .	292	31	<.05	. . .	. . .	. . .
CMV-IgG (EIA)	. . .	. . .	. . .	276	74	<.05	. . .	. . .	. . .
HSV-1-IgG (IHA)	. . .	. . .	. . .	154	82	NS	. . .	. . .	. . .
HSV-2-IgG (IHA)	. . .	. . .	. . .	140	34	NS	. . .	. . .	. . .
Measles-IgG (EIA)	. . .	. . .	. . .	548	289	.05	. . .	. . .	. . .

*Heterophil indicates heterophil antibody, measured by ox-cell hemolysin assay; EA-D-IgG, IgG against Epstein-Barr virus (EBV) early antigen, diffuse component; EA-R, EBV early antigen, restricted component; VCA, EBV viral capsid antigen; EBNA, EBV nuclear antigen; CMV, cytomegalovirus; HSV-1 and -2, herpes simplex virus types 1 and 2; IFA, indirect immunofluorescence assay; EIA, enzyme immunoassay; and IHA, indirect hemagglutination assay.
†Conditional logistic regression analysis; NS indicates not significant.
‡EBV serology performed by EIA.
§Not tested.
‖The Georgetown laboratory does not differentiate diffuse and restricted components of EA.

($P = .01$). Titers of VCA-IgM were undetectable in all 15 case-patients and in 118 noncase-patients (serology results were not available for one of the noncase-patients). Reciprocal geometric mean titers were significantly higher in case-patients only for VCA-IgG (254 in case-patients, 115 in noncase-patients, $P < .05$, two-tailed t test). In all these tests, there was a great deal of overlap in the titers of case- and noncase-patients.

We repeated the above comparisons between case- and noncase-patients, excluding the 18 noncase-patients who had illnesses lasting more than one month. Comparing the 15 case-patients with the remaining 101 noncase-patients, the factors for which there were significant differences were the same.

Case-Control Study

In the case-control study, higher percentages of case-patients than of control-persons had titers greater than or equal to each threshold tested for EA-R-IgG, EA-IgG, and VCA-IgG in all laboratories (Fig 2). These differences were significant in three instances—EA-IgG, 40 or greater (Georgetown, $P < .05$); VCA-IgG, 160 or greater (laboratory 1, $P < .05$); and VCA-IgG, 640 or greater (CDC, $P < .05$). Similar patterns were observed for EBNA-IgG, but the differences were not statistically significant. None of the case-patients or control-persons was seropositive for VCA-IgM. One case-patient and three control-persons were seronegative to EBV. Case-control results from the three laboratories indicated higher geometric mean titers in case-patients than in control-persons for all EBV antibody tests in all laboratories. However, conditional logistic regression analysis revealed that the higher titers in case-patients were significantly different only for EA-IgG as tested in the Georgetown laboratory (Table 2). Although case-patients tended to have higher EBV antibody titers than did control-persons, the EA-R-IgG, EA-IgG, and VCA-IgG test-result comparisons clearly indicate no threshold titers at which case-patients could be effectively differentiated from control-persons (Fig 3).

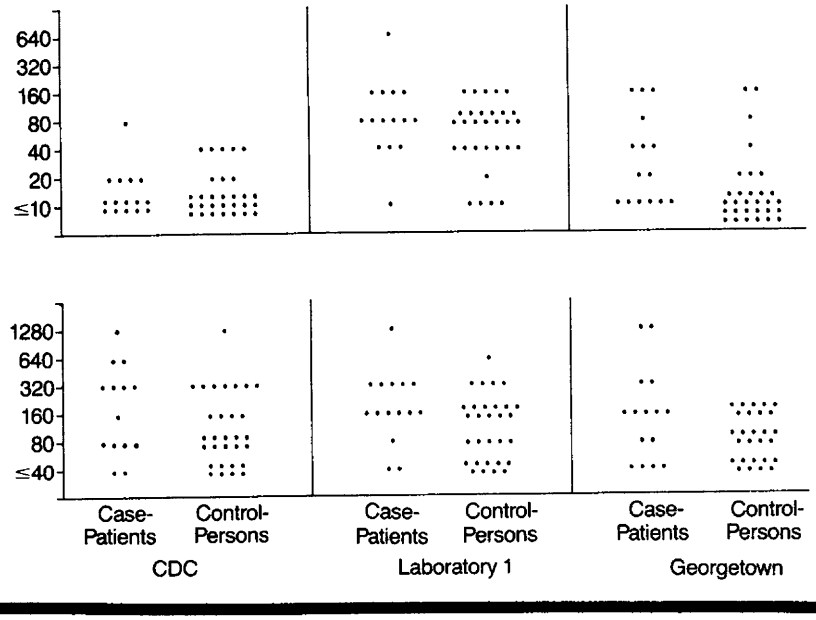

Fig 3.—Distribution of Epstein-Barr virus antibody titers in 15 case-patients and 30 age-, sex-, and race-matched control-persons, Incline Village, Nev. Top, IgG against early antigen, restricted component (IgG against early antigen in the Georgetown laboratory). Bottom, IgG against viral capsid antigen. CDC indicates Centers for Disease Control (Atlanta); Georgetown, Georgetown University Medical Center (Washington, DC).

