ORIGINAL RESEARCH

Prospective Study of the Natural History of Infectious Mononucleosis Caused by Epstein-Barr Virus

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Background: **Knowledge regarding the clinical characteristics and natural history of acute infectious mononucleosis is based largely on older, often retrospective, studies without systematic follow-up. Differences in diagnosis, methodology, or treatment between historical and current practice might affect an understanding of this illness.**

Methods: **Using a prospective case series design, we enrolled 150 persons with an acute illness serologically confirmed as Epstein-Barr virus infection. The goal of the study was to assess symptoms, physical examination findings, laboratory tests, and functional status measures during the acute presentation and 1, 2, and 6 months later.**

Results: **Acutely, infectious mononucleosis was characterized by the symptoms of sore throat and fatigue and substantial functional impairment. Objective physical and laboratory examination findings included pharyngitis and cervical lymphadenopathy, a moderate absolute and atypical lymphocytosis, and mildly elevated transaminase levels. The traditional signs of fever and splenomegaly were relatively uncommon. By 1 month, most symptoms and signs and all laboratory tests had returned to normal. Fatigue, cervical lymphadenopathy, pharyngitis, and functional health status improved more slowly.**

Conclusions: **In contemporary practice most of the classical illness features of infectious mononucleosis are observed. Symptoms, signs, and poor functioning might be protracted in some patients. (J Am Board Fam Pract 2001;14:234–42.)**

Infection with Epstein-Barr virus (EBV) has diverse clinical manifestations. In children, EBV infection is often asymptomatic, whereas in adolescents and young adults, it classically appears as infectious mononucleosis with fever, lymphadenopathy, and pharyngitis.[1,2] Although infectious mononucleosis is typically self-limited and treated only with supportive care,[1] its duration and severity can vary considerably.[2–14] Furthermore, most publications describing the natural history of infectious mononucleosis have been conducted in specialized populations; have incorporated nonstandard care; have evaluated only a limited number of biologic, psychologic, and functional measures; or have failed to provide systematic follow-up.[15–33] Finally, many studies were conducted before serologic tests for EBV were developed, bringing into question the actual composition of the study populations and the validity of subsequent findings.[34]

To examine the natural history of infectious mononucleosis, we observed a population-based cohort enrolled in a large health maintenance organization for 6 months after the onset of serologically confirmed infection with EBV. During the initial illness and 1, 2, and 6 months later, we obtained subjective and objective measures of clinical and functional status. The goal of this study was to describe systematically and comprehensively the characteristics and course of infectious mononucleosis in the setting of current medical practice.

Methods

Study Setting

This study was conducted in a large health maintenance organization in the Puget Sound area that

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provides prepaid health care through facilities that include 2 hospitals, 23 outpatient medical clinics, 3 specialty centers, and a progressive care facility. The plan serves a heterogeneous socioeconomic population whose age and sex composition is similar to that of the western region of Washington State.

Participant Selection and Enrollment

Patients who met the following criteria were eligible for the study: (1) were 16 years of age or older; (2) had a positive heterophile antibody test; (3) reported the onset of symptoms within 14 days of having the heterophile test performed; (4) were not suffering from a chronic, disabling medical condition; (5) were not being treated with steroids; and (6) showed serologic evidence of acute EBV infection with a positive immunoglobulin M (IgM) titer to the viral capsid antigen. All laboratory records of the health maintenance organization were reviewed three times each week to search for patients who had a positive heterophile test. These potential participants were asked to join in a study of medical and psychologic factors involved in recovery from viral infections. Final determination of eligibility was based on information from the chart review, patient interview, and EBV serologic studies performed at the initial evaluation (see below). The recruitment and evaluation protocols were approved by the institutional review boards of the University or Washington and the health maintenance organization.

Participants were evaluated in person at the initial, 1-, 2-, and 6-month visits. Initial and follow-up visits included the administration of self-report measures, a physical examination, and laboratory tests. Participants received a psychiatric assessment at the initial evaluation.

