

Clinical and laboratory presentation of EBV positive infectious mononucleosis in young adults

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SUMMARY

Clinical descriptions of Epstein–Barr virus (EBV) positive infectious mononucleosis (IM) are rare and their results are inconsistent. Over a 4-year period, we prospectively studied 590 young adults with clinically suspected IM, all of whom were tested for the presence of EBV IgM antibodies. We investigated the demographical, clinical and laboratory features of subjects with positive EBV IgM serology and heterophile antibodies. Contrary to previous studies, we found a seasonal disease pattern with a peak incidence during summer months, and a lower-than-expected prevalence of lymphadenopathy (88·9%), leucocytosis (46·2%), atypical lymphocytosis (89·2%) and elevated liver enzymes (57·9%). The prevalence of hyperbilirubinemia was relatively high (14·9%). The classic triad of fever, sore throat and lymph-adenopathy had relatively low sensitivity (68·2%) and specificity (41·9%) for EBV infection. Our study provides a complete and updated description of the clinical and laboratory presentation of laboratory confirmed IM, which is important for both clinicians and epidemiologists.

INTRODUCTION

Infectious mononucleosis (IM) was first described in 1889 [1]. In 1920, Sprunt and Evans [2] detailed the complete clinical picture and associated haematological changes, and in 1932, Paul and Bunnell [3] described, as an incidental finding, the heterophile antibody elevation in IM. The infective agent itself,

Epstein–Barr virus (EBV), was discovered in 1964 by electron microscopy of Burkitt's lymphoma tumour cells [4]. In 1968 EBV was identified as the causative agent of IM [5], and in 1973, its aetiological role in the disease was established [6].

IM is common, worldwide in distribution, and occurs most frequently in adolescents and young adults of higher socioeconomic groups in industrialized countries [7]. Its incidence is low in tropical and underdeveloped regions and in persons of low socioeconomic status, in whom EBV infection occurs mainly

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asymptomatically in early childhood [8]. The estimated annual incidence of IM in the United States is 45 cases per 100 000 in the general population [9, 10] and 345 to 671 cases per 100 000 in adolescents aged 15–19 years [10, 11]. In Belgium, seroprevalence is 51% by age 4 and 85% by age 19 [12]. College and military populations are characterized by especially high IM morbidity and subclinical EBV infection [13–18]. No seasonal pattern of EBV infections has been described. Detailed information on the impact of IM on the general population is not available because it is not a notifiable disease in many countries, and the non-specific symptoms can be attributed to a variety of other causes.

There are few published large, prospective studies of young adults with IM, some of which were carried out as long as 30–50 years ago [6, 11, 13, 19–27]. The diagnosis of IM in these studies was not always based on serological evidence of EBV infection, and cases included a mix of various aetiologies. The results of these studies were inconsistent as to the prevalence of various laboratory findings and clinical manifestations other than the classic triad of fever, pharyngitis and lymphadenopathy. The aim of the present study was to describe the clinical features of IM in a large series of young adults with serologically proven EBV infection and to compare them with a group of EBV seronegative patients. The study was performed in the Israel Defence Force (IDF), where IM is a notifiable disease with an annual mean incidence of 130 cases per 100 000 (range 45–250 cases per 100 000 for period between 1974 and 1991) [28]. For the present study, we studied the EBV serology in 590 cases of clinically suspected IM that were documented from 1988 to 1991. These cases were investigated for clinical, epidemiological and laboratory manifestations of the disease.

METHODS

Subjects

Regulations require military physicians to report all cases of clinical IM to the Epidemiology Section of the IDF Medical Corps. Epidemiological, clinical and laboratory data are collected for each patient. From 1988 to 1991, we summoned all patients with a reported diagnosis of clinical IM for physical and laboratory examination at the Epidemiology Section. Blood samples were drawn and tested for antibody response to EBV (EBV IgM) and cytomegalovirus (CMV IgM). Patients with intermediate EBV IgM

results or positive CMV IgM results were excluded from analysis. IM cases were defined by the presence of both heterophile antibodies and EBV IgM positive serology (EBV+/heterophile+). Patients with both negative EBV IgM serology and absence of heterophile antibodies (EBV–/heterophile–) were defined as controls.

