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Original article

Epstein Barr Virus hepatitis ☆

Diamantis P. Kofteridis *, Mairi Koulentaki, Antonios Valachis, Maria Christofaki, Elias Mazokopakis, George Papazoglou, George Samonis

Department of Internal Medicine-Infectious Disease Unit, University Hospital of Heraklion, Crete, Greece

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ABSTRACT

Objectives: Epstein-Barr Virus (EBV) infection has the potential to establish life-long, benign infections in their hosts. Although biochemical evidence of hepatocellular damage is common, jaundice is uncommon and complete recovery is the rule. The present study describes clinical characteristics and changes of liver function tests during the course of infectious mononucleosis.

Patients and methods: All immunocompetent patients with hepatic dysfunction associated with acute EBV infection, cared for at the University Hospital of Heraklion, over a 6-year period, were identified and retrospectively studied.

Results: The study included 41 patients with a median age of 18.5 (15–51) years. Aspartate-aminotrasferase (AST) and alanine-aminotrasferase (ALT) were increased in an average maximum of 5-fold. Both transaminase levels started to rise 2 days after the clinical onset of the disease, and returned to normal after a period of 20 days. Alkaline-phosphatase (ALP), γ-glutamyltransferase (γ-GT) and bilirubin levels also increased above the normal values during the course of the disease and returned to normal after a period of 20, 30 and 22 days respectively. The changes of mean AST and ALT levels over time were statistically significant, while those of mean ALP, γ-GT and bilirubin levels over time were not. Anicteric cholestatic liver disease was observed in 24 patients (59%), while icteric only in 2 (6%).

Conclusion: Liver involvement in acute EBV infection represents mild and self-limited hepatitis with predominantly cholestatic features.

1. Introduction

Epstein-Barr virus (EBV), a member of the family of herpes viruses, infects up to 90% of the general population by the age of 20 years [1,2].

The most common clinical presentation of EBV infection includes the triad of fever, generalized lymphadenopathy and pharyngitis, forming the picture of infectious mononucleosis [1,2].

Although hepatic involvement in patients with infectious mononucleosis is common, with 80 to 90% of cases demonstrating a moderate and transitory raise of liver enzymes, clinical manifestations of hepatitis are infrequent [2–6]. The levels of serum aminotransferases are referred as mildly elevated (two or three times the upper normal limit), consistent with parenchymal injury [3–7]. Cholestatic liver disease due to EBV infection, characterized predominantly by elevation of serum alkaline phosphatase and bilirubin, is uncommon [2–4,7,8]. In addition, chronic hepatitis linked to EBV infection has rarely been reported and in general was not well documented [9,10]. Nevertheless, half of the fatal infectious mononucleosis cases have been reported as a result of liver failure [11–13].

Limited and inconclusive information exists in the literature about hepatic manifestations of EBV infection. Hence, the aim of the present study was to describe the clinical characteristics and the changes in the levels of liver enzymes during the course of acute EBV infection.

2. Patients and methods

2.1. Patients

All documented cases of EBV infection with hepatic dysfunction cared for at the outpatient clinic or at the Department of Internal Medicine of the University Hospital of Heraklion, Crete, Greece, between February 2000 and June 2006 were retrospectively analysed.

A positive viral capsid antigen (VCA) immunoglobulin M (IgM) antibody test result, with or without detectable VCA-IgG antibodies against EBV, and negative tests for other viruses that could cause similar symptomatology in all patients with febrile illness, accompanied by infectious mononucleosis symptoms, were the inclusion criteria.

ELISA test for detection of IgM antibody to hepatitis A virus (anti-HAV), hepatitis B surface antigen (HBsAg), IgM and IgG hepatitis B core antibody (HBcIgM and HBcIgG), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), antibodies to hepatitis C (HCV), as

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* Corresponding author. Department of Internal Medicine, Infectious Disease Unit, University Hospital of Heraklion, 71 110, Heraklion, Crete, Greece. Tel.: +30 2810 392359; fax: +30 2810 392847.
E-mail address: kofterid@med.uoc.gr (D.P. Kofteridis).

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well as IgM and IgG antibodies for cytomegavirus were performed in all patients in order to rule out other potential viral causes of hepatic disease.

The onset of illness was defined as the first day of sore throat, fever, lymph-node swelling, and/or gastro-intestinal symptoms. Demographic characteristics as well as clinical findings on physical examination were recorded on the first visit. Blood pressure, respiratory rate, and body temperature were recorded every day during hospitalization or on every outpatient clinic visit. Blood for laboratory examination was taken at least twice weekly, if the patient was hospitalized and once weekly if followed at the outpatient clinic or after discharge until tests were repeatedly normal. Laboratory investigation included: full blood count with differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-Glutamyl transpeptidase (γ-GT) and total bilirubin.

Clinical findings, laboratory results, chest X-rays and abdominal ultrasounds, as well as treatment and outcome of every single patient were recorded and analyzed.

2.2. Statistical analysis

Data were analysed using the SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are presented as mean (Standard Deviation; SD), unless otherwise indicated. The Kolmogorov–Smirnov test was used to verify the normality of distribution of continuous variables. Since none of the examined laboratory values were normally distributed, the differences over time were compared through the non-parametric Kruskal–Wallis test for multiple comparisons. A two-tailed P value of <0.05 was considered to be statistically significant.