Measures of Biological Disease Activity

A physical examination was performed at each visit. Participants were examined by a physician (DB) or a nurse trained in examination procedures and the detection of possible abnormalities for the presence of fever; rashes; pharyngitis; cervical, axillary, and inguinal adenopathy; hepatosplenomegaly; and jaundice. Lymph node size was noted in centimeters, and liver and spleen size was recorded qualitatively. For the purposes of analysis, fever was defined as a temperature of 37.5°C or higher, and lymphadenopathy was considered present when anterior cervical, axillary, or inguinal lymph nodes were 1 cm or larger and posterior cervical lymph nodes were 0.5 cm or larger. Pharyngitis was coded based on the presence or absence of pharyngeal or tonsillar erythema. Only patients with a palpable liver or spleen were deemed to have hepatomegaly or splenomegaly, respectively. A diagnosis of jaundice required the finding of scleral icterus.

A complete blood count, with a differential leukocyte count, serum transaminase levels (aspartate aminotransferase [AST], alanine aminotransferase [ALT]), and bilirubin level were obtained using standard laboratory methods at each evaluation. A manual review of the differential leukocyte count was performed by the laboratory pathologist to ensure that atypical lymphocytes, if present, were detected and accurately quantified. Serologic testing for EBV that included IgG and IgM antibodies to the viral capsid antigen (VCA-IgG, VCA-IgM) was also performed at each study visit. Indirect immunofluorescence (with induced cells) using serial twofold dilutions was used to determine antibodies to VCA-IgG (1:10–1:1280) and VCA-IgM. (1:10–1:40).[35] Titers for VCA-IgG and VCA-IgM were expressed as the reciprocal of the highest dilution to register a positive reaction and were considered positive if greater than 10.

Measures of Symptoms and Functional Status

Measures obtained at each visit were from the Symptom Checklist-90 (SCL-90) and the Medical Outcomes Study Short-Form General Health Survey (SF-36). The SCL-90, typically used to assess the presence and severity of somatic and psychologic complaints,[36] was modified to include those symptoms associated with infectious mononucleosis that were most frequently mentioned in previous publications and standard textbooks: fatigue, sore throat, painful lymph nodes, fever, sleeping too much, headache, sore muscles, nausea, sore joints, cough, and rash. Symptom severity on the SCL-90 was graded as 1 = not at all, 2 = a little bit, 3 = moderately, 4 = quite a bit, or 5 = extremely. Only responses of 3 or higher were used in calculating the frequency of symptoms.

To assess health-related functional status, we used the SF-36.[37] This instrument has the following eight subscales: general health, mental health, vitality, pain, physical and social functioning, and role limitations related to physical and emotional functioning. Each subscale is scored from 0 to 100

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with higher scores indicating better function or less pain. Finally, the National Institute of Mental Health Diagnostic Interview Schedule (DIS)[38] was administered at enrollment to characterize current and lifetime psychiatric disorders. The DIS is a reliable and valid structured psychiatric interview yielding *Diagnostic & Statistical Manual of Mental Disorders: DSM-III-R* diagnoses.[39] The modules on major depression, panic, and generalized anxiety disorders were administered to all participants at the initial evaluation by research assistants trained in its use.

Results

Eligible persons who declined participation (n = 111) or could not be contacted despite multiple attempts (n = 72) were similar in age (22 ± 7 years) and sex (48% female) composition to the study participants. Of the 150 participants who were initially enrolled, 140 successfully completed all three follow-up evaluations. The average age of the participants was 21.3 years (range 16–46 years) and 53% were women. Most were single (93%), white (90%), and students (64%). Participants had a mean of 12.6 (SD ± 2.6) years of education. No participant required hospitalization for infectious mononucleosis during the course of the study. Using the DIS at baseline, the current and lifetime prevalence of depression (5% and 11%, respectively) and anxiety-panic disorder (2% and 3%, respectively) were generally low and comparable to an age-matched population.[40–42]

The mean number of symptoms at each visit was 4.4 initially, 1.3 at 1 month, 1.0 at 2 months, and 0.9 at 6 months. Individual symptom frequencies at each visit are shown in Table 1. At the first visit, sore throat and fatigue were the most common symptoms and were experienced by about three quarters of the participants. At the 1-month follow-up visit, there was substantial diminution in the frequency of all symptoms, although 28% still experienced fatigue. Only a relatively small improvement in symptom frequency was observed at the 2-month visit. Fatigue remained the most prominent residual complaint. Although the frequencies of fatigue and sleeping too much declined modestly between the 2- and 6-month visits, the frequencies of other symptoms were relatively unchanged during this interval. By 6 months, most symptoms associated with infectious mononucleosis were reported by less than 10% of participants.