Data collection

Data were collected on demographic variables, clinical features of illness and laboratory findings. Demographic variables included gender, type of military service (mandatory *vs.* career), education (<12 *vs.* ≥12 years of schooling) and number of siblings (≤2 *vs.* >2). Clinical features included presence or absence of myalgia, arthralgia, headache, malaise, sore throat, abdominal pain, nausea, vomiting, diarrhoea, rash, fever (>38 °C), jaundice, hepatomegaly, splenomegaly, lymphadenopathy, loss of appetite, hospitalization in a military health care facility or civilian hospital, and the triad of sore throat, fever and lymphadenopathy. Laboratory features included results of haemoglobin concentration (<14 g% *vs.* ≥14 g%), WBC (<5000/ml, 5000–10 000/ml or >10 000/ml), per cent lymphocytes (<50% *vs.* ≥50%), presence of atypical lymphocytes, per cent atypical lymphocytes (<10% *vs.* ≥10%), bilirubin (<1 mg% *vs.* ≥1 mg%), aspartate aminotransferase (AST) (<70 IU *vs.* ≥70 IU) and alanine aminotransferase (ALT) (<60 IU or ≥60 IU). Data were collected from patient medical records, physical examination and medical interviews. Medical records were the source of data for disease presentation, symptoms and signs and for laboratory results including ALT, AST, bilirubin, and haemoglobin values, white blood cell (WBC) and lymphocyte counts, and the presence and percentage of Downey cells (atypical lymphocytes). The medical interview and physical examination were performed by a physician from the Epidemiology Section. The interviews were designed to supplement the data from the patient records, to collect demographic data, and to provide an opportunity to draw a blood sample for serological analysis. These interviews were conducted 1–18 days after disease onset (median 9 days).

Laboratory methods

Routine laboratory tests for all subjects were performed at the central IDF laboratory, such that all results extracted from patient files originated from

a single source. ALT, AST and bilirubin levels were measured by fast spectrophotometric analyser (Monarch™ 2000, Instrumentation Laboratory, Lexington, MA, USA). Haemoglobin level and white blood cell (WBC) and lymphocyte counts were measured with an automated analyser (Cell-Dyn® 1600, Abbott Diagnostics, Abbott Park, IL, USA). The presence and percentage of Downey cells (atypical lymphocytes) were examined in a May-Grunwald-Giemsa stained blood smear. The presence of heterophile antibodies was tested with the commercial Mono-Latex® test (Wampole Laboratories, Cranbury, NJ, USA). EBV IgM antibodies to viral capsid antigen (VCA) and CMV IgM antibodies were detected with commercial ELISA kits (VCA IgM Clin-ELISA Assay, Incstar Corporation, Stillwater, Minnesota, USA and ETI-CYTOK-M, DiaSorin, Saluggia, VC, Italy, respectively).

Data analysis

To investigate seasonality, we calculated the monthly incidence of EBV +/heterophile+ cases by dividing the number of new cases each month by the total number of soldiers in service each month. This was done for the whole study period. We also compared the overall incidence during the summer months of June–August to that of rest of the year. We compared the distributions of each of the demographical, clinical and laboratory variables among cases and controls.

Statistical analysis

Incidence of EBV cases for summer and winter periods were compared using the Z-test for person-time denominators and a two-tailed exact mid-*P* value. Distribution of categorical variables between cases and controls were compared using the χ^2 test. Continuous variables were compared using Student's *t*-test. Statistical analyses were performed using PEPI Computer Software for Epidemiological Analysis (version 2.07, copyright JH Abrahamson, PM Gahlinger, 1993–97) and SPSS™ software (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 938 patients aged 18–23 were reported as having clinical IM over the 4-year study period. Of these, 858 (91.5%) agreed to participate and provided