3. Results

3.1. Clinical characteristics

The study was performed in the 650-bed University Hospital of Heraklion, Crete, Greece. The records of 47 patients hospitalised or cared for at the outpatient clinic with documented EBV infection between February 2000 and June 2006 were retrospectively reviewed. Among them 41 patients (87%) were diagnosed as suffering from EBV infection with hepatic dysfunction. Their median age was 18.5 (18–51) years. Twenty (49%) were men.

Twenty four patients (58.5%) had been cared for at outpatient clinic. Fever was the most common clinical feature upon admission, noted in 38 patients (93%), with a median duration of 4 days (3–14). Fifteen patients (37%) suffered from sweats, 13 (32%) from headaches, and 12 (30%) from rigors. Gastrointestinal symptoms, such as vomiting, were noted in 5 (12%). Six patients (15%) had two or more systemic inflammatory response syndrome criteria. Table 1 shows signs and symptoms on admission.

Palpable lymph nodes were detected in 33 patients (80.5%) with cervical being the most common [in 27 out of 33 (82%)]. Twenty five patients (66%) had splenomegaly and 11 (27%) hepatomegaly. The median enlargement of the spleen, as identified by ultrasonography, was 15 cm (13–19). The size of the spleen returned to normal in a median time of 26 (22–56) days after the onset of the disease.

3.2. Laboratory findings

Twenty seven patients (66%) had leukocytosis with lymphocytosis (median lymphocyte count: 8760, range: 4600–20,000), while 10 of the 14 (71%) who had normal leukocyte count had also a relative lymphocytosis (median: 5400, range: 4100–8200). ESR was elevated [median: 44 mm/h (22–88)] in 35 out of the 41 patients (85.4%). Table 2 shows laboratory values on admission.

Table 1
Frequency of associated signs and symptoms in patients[a] with EBV infection.

Signs and symptoms	No of patients (%)
Fever	38 (93)
Sweats	15 (37)
Headache	13 (32)
Rigor	12 (30)
Rash	5 (12)
Vomiting	5 (12)
Myalgia	5 (12)
Palpable lymph nodes	33 (80.5)
Cervical	27 (82)
Cervical-axillary	4 (12)
Inguinal	1 (3)
Splenomegaly	27 (66)
Hepatomegaly	11 (27)

[a] Total number of patients: 41.

An average of 2.9 liver function tests were performed for each patient during hospitalisation, outpatient clinic examination and subsequent follow-up. Nineteen patients (46%) had 3 or more liver function tests done (maximum 6).

The changes over time of mean AST and ALT levels were statistically significant ($P=0.004$ and 0.001, respectively). AST started to rise 2 days after the onset of illness showing 2 peaks [on day 8 (mean 197 +/− 124 U/l) and on day 11 (190 +/− 130 U/l)], while it returned to normal 20 days later. ALT followed the same pattern but showed 3 peaks [on day 8 (mean 274 +/− 119 U/l), on day 11 (291 +/− 182 U/l) and on day 13 (274 +/− 191 U/l)]. No correlation between ALT and AST changes and those of lymphocytes was found. Mean γ-GT levels were above the upper normal limits during the course of the disease until 20 days after diagnosis. Mean ALP levels remained also above normal limits even 30 days after the onset of illness. A mild elevation in bilirubin levels, gradually rising during the 10 days following the disease's onset, was observed only in 20% of the patients. Bilirubin started returning to normal 12 days later. In all of them the increased bilirubin was mainly conjugated (Table 3). No statistically significant changes over time were noted in mean serum levels of ALP, γ-GT and bilirubin. Fig. 1 presents values of liver enzymes during the course of illness.

Transient cholestatic liver disease was the predominant type of hepatic involvement in 24 patients (59%). Only 2 (6%) became icteric.

Mean prothrombin time (PT) and albumin levels remained normal (1.15 ± 0.10 and 4.0 ± 0.4 respectively).

Table 2
Laboratory values on admission of the 41 patients with EBV infection.

Laboratory value	Mean (+/−SD)
White blood cells count, cells/μl	12632 (5011)
Neutrophils (cells/μl)	3819 (2335)
Lymphocytes (cells/μl)	7287 (2021)
[a]ESR (mm/h)	41.5 (26.3)
Total protein (g/dl)	7.54 (0.64)
Serum albumin (g/dl)	4.00 (0.40)
Serum creatinine (mg/dl)	0.80 (0.18)
[b]AST (U/l)	114 (73)
[c]ALT (U/l)	129 (104)
[d]γ-GT (U/l)	89 (50)
[e]ALP (U/l)	197 (145)
Total bilirubin (mg/dl)	0.98 (0.47)
[f]LDH (U/l)	417 (185)

[a] ESR: erythrocyte sedimentation rate.
[b] AST: aspartate-aminotrasferase.
[c] ALT: alanine-aminotrasferase.
[d] ALP: alkaline-phosphatase.
[e] γ-GT: γ-glutamyltransferase.
[f] LDH: lactate dehydrogenase.