Clinical and Biological Aspects of Liver Damage (Hepatitis) in Children with Infectious Mononucleosis

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Citation

Abstract
Infectious Mononucleosis due to Epstein Barr virus infection sometimes causes acute hepatitis, which is usually self limiting with mildly elevated aminotransferases, but rarely with jaundice. The demographics, clinical features and outcome of EBV hepatitis in children are incompletely understood. So we conducted a study, which is a retrospective one and includes all the cases with Infectious Mononucleosis hospitalized in Pediatric Infectious Disease Ward in the University Hospital Center “Mother Teresa” Tirana Albania during 2010-2014, to identify demographic, presenting features, clinical characteristics and changes of liver function tests during the course of the disease. From 107 children hospitalized with IM 53(50%) showed laboratory evidence of hepatocellular involvement (hepatitis). 30(57%) were males, 5(9%) belonged to the age group (0-2y), 19(36%) to the age group (2-5y) and 29(55%) to the age group >5y. 38(72%) presented with classic features of Infectious Mononucleosis (fever, pharyngitis and lymphadenopathy), 8(7%) showed clinical evidence of hepatitis as the presenting feature, 50(94%) presented with fever, 43(82%) showed lymphadenopathy, 30(57%) showed splenomegaly, 18(34%) showed hepatomegaly, 3(6%) showed cholestasis. 8(15%) experienced rash from AB use. Leucocytes >10000 were present in 45(85%), Lymphocytes >60% were present in 36(68%). The degree of liver involvement associated with EBV infection varies, in general mild self-limited hepatocellular liver disease is common and is manifested by a transient elevation of alanine-aminotransferase levels. Cholestatic liver disease is less frequent and is also self-limited. Clinical evidence of hepatitis is rarely the presenting feature of Infectious Mononucleosis.

1. Introduction

EBV belongs to the family of human herpesviruses and is widely spread in nature. Epstein was the first to describe in 1964 the first human tumor virus when he found virus particles in a Burkitt lymphoma cell line [7]. Henle reported the relationship between acute infectious mononucleosis and Epstein-Barr virus in 1968 [14]. A large prospective study of students of Yale University firmly established Epstein-Barr virus as the etiologic agent of infectious mononucleosis [27]. Like other herpesviruses EBV virions have a double-stranded, linear DNA genome surrounded by a protein capsid. Initial infection occur in oral compartment, the host cells of EBV lymphocytes and epithelial cells [20]. EBV attaches to B cells via binding of the viral gp350 protein to CD21 on B cells [28], via endocytosis the nucleocapsid is released into the cytoplasm then the nucleocapside dissolves and the genome is transported to the nucleus, where it replicates by DNA
polymerase and thus the lytic phase of the virus life circle is accomplished [30]. Infected memory B cells are released into the peripheral circulation, those number decreases over time after the onset of symptoms of primary infection [12], but these cells are never eliminated entirely. It is thought that one in a million B cells carry EBV genome in an individual. After recovery from acute infection [3]. A potent innate and adaptive immune response occur during primary EBV infection. The innate immune system is an important first line defense against viral infections then adaptive both humoral and cellular immune responses are generated. The humoral or antibody response is important in diagnosing infectious mononucleosis and the cellular response (particularly CD8 T-cell response) is important for controlling viral replication but may also contribute to the severe symptoms of infectious mononucleosis.

Most people encountered the virus during infancy but before the age of 10 primary infection is usually asymptomatic or produce an acute illness that is rarely recognized as being caused due to EBV [29]. In adolescents and young adults primary EBV infection frequently presents as infectious mononucleosis. The main way of transmission is through saliva exchange via kissing shared items such as toys, utensils, bottles. Beside oral transmission, EBV has been acquired from blood [11], indicating that virus present in peripheral circulation, in memory B cells, or may become infectious [12]. EBV can also be acquired from transplanted hematopoietic cells [1, 29], or solid organs [13], and such infections can be life-threatening especially if recipients contact the virus for the first time after transplantation.