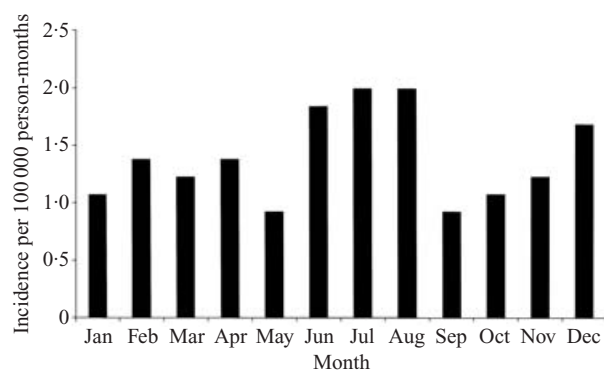


Fig. 1. Monthly incidence of EBV-IgM and heterophile antibody positive infectious mononucleosis in the Israel Defence Force, 1988–1991.

their written informed consent. Blood samples were available for 590 (62.9%). A total of 17 patients were excluded from analysis, 9 (1.5%) due to intermediate results for EBV IgM and 8 (1.4%) due to positive results for CMV IgM. A total of 330 patients (55.9%) were EBV IgM positive and 243 (41.2%) were EBV IgM negative. Mono-latex® test was available in 279 patients. A total of 114 patients were EBV +/heterophile+ and 65 patients were EBV –/heterophile –.

Figure 1 presents the monthly incidence of EBV +/heterophile+ cases during the 4-year study period. A marked seasonality was noted, with a peak incidence during the summer months (June–August). The overall incidence of disease in June–August was 1.93 per 100 000 person-months, compared to 1.21 per 100 000 person-months during the rest of the year ($P < 0.022$).

The distribution of demographical variables among EBV +/heterophile+ cases as compared to EBV –/heterophile – cases is presented in Table 1. Level of education, number of siblings and proportion of career personnel did not differ significantly between the groups. The percentage of males was higher in the EBV –/heterophile – groups as compared to EBV +/heterophile+ group (57.0% vs. 73.8%, $P = 0.011$), whereas the overall proportion of males in the IDF during the study period was approximately 72%. The proportion of males in the total study cohort was 68.4%.

The comparison of clinical characteristics of the two groups is shown in Table 2. The prevalence of splenomegaly and lymphadenopathy was higher among EBV +/heterophile+ patients (53.3% vs. 28.6%, $P = 0.005$ and 88.9% vs. 75.0%, $P = 0.034$, respectively). The classic triad of sore throat, fever, and

Table 1. *Distribution of demographic variables among EBV+/heterophile+ and EBV-/heterophile- groups*

Variable	Case definition ... EBV+/heterophile+ (n=114)		EBV-/heterophile- (n=65)		P-value*
	Available	n (%)	Available	n (%)	
% males†	114	65 (57.0)	65	48 (73.8)	0.011
Age >21 years	109	15 (13.8)	65	12 (18.5)	0.359
Years of schooling <12	109	6 (5.5)	64	7 (10.9)	0.180
Number of siblings >2	109	34 (31.2)	63	23 (36.5)	0.476

* P-values are for comparison between EBV+/heterophile+ and EBV-/heterophile-.

† Proportion of males in the IDF is 72%.

Table 2. *Clinical manifestations among EBV+/heterophile+ and EBV-/heterophile- groups*

Variable	Case definition ... EBV+/heterophile+		EBV-/heterophile-		P-value*
	Available	n (%)	Available	n (%)	
Loss of appetite	111	82 (73.9)	63	48 (76.2)	0.735
Myalgia/arthralgia	111	36 (32.4)	63	26 (41.3)	0.242
Headache	112	93 (83.0)	63	46 (73.0)	0.115
Malaise	112	96 (85.7)	63	58 (92.1)	0.215
Sore throat	114	95 (83.3)	63	46 (73.0)	0.103
Abdominal pain	112	42 (37.5)	63	28 (44.4)	0.368
Nausea/vomiting	111	46 (41.4)	63	29 (46.0)	0.557
Diarrhoea	112	17 (15.2)	63	13 (20.6)	0.358
Rash	114	19 (16.7)	63	9 (14.3)	0.678
Temperature >38.0 °C†	105	83 (79.0)	56	49 (87.5)	0.184
Jaundice	114	19 (16.7)	63	13 (20.6)	0.511
Hepatomegaly	90	33 (36.7)	48	13 (27.1)	0.255
Splenomegaly	90	48 (53.3)	49	14 (28.6)	0.005
Lymphadenopathy	90	80 (88.9)	48	36 (75.0)	0.034
Triad‡	85	58 (68.2)	43	25 (58.1)	0.259
Required hospitalization	114	86 (75.4)	65	54 (83.1)	0.234