Table 1. Frequency of Symptoms of Infectious Mononucleosis at Four Time Points for 140 Patients Who Completed All Four Visits

Symptom	Initial No. (%)	1 Month No. (%)	2 Months No. (%)	6 Months No. (%)
Sore throat	104 (74)	22 (16)	16 (11)	16 (11)
Fatigue	108 (77)	39 (28)	29 (21)	18 (13)
Fever	63 (45)	3 (2)	3 (2)	2 (1)
Sleeping too much	64 (45)	26 (18)	20 (14)	12 (9)
Painful nodes	80 (57)	15 (11)	8 (6)	5 (4)
Headache	71 (50)	21 (15)	21 (15)	23 (16)
Rash	21 (15)	5 (4)	4 (3)	5 (4)
Cough	31 (22)	15 (11)	14 (10)	11 (8)
Sore muscles	39 (28)	19 (14)	16 (11)	15 (11)
Sore joints	33 (23)	21 (15)	9 (6)	13 (9)
Nausea	38 (27)	11 (8)	11 (8)	8 (6)

As shown in Table 2, at study entry, most participants had anterior cervical lymphadenopathy, posterior cervical lymphadenopathy, and pharyngeal inflammation, whereas 28% of participants were febrile. Less than 10% had hepatomegaly, splenomegaly, or extracervical (inguinal or axillary) lymphadenopathy. No participant was jaundiced. The cervical lymphadenopathy and pharyngitis resolved gradually during the course of the study but were still evident in approximately one quarter of participants at the 6-month follow-up visit.

Table 2 also displays the laboratory and serology results. An absolute, relative, and atypical lymphocytosis was found initially but had subsided by the 1-month visit. Platelet counts were typically normal during both the acute infection and the convalescent evaluations. As exhibited by elevated transaminase levels, more than one half of the participants had laboratory evidence of hepatitis when initially evaluated, which resolved in nearly all cases in the ensuing month. Elevations in bilirubin either initially or during follow-up period were rare (only 1 person had a value ≥ 2.5 mg/dL). All participants were positive for VCA-IgM (as required for study eligibility) and VCA-IgG during the acute infection. The IgG titer remained positive in all cases and had only a twofold median decrease during the 6 months of follow-up. Participants, however, steadily lost IgM reactivity, with only 13% being IgM positive by 6 months.

Finally, as shown in Table 3, scores on the social functioning, pain, vitality, and physical role limitations subscales of the SF-36 at the initial visit were

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Table 2. Frequency of Physical Examination and Laboratory Findings in Infectious Mononucleosis at Four Time Points for 140 Participants Who Completed All Four Visits.

Finding	Initial	1 Month	2 Month	6 Month
Physical examination abnormalities, No. (%)				
Any cervical adenopathy	109 (77)	77 (55)	55 (39)	41 (29)
Anterior cervical adenopathy	87 (62)	56 (40)	33 (24)	28 (20)
Pharyngitis	103 (73)	66 (47)	29 (21)	35 (25)
Posterior cervical adenopathy	83 (59)	49 (35)	38 (27)	20 (14)
Temperature ≥37.5°C	39 (28)	23 (16)	16 (11)	14 (10)
Splenomegaly	11 (8)	4 (3)	0 (0)	0 (0)
Hepatomegaly	10 (7)	3 (2)	1 (1)	2 (1)
Axillary or inguinal adenopathy	7 (5)	2 (1)	2 (1)	1 (1)
Routine laboratory tests and serologic measures				
Lymphocytes/mm^3, mean (median)	3,248 (3,060)	2,010 (1,984)	2,006 (1,961)	1,961 (1,925)
Lymphocyte %, mean (median)*	49 (49)	35 (36)	34 (34)	33 (32)
Atypical lymphocytes %, mean (median)*†	9 (8)	4 (3)	3 (2)	3 (2)
Platelets/mm^3, mean (median)‡	279 (270)	239 (228)	241 (234)	238 (232)
SGOT >48 U/L, No. (%)	44 (31)	1 (1)	2 (1)	3 (2)
SGPT >42 U/L, No. (%)	86 (61)	7 (5)	4 (3)	4 (3)
Bilirubin >1.2 mg/dL, No. (%)	8 (6)	6 (4)	5 (4)	6 (4)
VCA-IgG titer, median‖	160	80	80	80
VCA-IgM titer, median‖	40	20	0	0