The serological differences between case-patients and control-persons were not limited to EBV. The case-patients also tended to have higher titers of antibody than did control-persons against CMV, HSV-1 and -2, and measles (Fig 4), although significant differences were noted only for CMV-IgG (IHA), 512 or greater ($P < .05$) and 16 000 or greater ($P < .05$); HSV-2-IgG, 128 or greater ($P < .05$); and measles-IgG, 512 or greater ($P = .01$). The case-patients had higher geometric mean antibody

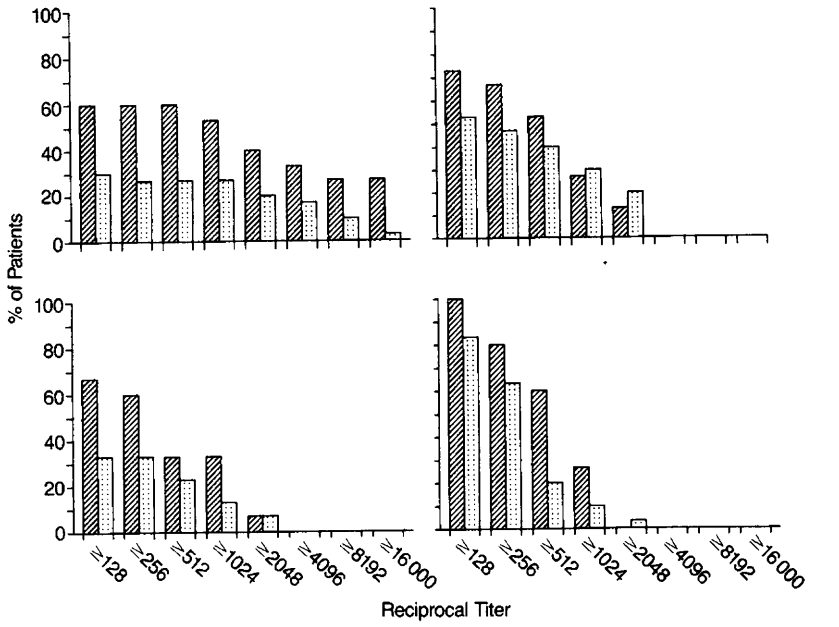

Fig 4.—Percentages of IgG antibody titers at or above given threshold values against cytomegalovirus (indirect hemagglutination assay) (top left), herpes simplex virus types 1 (top right) and 2 (bottom left), and measles virus (bottom right) in 15 case-patients (slashed bar) and 30 age-, sex-, and race-matched control-persons (dotted bar), Incline Village, Nev. Significant differences were noted for IgG against cytomegalovirus, 512 or greater ($P<.05$) and 16 000 or greater ($P<.05$); IgG against herpes simplex virus type 2, 128 or greater ($P<.05$); and IgG against measles virus, 512 or greater ($P=.01$).

titers than did control-persons against CMV, HSV-1 and -2, and measles in the results from the CDC laboratory. When the matched results were compared, significant differences were found in CMV-IgG titers using both IHA and EIA techniques ($P<.05$ for both) (Table 2). The difference in measles-IgG titers was of borderline significance ($P=.05$).

Even though the case-patients tended to have higher antibody titers than did the control-persons to several different viruses, mean total IgG, IgA, and IgM concentrations were comparable in the two groups (887 vs 882 mg/dL [8.87 vs 8.82 g/L], 165 vs 165 mg/dL [1.65 vs 1.65 g/L], and 199 vs 178 mg/dL [1.99 vs 1.78 g/L], respectively).

Comparability of EBV Serology Results

Comparing the original and the repeated test results (laboratory 1) for EA-D-IgG, EA-R-IgG, and VCA-IgG on the 25 recovered frozen serum samples from case- and noncase-patients, fourfold or greater differences in EA-D-IgG titers were found in three (13%) of 23 serum specimens, in EA-R-IgG titers in seven (30%) of 23, and in VCA-IgG titers in five (20%) of 25.

Among the three laboratories, there was considerable variation in test results, exemplified by the different percentages of titers that were greater than or equal to the various threshold values (Fig 2) and the ranges in the geometric mean titers (Table 2). The results from the Georgetown laboratory, using an EIA test, were not directly comparable with the results from the other two laboratories, which used IFA tests. When we compared the case-control study results from laboratory 1 and the CDC, 36 (80%) of the 45 serum samples had fourfold or greater differences in EA-R-IgG results; 18 (40%) had eightfold or greater differences. Fourfold or greater differences in VCA-IgG titers were found for 11% of specimens.