* P-values are for comparison between EBV+/heterophile+ and EBV-/heterophile-.

† Refers to maximal temperature during illness.

‡ Sore throat, fever >38 °C, lymphadenopathy.

lymphadenopathy was found in 68.2% of EBV+/heterophile+ patients and 58.1% of EBV-/heterophile- patients. This difference was not statistically significant ($P=0.259$). The need for hospitalization in a military health-care facility or civilian hospital was high in both groups, with no significant difference between them.

Categorized laboratory findings are presented in Table 3. WBC >10 000/ml, lymphocytes >50%, atypical lymphocytes >10%, and elevated liver enzymes were more common among patients in the EBV+/heterophile+ group. Among EBV-/heterophile- patients, anaemia (haemoglobin <14 g%) and WBC <5000/ml were more prevalent. These differences were statistically significant. Hyperbilirubinemia

was also more prevalent among EBV-/heterophile- patients but the difference was not statistically significant.

Comparison of continuous clinical and laboratory variables is presented in Table 4. EBV+/heterophile+ patients had a higher WBC count, higher levels of lymphocytes and atypical lymphocytes, and lower levels of haemoglobin.

DISCUSSION

We studied the clinical and laboratory presentation of 330 patients with EBV IgM-positive IM aged 18–23 years. This is the largest such study to date in this age

Table 3. Laboratory findings among EBV +/heterophile + and EBV –/heterophile – groups

Variable	Case definition ... EBV +/heterophile +		EBV –/heterophile –		P-value*
	Available	n (%)	Available	n (%)	
Haemoglobin < 14 g %	93	62 (66.7)	58	25 (43.1)	0.004
WBC < 5000/ml	93	6 (6.5)	57	12 (21.1)	0.008
WBC > 10 000/ml	93	43 (46.2)	57	13 (22.8)	0.004
% lymphocytes > 50	55	21 (38.2)	33	6 (18.2)	0.049
Atypical lymphocytes	65	58 (89.2)	33	25 (75.8)	0.080
% atypical lymphocytes > 10	32	21 (65.6)	14	4 (28.6)	0.020
Bilirubin > 1 mg %	67	10 (14.9)	41	8 (19.5)	0.535
AST > 70 IU	95	33 (34.7)	54	17 (31.5)	0.686
ALT > 60 IU	94	50 (53.2)	53	18 (34)	0.025
Elevated liver enzymes	95	55 (57.9)	54	22 (40.7)	0.044

* P-values are for comparison between EBV +/heterophile + and EBV –/heterophile –.

Table 4. Comparison of continuous clinical and laboratory variables among EBV +/heterophile + and EBV –/heterophile – groups

Variable	Case definition ... EBV +/heterophile +		EBV –/heterophile –		P-value
	Mean	95 % CI	Mean	95 % CI	
Temperature (°C)*	38.7	38.6–38.9	39.0	38.8–39.2	0.096
Haemoglobin (mg %)	13.3	12.9–13.7	14.2	13.9–14.6	0.001
WBC (10 000/ml)	10.6	9.5–11.7	7.9	6.9–8.9	0.001
% lymphocytes	45.9	41.2–50.6	35.5	29.8–41.2	0.006
% atypical lymphocytes	20.3	15.8–24.7	7.3	3.2–11.5	<0.001
Bilirubin (mg %)	0.8	0.6–1.1	1.0	0.6–1.4	0.493
AST	76.2	59.6–92.7	61.0	43.1–102.4	0.980
ALT	94.1	69.2–119.0	94.8	33.3–156.3	0.279