*Percent of total leukocyte count.
†A subset of 120 of the 140 participants had atypical lymphocytes manually quantified.
‡×1000.
‖Expressed as the reciprocal value.

indicative of moderate disability and distress. Functional status steadily improved across all domains and throughout the entire follow-up period.

Discussion

We prospectively and systematically evaluated the clinical aspects of acute EBV infection in a population-based cohort of persons aged 16 years old or older who were cared for as outpatients with supportive, nonspecific measures.[1] The initial diagnosis of infectious mononucleosis was dependent on the finding of both a positive heterophile antibody and VCA-IgM titers in the setting of acute symptoms. During the acute phase, infectious mononu-

Table 3. Functional Status in Infectious Mononucleosis at Four Time Points for 140 Participants Who Completed All Four Visits.

	Mean Score (±SD)*			
SF-36 Subscale	Initial	1 Month	2 Months	6 Months
General health	69 (±18)	71 (±19)	72 (±19)	73 (±19)
Physical functioning	70 (±21)	84 (±16)	90 (±12)	93 (±10)
Social functioning	48 (±25)	72 (±26)	82 (±21)	87 (±20)
Emotional well-being	66 (±18)	71 (±17)	72 (±17)	76 (±17)
Pain	51 (±25)	79 (±21)	85 (±17)	89 (±15)
Vitality	33 (±19)	50 (±21)	60 (±20)	66 (±20)
Physical role limitation	21 (±29)	55 (±43)	77 (±34)	88 (±28)
Emotional role limitation	62 (±41)	70 (±40)	78 (±36)	85 (±30)

*Range from 0 = poorest function to 100 = best function.
SF-30—Medical Outcomes Study Short-Form General Health Survey.

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cleosis was characterized by the symptoms of sore throat, fatigue, and substantial functional impairment; objective physical and laboratory examination findings of pharyngitis; cervical lymphadenopathy; a moderate absolute and atypical lymphocytosis; and mildly elevated transaminase levels. The traditional signs of fever and splenomegaly were relatively uncommon. By 1 month most symptoms and signs and all laboratory tests had returned to normal. Fatigue, cervical lymphadenopathy, pharyngitis, and functional health status improved more slowly than other parameters.

Our methods stand in contrast to those of previous studies that have had one or more methodologic limitations. First, previous publications often focused on unique samples (eg, military recruits) or hospitalized patients who received multiple evaluations during the acute phase, but few or none during convalescence.[15–33] Second, older research was frequently retrospective or had methods that were not clearly stated.[15,20–24,28–31] Third, surrogate hematologic or serologic markers were often relied on to diagnose infectious mononucleosis. Finally, some investigations that described infectious mononucleosis illness features used treatment with antiviral, antibiotic, or steroid medications.[17–19,32] Such differences in definition, study design, or care could have a major impact on the reported characteristics and clinical course of infectious mononucleosis.

Demographics

As in other studies,[2,15,17,28] we found that infectious mononucleosis predominantly affected unmarried, young, white adults with men and women in comparable proportions. Moreover, students comprised nearly two thirds of our participants. Although a student predominance among persons with infectious mononucleosis is typically assumed, this observation, with few exceptions,[28,43,44] has been a product of selection factors imposed by previous study designs.

