Infectious Mononucleosis, Epstein-Barr Virus, and Chronic Fatigue Syndrome: A Prospective Case Series

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Epstein-Barr viral infection, specifically infectious mononucleosis, typically has a more protracted course than other acute viral illnesses. Some recent observers have additionally suggested the possibility that Epstein-Barr virus (EBV) is the etiologic infectious agent in chronic fatigue syndrome, based on the finding of higher proportions of elevated antibodies to the EBV early antigen in some patients complaining of chronic fatigue. Straus et al[1] reported on 23 patients with chronic fatigue, 83% of whom exhibited persistently elevated antibodies in modest titer to the early antigen. Ten of these patients had never fully recovered from an episode of acute infectious mononucleosis. Other studies[2–4] had noted similar associations between persistently elevated antibodies to EBV-specific antigens and chronic symptoms in patients who presented with chronic symptoms after mononucleosis.

Three important antigen complexes, demonstrable by immunofluorescence procedures, are expressed in EBV-infected cells. The early antigen is thought to function perhaps in early replication of viral DNA. A late antigenic complex, the viral capsid antigen, may represent, in addition to structural capsid proteins, components of the viral enzymatic machinery for late phases of replication or transformation. The Epstein-Barr nuclear antigen is felt to function in viral transformation of host cells.[5] *J Fam Pract 1991; 32:202-209.*

Serum immunoglobulin G (IgG) antibody levels to these three antigens, viral capsid antigen, nuclear antigen, and early antigen, are commercially available. The contribution of each of these antibodies to humoral immunologic control of EBV infection is not known in detail, although antibodies toward some of the glycoprotein antigenic determinants of the viral capsid antigen complex have been found to be associated with antibody-dependent cellular cytotoxicity.[5]

Serum levels of immunoglobulin M (IgM) and IgG antibodies toward viral capsid antigen appear acutely with EBV infection. Serum levels of IgM antibody to viral capsid antigen peak at 3 to 4 weeks postinfection, rapidly decline thereafter, and are undetectable at 12 weeks.[6] Serum levels of IgG antibody to viral capsid antigen persist lifelong. Though of somewhat higher titer in acute infection, a high titer of IgG antibody to viral capsid antigen is not considered specific for acute infection.[7]

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Antibody to nuclear antigen develops 1 to 3 months after acute infection and also persists lifelong.[8,9]

Antibody to early antigen appears acutely with EBV infection concomitantly with antibody to viral capsid antigen or shortly after antibody to viral capsid antigen appears.[7] There is disagreement, however, whether antibody to early antigen persists only 8 to 12 weeks,[8,10] to then perhaps reemerge in later life,[9] or whether antibody to early antigen persisting beyond 1 to 3 years is a common occurrence.[11]

Prospective studies in the literature examining long-term serologic trends after acute infectious mononucleosis, especially those that correlate serologic abberations with initial clinical manifestations, are few. Lamy et al[9] followed 26 cases of infectious mononucleosis, finding elevated anti-early antigen up to 9 months after infection. Horwitz et al[11] studied 88 patients with documented acute infectious mononucleosis 10 to 104 months prior, and determined antibodies to EBV-specific antigens at roughly 1, 2, and 3 years postinfection. Elevated antibodies to early antigens (>1:40) were detectable in 41%, 23%, and 19% of patients, respectively, at 1, 2, and 3 years, suggesting that persistent elevation of antibodies to EBV-specific antigens is common in individuals recovering from acute infectious mononucleosis.

continued on page 205

ISSN 0094-3509

continued from page 202

That EBV-specific profiles alone may act as a reliable and useful marker for chronic fatigue syndromes is also discounted by the studies of Holmes et al,[12] Buchwald et al,[13] and Hellenger et al,[14] who found that patients complaining of fatigue tended toward higher titers of EBV antibodies and that there was no threshold titer at which a differentiation between case and noncase patients could be made.

Thus, the nature and significance of modestly elevated antibodies to early antigen remains obscure. Given the tendency for an EBV-specific antibody to reemerge in higher titers in certain immunodeficiency states[15,16] or to rise to very high titers in some syndromes of familial immunodeficiency to EBV infection,[17] the notion that the ultimate degree of antibody titer to early antigen somehow reflects early immunomodulatory regulation of EBV infection seems compelling.

The study reported here examines whether events early in the course of acute infectious mononucleosis, either clinical features or immunologic phenomena, might influence the ultimate serologic response.

Methods

All patients seen within a 1-year period between September 1987 and September 1988 with a diagnosis of infectious mononucleosis from a primary care family practice in Boyne City, Michigan (population 3500), were asked to enlist in the current study; seven patients consented to participate. Each of these seven patients was followed by one physician (the author) prospectively for 1 year after confirmation of a diagnosis of infectious mononucleosis by the rapid slide agglutination or heterophile test. Routine serum specimens for serum aspartate aminotransferase (AST) and a complete blood count were obtained at approximately 1 to 2 weeks after onset of symptoms for each patient.

Patients were asked to return in 1 year for a serum specimen to determine titers of IgG and IgM antibodies to viral capsid antigen and of antibodies to early antigen and Epstein-Barr nuclear antigen. These studies were performed at Mayo Clinic Laboratories.

Clinical progress was also ascertained at the time of follow-up phlebotomies, with particular attention toward historical protractedness or recurrence of symptoms of fatigue, sore throat, myalgias, and swollen glands. Many patients were seen in the interim between initial presentation and 1-year follow-up for a variety of minor acute illnesses.

Results

Results of clinical presentations and serologic studies are displayed in Table 1. Antibodies to nuclear antigen and IgM antibody to viral capsid antigen are not shown, as all patients exhibited antibodies to nuclear antigen in titer of $\geq$1:5, antibodies to viral capsid antigen (IgM) being absent in all patients at 1 year. Complete blood count results were unremarkable.