COMMENT

In our study, the case-patients appeared to differ as a group from the noncase-patients and from the matched control-persons. In addition to their severe and persistent fatigue, case-patients were significantly more likely than the noncase-patients to have had palpable splenomegaly noted in their medical records, and they tended to have higher antibody titers against EBV at all thresholds in all of the tests. The case-noncase comparison may have been biased against finding such differences, because patients with milder forms of the fatigue syndrome may have been included in the noncase group. The case-patients also differed from their matched control-persons in having higher EBV titers and higher titers against CMV, HSV-1 and -2, and measles virus. Thus, as a group, the case-patients appear to have had an abnormality (or abnormalities) that distinguished them from the comparison groups.

One purpose of our investigation was to determine whether an epidemic of a fatigue syndrome had occurred in Incline Village. According to the two Incline Village physicians, the number of patients with persistent fatigue had increased from previous years. Also, the fact that eight case-patients reported onset of illness in a single month suggested an epidemic. However, the relatively high proportion of case-patients who resided outside Incline Village suggests that patients with fatigue who would not otherwise have traveled to Incline Village for medical care had referred themselves specifically for EBV testing in 1985, thus creating the impression of an increase in cases in the area. (This self-referral of patients from outside the Incline Village area was confirmed during the telephone interviews with several patients.) Since the physicians did not begin testing their patients for EBV until late 1984, no equivalent data from previous years for ascertaining cases of fatigue syndrome were available. Therefore, we could not prove or disprove the occurrence of an epidemic.

The fatigue syndrome experienced by our case-patients appears similar to that described previously for CEBV,[15-18] as well as to some of the milder forms of other chronic fatigue syndromes of undetermined etiology,[5-9] although there are some differences. At the time of our investigation, few of the patients had been ill as long as those described in previous reports of CEBV. However, 12 of the 14 case-patients whose status was known were still symptomatic 14 months after our investigation. Lymphadenopathy and splenomegaly were more common in our patients than in the CEBV patients described in published reports.[15-18] This may be because our group was studied earlier in the evolution of illness than the other patients. In support of this premise, lymphadenopathy and splenomegaly were usually noted early in the course of illness in our patients and frequently resolved within a few weeks to months. Alternatively, it is possible that the fatigue syndrome experienced by the Lake Tahoe patients was etiologically different from those described elsewhere.

Our study indicates that EBV serology was of little value in diagnosing individual patients thought to have the

fatigue syndrome. Although, as a group, case-patients tended to have higher EBV titers than did comparison groups, there clearly was no threshold titer in any test that could differentiate case-patients from noncase-patients or from matched control-persons. Furthermore, our study indicates that EBV serology lacks sufficient reproducibility to allow direct comparison of results from different laboratories or of results from a single laboratory that were not tested in parallel. This finding is not unexpected, because IFA tests are well known to be highly subjective. Laboratory workers readily describe difficulty in determining end points with these tests. Results are also known to vary between batches of slides and reagents, as well as among individual technicians.[29,30] The variations found in the retested results from laboratory 1 did appear to be somewhat higher than expected and may have been related to the fact that several new technicians began working in the serology laboratory during the period between the original and the repeated procedures.

Our study also raises questions concerning the relationship between the chronic fatigue syndromes and EBV. Our case-patients tended to have higher EBV titers than did the comparison groups, supporting the findings in previous reports of CEBV that suggested a possible etiologic relationship with EBV.[15-18] However, the case-patients in our study also had higher antibody titers than did controls against CMV, HSV-1 and -2, and measles. These findings raise the possibility that a nonspecific polyclonal B-lymphocytic response may be present in these patients, although total immunoglobulin concentrations were comparable in the two groups. The possibility that the syndrome represents an exaggerated immunologic response to one inciting stimulus or a variety of stimuli should also be considered.

The recent research focus on EBV as the etiologic agent of chronic fatigue syndromes appears to have been too restrictive. Other agents must be considered, including both known and as yet unidentified viruses. Because this syndrome has not yet been shown to be a single disease and is of undetermined etiology, the currently popular descriptive terms—*chronic EBV disease* and *chronic mononucleosis*—are inappropriately specific. We propose a more generalized term—*chronic mononucleosis-like syndrome*—that is descriptive of the syndrome, yet is open to a variety of potential etiologies. It is clear that more studies are needed to identify the clinical characteristics, epidemiologic risk factors, and etiologic agent or agents of chronic mononucleosis-like syndrome.

In the meantime, the diagnosis of chronic mononucleosis-like syndrome (or whatever name is used) should be understood as provisional, not final. Physicians caring for patients who are thought to have this syndrome should continue to search for more definable and often treatable conditions that may be responsible for their patients' symptoms, including lymphomas and other malignancies; chronic heart, liver, kidney, lung, and endocrine diseases; anxiety and depression; immunodeficiency states; chronic infectious diseases such as tuberculosis; autoimmune diseases; and other chronic inflammatory conditions.

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