Acute Illness

In his classic work on infectious mononucleosis among military personnel, Hoagland[2] concluded that the "subjective manifestations of IM are characteristic, but far from specific." He and others noted that the hallmark symptom of infectious mononucleosis was sore throat, occurring in approximately 80% of persons.[2,15,19,29] Several studies reported that about 50% of patients also had malaise, painful lymph nodes, headache, and subjective fever.[2,28,29] Cough, rash, arthralgias, myalgias, nausea, and somnolence were unusual symptoms (ie, $< 10\%$).[2,15,28,29,33] We found that sore throat and fatigue were reported by approximately 75% of patients when initially examined, whereas subjective fever, headache, and lymphadenopathy were noted by about 50%. Surprisingly, so-called uncommon symptoms, such as cough, sore joints, and nausea, were reported by a quarter of participants, suggesting that these symptoms might not possess the negative predictive value for infectious mononucleosis previously ascribed to them.[2]

Our physical examination results were generally consistent with published reports of acute infectious mononucleosis in which cervical lymphadenopathy, pharyngitis, and fever were observed in most of the patients (75%–100%);[2,20,22,27,29,44,45] splenomegaly was variably detected (25%–75%), and rash, hepatomegaly, and jaundice were infrequently reported ($<10\%$). Among our study participants, however, fever and splenomegaly were relatively uncommon (28% and 10%, respectively) perhaps because, in contrast to most other investigations, our study participants were not repeatedly assessed during the acute phase. Previous studies that have conducted only a few initial assessments have revealed a similarly small proportion of febrile patients.[18,27,46] Alternatively, because fever in infectious mononucleosis peaks for 5 to 7 days then gradually returns to normal,[1] the interval between diagnosis and the study evaluation (typically < 1 week) might account in part for the relatively low rate of fever we observed. Thus, the absence of fever or splenomegaly on a single occasion should not deter clinicians from pursuing a diagnosis of infectious mononucleosis. Finally, this study confirms the common occurrence of posterior cervical lymphadenopathy (59%), a finding that has been debated as being characteristic of acute infectious mononucleosis.[2,46]

The differential leukocyte count plays an important, although unsettled, role in the diagnosis of infectious mononucleosis. One early criterion for diagnosis required an absolute lymphocytosis of more than 4,500/mL, a differential leukocyte count with more than 50% lymphocytes, and the presence of a great many atypical lymphocytes.[2] Another considered the diagnosis only when atypical lymphocytes comprised more than 20% of the total

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leukocyte count.[47] During the initial examination, we observed a mean absolute lymphocytosis of 3,248/mL and lymphocyte fraction of 49%, with atypical lymphocytes constituting, on average, 9% of total leukocytes. Explanations for the consistently lower frequency of such abnormal values in our study are the single measurement at each time point and the aforementioned use of strict hematologic selection or entry criteria in some previous investigations.[2,15,22,47] Similar to other studies of infectious mononucleosis, most of our sample had mildly abnormal serum transaminase levels in the absence of overt clinical hepatitis.[21,22,28,45] Finally, none of the participants in this study experienced complications of infectious mononucleosis, such as splenic rupture, encephalitis, Guillain-Barré syndrome, agranulocytosis, or severe thrombocytopenia.[2,3,6,8,9,48,49]

Convalescence

Descriptive, longitudinal studies on illness resolution after acute infectious mononucleosis using standardized assessments are lacking. Although symptoms associated with the acute illness typically resolve in the first month,[15,17,18,22,24,29,31] a prolonged recovery period associated with clinical and laboratory sequelae has been reported in the medical literature.[26,29,31] An early description of "chronic mononucleosis syndrome" cited "weakness, aching legs, low-grade fever, and depression" as typical symptoms.[12] More recently, a prospective study of EBV-induced glandular fever showed that 9% of patients developed a syndrome of chronic fatigue up to 6 months after illness onset.[50] Still others have reported unusual hematologic or immunologic responses among patients with persistent symptoms after infectious mononucleosis.[51–53]

We found that symptoms had generally resolved by the 1-month visit; after 2 months there was little further improvement. Fatigue and sleeping too much abated more slowly than other symptoms, however, and continued to improve between the 2- and 6-month assessment. It is unknown whether the 10% prevalence of most symptoms at 6 months reflects the underlying frequency of these symptoms in the general population[54] or, alternatively, a small and enduring excess of postinfectious mononucleosis symptoms.