Primary EBV infection occurs at a younger age among people of lower socioeconomic status [9, 22], which has been attributed to crowded living conditions [29]. Healthy people continue to shed the virus for months after acute infection and are capable of transmitting it [2, 8]. Infectious mononucleosis most often begins insidiously with malaise, followed several days later by fever, sore throat, swollen posterior cervical lymph nodes and fatigue, some patients experience an abrupt influenza-like onset with fever, chills, body aches and sore throat [6, 10, 15, 23, 24]. The median duration of infectious mononucleosis is 16 days, so much longer than the duration of most acute viral illnesses, recovery is gradual and it may take months for the patient to feel entirely well [24]. Fatigue compromise life quality and is the last symptom to resolve. Infectious mononucleosis is associated with many complications, which may be due to tissue-invasive viral disease or immune mediated damage. The more frequent complications are airway obstruction, meningocencephalitis, hemolytic anemia, thrombocytopenia, rash, hemophagocytic syndrome, psychological disorders and splenic rupture [5, 16, 18, 25, 31].

2. Aim

Gastroenterological manifestations of EBV infection range from mild hepatitis to lymphoproliferative disorders, hepato-splenomegaly and rarely acute liver failure. EBV hepatitis is generally regarded as a complication of IM, but recently EBV hepatitis and jaundice have been described in patients without clinical features of IM and cholestatic jaundice due to EBV has also been documented. The aim of this study is to identify the demographic, presenting features and to describe clinical characteristics and changes of liver function tests during the course of Infectious Mononucleosis.

3. Method and Material

Retrospective review of children with Infectious Mononucleosis hospitalized in Pediatric Infectious Disease Ward in University Hospital Center of Tirana “Mother Teresa” Albania during 2010-2014.

Medical records were reviewed for patients: demographic information, presenting features, clinical and laboratory parameters, clinical course and outcome. The diagnosis of primary EBV hepatitis was made based on the elevation of serum alanine aminotransferase (ALT) level over 45IU/L and early positive immunoglobulin M antibody to EBV viral capsid antigen anti EBV VCA IgM. All patients undergo abdominal ultrasound examination for evidence of parenchymal liver disease or biliary obstruction. Collected data were analyzed using SPSS ver. 19.0.

4. Results

Demographics and clinical features:

Elevation of liver enzymes occurred in 53(50%) of the 107 patients who were diagnosed with acute EBV infection. 53 patients aged 16 months to 13 years were included in the study. 38(72%) of patients are less than 7 years old. 30(57%) are males.

![Age distribution chart](image)

The most common clinical feature is fever in 50(94%) of patients, high fever over 40°C was present in 11(20%), mean duration of fever was 8,5 days (range 1-20 days). Cervical lymphadenopathy is the second most common clinical feature noted in 43(81%) of patients, 15(28%) presented generalized lymphadenopathy. Pharyngitis was present in 38(72%) patients, tonsillar exudates was present in 27(51%). The classic features of IM (fever, pharyngitis, lymphadenopathy) were present in 38(72%) of patients. Hepatomegaly and splenomegaly were present in 21(40%) and 30(57%) of
patients respectively. Gastrointestinal symptoms included abdominal pain (7(13%), vomiting (3(6%), jaundice (3(6%). Skin rashes were present in (7(13)) patients.

Gall bladder wall thickening was identified in (3(6)) patients who were examined by abdominal ultrasonography. 8 (15%) patients presented with clinical evidence of hepatitis as the presenting feature of the infection.