* Refers to maximal temperature during illness.

group. Although EBV is believed to cause 90 % of all cases of IM, we demonstrated EBV IgM antibodies in only 55.9 % of IM cases (330/590). Of the 279 patients with both EBV IgM and heterophile antibody results, 114 (40.9 %) were positive for both tests. White et al. [29] noted a similarly low rate of seropositivity, a finding which may be attributable to the prospective design of both studies. We also demonstrated a peak incidence during the summer months, which has not been described previously. A possible explanation could be that in the summer there is more socializing of young people which might explain increased EBV transmission. Regarding the clinical and laboratory manifestations, our results differed somewhat from earlier studies, particularly those of Hoagland [21] and Sumaya and Ench [27]. Hoagland [21] prospectively studied 200 young adults with heterophile-positive IM in an army hospital, and Symaya and Ench [27] prospectively evaluated 113 children aged

16 and younger with a serological diagnosis of EBV IM. Specifically, differences were noted in rates of lymphadenopathy (88.9 % in our series vs. 90–100 % in earlier reports) [11, 13, 19–24, 27, 30]; splenomegaly (53.3 % vs. 41–100 %) [31]; jaundice (16.7 % vs. 10 % or less) [11, 13, 19–24, 30]; leucocytosis (46.2 % vs. 90 %) [6, 11, 26, 27, 30, 32]; atypical lymphocytes (89.2 % vs. 20–100 %) [6, 11, 13, 19, 20, 23, 24, 26, 30, 32]; and elevated liver enzymes (57.9 % vs. 50–90 %) [22, 26, 30, 32]. We also noted mild anaemia, which has not been previously described in IM. The classic triad of fever, sore throat and lymphadenopathy [25, 27] was present in 68.2 % of EBV +/heterophile + patients. However, it was a feature of the clinical presentation in 58.1 % of EBV –/heterophile – patients. This represents a sensitivity of 68.2 %, a specificity of 41.9 % and a positive predictive value of 69.9 % for this clinical triad as a diagnostic sign of EBV seropositive IM.

There are several possible explanations for the dissimilarities in the clinical and laboratory presentation of IM in our study and others. First, we limited inclusion solely to serologically confirmed cases, whereas some of the earlier studies were conducted before the relationship between EBV and IM was established. Second, our samples consisted of young adults in whom the disease is most common, whereas most other studies included children. Finally, our study is based on a database of the IDF where IM is a reportable disease, which may have led to a unique mix of patients with a different spectrum of clinical manifestations.

Our study had several limitations. We did not have a control group of healthy patients, although we did compare our patients to a control group of EBV-IgM-negative subjects who most likely had other diseases, such as toxoplasmosis, streptococcal pharyngitis, influenza or other viral disease such as CMV infection. Additionally, the interviews, physical examination and blood sampling took place at different times after disease onset. However, most data concerning disease symptoms, signs and routine laboratory data were extracted from patients' files, and therefore represent the early manifestations of disease.

Infectious mononucleosis is common among young adults, especially in selected populations such as college students and army personnel. In a study performed at the University of Wisconsin, IM accounted for 5% of all hospitalizations, with an annual incidence of 450 admission/100 000 students [13]. Other American universities have reported similar rates with approximately 12% of susceptible college students undergoing EBV seroconversion yearly [14, 15]. Many of these infections are subclinical [14, 16]. Although primary EBV infection may be clinically apparent in only about 10% of military cases, IM was the fourth most common cause of illness-associated lost work days among army personnel [17, 18]. In our study, 85% of suspected IM cases were hospitalized.

This report has important clinical implications for the differential diagnosis of infectious mononucleosis-like symptoms and signs. The variable nature of the clinical presentation of IM and the occasional presence of unusual features may mislead clinicians, resulting in delayed diagnosis or misdiagnosis. Our study provides an updated and complete description of the clinical and laboratory presentation of the disease. This study is also of epidemiological importance, as these data can assist in the differentiation of IM from other diseases with hepatic involvement,

especially hepatitis A and B, which require immediate epidemiological intervention.

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