In terms of objective findings, we found that pharyngitis and cervical lymphadenopathy were evident in a substantially larger fraction of participants than the corresponding symptoms of sore throat and painful lymph nodes at each point during follow-up. Although more prolonged laboratory abnormalities after infectious mononucleosis have been noted,[28] our results concur with investigations that have reported such findings typically resolve in 2 to 4 weeks.[2,17,19,29] For example, transaminase levels and the differential leukocyte counts had largely returned to normal by the 1-month evaluation and subsequently remained stable. During the acute period, all participants were positive for VCA-IgG, and congruent with other studies,[19,32,34] all remained VCA-IgG positive with only a modest decrease in titer during the subsequent 6 months. VCA-IgM titers declined more rapidly in a pattern consistent with other investigations,[19,32,34] although 34% and 13% were still positive at 2 and 6 months, respectively.

Systematic measurement of functional status has not been previously obtained among patients with infectious mononucleosis. In this study, the SF-36 scores obtained during acute infection were indicative of a moderate but widespread impact on social, physical, and emotional aspects of functioning. Although a relatively greater proportion of recovery came in the first month, functional health status consistently improved in all domains throughout the follow-up period. The limitations reflected by SF-36 scores better characterize the incapacity noted among persons diagnosed with glandular fever caused by EBV infection[55] and anecdotal reports of withdrawal from school or prolonged work absence as consequences of delayed recovery from infectious mononucleosis.[21,26]

This study has several limitations. First, the selection of participants relied on a positive heterophile antibody test that was ordered based on clinical discretion. Thus, factors such as providers' understanding of infectious mononucleosis and time constraints could affect their use of this test, most likely excluding those with unusual or less severe symptoms and signs of infection.[7] Second, the heterophile antibody test can infrequently be either falsely positive or negative. A few patients with a non-EBV mononucleosis-like illness might test positive for heterophile antibody; most, if not all, of these false-positive tests would be appropriately excluded by a negative VCA-IgM.[34] In addition, false-negative responses occur in up to 10% of nonpediatric cases of EBV infectious mononucleosis. Because a positive heterophile antibody test was

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required to be eligible for this study, our findings might not reflect the illness characteristics seen in the few persons with heterophile-negative, acute EBV infection. Third, the interval between the time of diagnosis and the initial study evaluation could have affected measures taken during the acute illness.

Ideally, participants would be enrolled before the onset of infectious mononucleosis and observed longitudinally, but the costs and logistics of such an endeavor are prohibitive. Of importance, however, all our participants had been ill for 14 days or less and were still acutely symptomatic at their initial study visit. Finally, because our study design excluded a few patients with certain characteristics (chronic disabling medical illness, initial steroid treatment) and precluded enrolling persons with infectious mononucleosis who did not seek medical care, our results might not be generalizable to all persons with infectious mononucleosis.

In summary, in our population-based study, infectious mononucleosis usually affected young, single, white, students without a sex predilection. When the patients were first encountered, infectious mononucleosis was characterized by symptoms of sore throat and fatigue, cervical lymphadenopathy and pharyngitis on examination, and substantial social, emotional, and physical functional disability. Typical laboratory findings consisted of a moderate absolute and atypical lymphocytosis, normal platelet count, and mildly elevated transaminase levels. Notably, the traditionally uncommon symptoms of cough, sore joints, nausea, and sore muscles were present in a substantial minority, whereas the classical signs of fever and splenomegaly were relatively infrequent manifestations. During convalescence, most symptoms and all laboratory test results had returned to normal by 1 month. Fatigue, cervical lymphadenopathy, pharyngitis, and functional health status, however, improved more slowly. Further studies are needed to understand the process of recovery in infectious mononucleosis. For now, the results of the current study can be used to educate and reassure patients that the persistence of some symptoms and signs many months after acute infection should not be unexpected.

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