There are certain features of special note within Table 1. Two patients, C and F, exhibited modestly high antibody titers to early antigen (>1:160). Two patients, B and C, exhibited a protracted course, especially fatigue. No patient developed unremitting or recurrent chronic fatigue during the study period. Three cases (C, F, and G) were considered to be severe in presenting symptoms. Two patients (C and F) complained of severe nausea and acute vomiting. Three patients (C, D, and F) had high elevations in aminotransferase.

Discussion

The clinical utility of modestly elevated antibodies to EBV-specific antigens in the diagnosis of chronic fatigue syndromes has been called into question by recent reports.[7–9] Although higher percentages of patients with chronic fatigue tend toward higher titers of antibody to EBV-specific antigens, the finding is not specific and is found in many normal individuals. Elevated antibodies to early antigen, found in 41% at 1 year, may merely indicate a resolved or unrecognized episode of acute infectious mononucleosis within the preceding 1 to 3 years.

In this study an attempt was made to determine whether the severity, protractedness, or uniqueness of the initial clinical presentation of infectious mononucleosis predicted later atypical serologic profiles.

Although the two patients (C and F) with antibody titers of >1:160 to early antigen experienced severe initial infections, such a titer was not a specific marker for severity of initial infection, as patient G was also judged to have a severe initial infection. The complaint of nausea and vomiting, however, was unique to patients C and F. Although nausea and vomiting might be considered to reflect the degree of clinical hepatitis (patients C and F had generally higher aminotransferase elevations), this finding again was not specific. Patient D also exhibited a similar aminotransferase elevation, with a later early antigen antibody titer of 1:20. Protractedness of fatigue occurred in two patients (B and C); however, this finding did not reliably predict the later disposition toward a higher titer of antibody to early antigen.

Table 1. Clinical Summaries of Mononucleosis Patients

Patient	Age (y)	Sex	Presenting Symptoms	Physical Examination			Treatment	Illness Severity	Duration of Acute Illness	AST μk/L (U/L)	Antibody to Early Antigen	Antibody to Viral Capsid Antigen
				Adenopathy	Splenomegaly	Other						
A	23	F	Sore throat	Moderate cervical	Yes	Exudates on tonsillar remnant, moderate pharyngeal erythema	Erythromycin until diagnosis	Mild	1.5 wk	0.35(21)	1:40	1:160
B	14	M	Swollen glands initially, sore throat	Prominent cervical	No	Hypertrophic mildly exudative tonsils	Symptomatic	Moderate	6 wk, protracted residua of fatigue	0.53(32)	1:20	1:640
C	33	F	Headache, nausea, vomiting, myalgias, weakness	Mild occipital	No	Minor pharyngeal erythema	Symptomatic	Severe	8 wk, protracted residua of fatigue	1.40(84)	1:160	1:640
D	17	M	Headache, solitary swollen gland, rash	Solitary preauricular	No	Pharynx normal, 8-cm area of abdominal macules	Symptomatic	Mild	2 wk	1.58(95)	1:20	1:160
E	15	M	Sore throat, headache, abdominal pain, fatigue	Shotty cervical	No	Minor pharyngeal erythema	Symptomatic	Moderate	2–2.5 wk	0.93(56)	1:10	1:640
F	18	M	Solitary swollen gland, headache, nausea, vomiting, fatigue	Prominent cervical	No	Prominent pharyngeal erythema	Erythromycin until diagnosis	Severe	3–4 wk	3.08(185)	1:160	1:640
G	13	F	Sore throat, headache, fever, swollen glands, otalgia	Moderate cervical	Yes	Left otitis, exudative hypertrophic tonsils	Amoxicillin, hospitalized to rule out splenic rupture, steroids	Severe	2–2.5 wk	0.75(45)	1:10	1:40

AST—serum asparate aminotransferase

continued on page 20

continued from page 206

In this study the significance of a modest and persistent elevation of antibody to EBV early antigen after infectious mononucleosis is unclear. Patients with an initially severe infection, especially when complicated by severe nausea, may be more likely to evolve an atypical serologic profile characterized by a modestly high titer of antibody to the early antigen. Because of the small sample size, it is difficult to claim causal inference from the findings in this study. A similar study on a larger scale would be useful.

This study does support the findings of Buchwald et al[13] in that the clinical utility of EBV antibodies, especially antibody to early antigen, in diagnosing chronic fatigue syndromes is limited. Use of these tests at the primary care level should probably be abandoned. Those individuals in this study exhibiting modestly high titers of antibody to the early antigen were asymptomatic and fully recovered from infectious mononucleosis after 1 year.

IgM antibodies to viral capsid antigen, however, have some clinical utility when diagnosing acute infectious mononucleosis prior to emergence of heterophile antibodies, which become positive in only 60% of young adults by 2 weeks and 90% by 4 weeks,[18] with 10% of the cases never becoming heterophile positive.[7] Similarly, in children younger than 5 years old, the heterophile test is insensitive, and IgM antibodies to viral capsid antigen are usually necessary to demonstrate acute EBV infection.[18,19]

Serologic abnormalities described in some patients with persistent symptoms following acute infectious mononucleosis suggesting a true "chronic mononucleosis" are the absence of antibodies to nuclear antigen or a markedly elevated antibody to early antigen in excess of 1:1026, but these cases are rare and may represent syndromes of familial susceptibility and acquired immunodeficiency to EBV.[17,20,21,22]

In summary, this study does not support the inclusion of EBV antibodies in the evaluation of patients with chronic fatigue presenting for primary care.

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