**Tab. Clinical features of 53 patients with EBV hepatitis.**

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>50(94%)</td>
</tr>
<tr>
<td>High fever &gt; 40°C</td>
<td>11(20%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7(13%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3(6%)</td>
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<tr>
<td>Rash</td>
<td>7(13%)</td>
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<tr>
<td>Icteric sclera</td>
<td>3(6%)</td>
</tr>
<tr>
<td>Cervical lymphadenopathy</td>
<td>43(81%)</td>
</tr>
<tr>
<td>Tonsillar exudate</td>
<td>27(51%)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>21(40%)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>30(57%)</td>
</tr>
<tr>
<td>Eyelid swelling</td>
<td>4(8%)</td>
</tr>
</tbody>
</table>

**Laboratory findings**

Leukocytes >10000 were found in 45(85%) patients (range 8300-26900). Lymphocytes over 60% were found in 34(64%) patients. The mean value of ALT was 205 UI\L (range 96000-195000). Serum levels of ALT elevated 5 times over the upper limit was found in 20(38%) patients. Elevated serum direct bilirubin levels was found in 4(8%) patients. Elevated serum aminotransferases levels. Elevated liver enzymes, especially alanin-aminotransferase, strengthen the clinical impression of hepatic manifestations of EBV infection usually occurred to those less than 7 years of age. Primary EBV hepatitis with elevation of ALT occurred frequently but jaundice was rare. Classic features of IM were present in the majority of the patients.

In the literature hepatic involvement in primary EBV infection occurred in 80-90% of patients, and is mostly mild and self-limited. Serum aminotransferases levels are usually elevated less than 5 times the upper normal limit, the elevation occurred the first week of onset of EBV infection, reached the peak level the second week and normalized after the third week.

In our study liver enzymes increased in 53(50%) of all patients. Serum ALT levels were elevated by more than 5 times the upper normal level in approximately one third of the patients. Serum ALT levels peaked within the second week and returned to normal after the third week of the onset of EBV infection such as fever, sore throat and lymphadenitis. Cholestatic jaundice with elevation of direct bilirubin levels were reported in a small number of cases during acute EBV infection.

Hepatomegaly and splenomegaly were present in 40% and 57% of cases respectively higher than in literature probably because enrollment was restricted in patients with elevation of aminotransferases in the study. Gallbladder wall thickening (GBWT) with or without GB distention may occur during the IM [32, 17] and could be a sign of severity of IM. However GBWT is not a specific sign that can be seen in many conditions, including acute cholecystitis and acute hepatitis. In our study there were no significant difference in hospitalization between patients with or without GBWT. Most patients with EBV hepatitis recovered spontaneously with supportive care. All of our patients recovered completely without any chronic or serious illness.

The pathogenesis of EBV hepatitis is still poorly understood. In contrast to hepatotropic viruses, no direct EBV cytopathic effect has been proven on hepatocytes [16]. EBV receptors CD21 have been found in the liver but not in hepatocytes. Experimental reports have shown that EBV-infected CD8+T cells accumulate in the liver and produce some soluble products, especially interferon-γ, tumor necrosis factor α, which can destroy hepatocytes [21,19] these inflammation markers has been found to be in high levels in the plasma of these patients. It appears that severe liver injury is primarily caused by the intense immune response to viral antigens expressed by infected hepatocytes [4, 26]. Histology typically demonstrates mononuclear infiltrate within portal tracts and along sinusoids in a distinct single file pattern, occasional plasma cells and neutrophil polymorphs may be present, Kupffer cells are prominent and occasional granulomatous foci may be present. Hepatocellular necrosis is uncommon but occurs in severe cases, T lymphocytes usually predominate in the biopsy of severe hepatitis.

6. Conclusion

EBV is known to be one of the causes of viral hepatitis. The degree of liver involvement associated with EBV infection always varies, mild self-limited hepatocellular liver disease is common. It manifests by a transient elevation of serum aminotransferases levels. Elevated liver enzymes, especially alanin-aminotransferase, strengthen the clinical impression of infection. Severe hepatocellular liver injury is rare and its pathogenesis uncertain. Cholestatic liver disease is less frequent approximately 5% of cases, possibly caused by cholestasis or virus induced hemolysis and is also self-limited. Clinical evidence of hepatitis is rarely the presenting feature of the infection.
References


