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Primary EBV Infection and Hematological Findings in Turkish Children: A Retrospective, Single-Center Study

Türk Çocuklarında Primer EBV Enfeksiyonu ve Hematolojik Bulguları: Retrospektif Tek Merkezli Bir Çalışma

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Abstract

Aim: Primary infection with EBV during childhood is usually asymptomatic. Hematologic abnormalities such as hemolytic anemia, thrombocytopenia, and neutropenia are relatively common, but aplastic anemia, severe thrombocytopenia, severe neutropenia, and lymphoid malignancies are rare. In this retrospective study, we have analyzed data from children with primary EBV infection who were examined at our center over 12 years to describe the distribution, clinical features, complications, and outcome of EBV in Turkish children.

Material and Method: Data from all children (age<18 years) with primary EBV infection who were examined in our center between 2008 and 2020 were retrospectively reviewed.

Results: In total, 120 patients were included in the study. Anemia was detected in 13 (11%) children. Mild and severe neutropenia was detected in 12 (10%) and 1 (0.8%) children, respectively. Mild thrombocytopenia without bleeding complications was present in 10 (8%) children with a mean platelet count of 250×10^9/L $\pm113\times10^9$/L. Seven patients presented with acute idiopathic thrombocytopenia (lowest platelet count, 2×10^9/L). Large diffuse cell lymphoma developed in 0.8% (n:1) patients.

Conclusion: The prognosis for infectious mononucleosis is excellent, although various acute complications may occur. However, severe complications are very rare, and most of the complications resolve spontaneously without certain therapy.

Keywords: Primary EBV infection, Turkish children, hematologic findings

Öz

Amaç: Çocukluk döneminde EBV ile birincil enfeksiyon genellikle asemptomatiktir. Hemolitik anemi, trombositopeni ve nötropeni gibi hematolojik anormallikler nispeten yaygındır, ancak aplastik anemi, şiddetli trombositopeni, şiddetli nötropeni ve lenfoid maligniteler nadirdir. Bu retrospektif çalışmada, EBV'nin Türk çocuklarındaki dağılımını, klinik özelliklerini, komplikasyonlarını ve sonuçlarını tanımlamak için 12 yıl boyunca merkezimizde izlenen primer EBV enfeksiyonu olan çocuklardan elde edilen verileri analiz ettik.

Gereç ve Yöntem: Hastanemizde 2008-2020 yılları arasında izlenen primer EBV enfeksiyonlu tüm çocuklara (18 yaş altı) ait veriler retrospektif olarak incelendi.

Bulgular: Çalışmaya toplam 120 hasta dahil edildi. 13 (%11) çocukta anemi saptandı. 12 (%10) çocukta hafif, 1 (%0,8) çocukta şiddetli nötropeni saptandı. Ortalama trombosit sayısı 250×10^9/L $\pm113\times10^9$/L olan 10 (%8) çocukta kanama komplikasyonu olmaksızın hafif trombositopeni mevcuttu. Yedi hasta akut idiyopatik trombositopeni (en düşük trombosit sayısı, 2×10^9/L) ile başvurdu. Hastaların %0,8'inde (n:1) büyük diffüz hücreli lenfoma gelişti.

Sonuç: Çeşitli akut komplikasyonlar oluşabilmesine rağmen enfeksiyöz mononükleozun prognozu mükemmeldir. Bununla birlikte, ciddi komplikasyonlar çok nadirdir ve komplikasyonların çoğu belirli bir tedavi olmaksızın kendiliğinden düzelir.

Anahtar Kelimeler: Primer EBV enfeksiyonu, Türk çocukları, hematolojik bulgular

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INTRODUCTION

Epstein- Barr virus (EBV) is a DNA virus that is a member of the gammaherpesviruses.[1] The reported prevalence of EBV infections varies widely depending on countries' economic status and geographic location. Infection with EBV in developing countries usually occurs during infancy and early childhood. Infectious mononucleosis (IM) is the best-known clinical syndrome caused by EBV.[2-5] Although primary infection with EBV during childhood is usually asymptomatic, adolescents and adults manifest in 30–50% of cases as the classic triad of fatigue, pharyngitis, and generalized lymphadenopathy, which constitute the major clinical manifestations of IM.[6-7] Hematologic abnormalities such as hemolytic anemia, thrombocytopenia, and neutropenia are relatively common, but aplastic anemia, severe thrombocytopenia, and severe neutropenia are rare.[8-10] EBV is associated with lymphoid malignancies, such as Burkitt lymphoma, Hodgkin lymphoma, aggressive NK cell leukemia, T- and NK cell lymphoproliferative disorder, and epithelial cell malignancies such as nasopharyngeal carcinoma.[11-15] EBV increases the risk for Hodgkin lymphoma by a factor of 2-4. The risk of developing Hodgkin lymphoma peaking at 2.1 years following infectious mononucleosis.[16-20] Hemophagocytic lymphohistiocytosis (HLH) can develop rare serious, life-threatening complications with primary EBV infection.[21-22]

A variety of neurologic conditions have been associated with EBV infection. Although headache is a common symptom, severe neurologic manifestations, such as seizures and ataxia, may occur in 1–5% of cases.[23]

In this retrospective study, we have analyzed data from children with primary EBV infection who were examined at our center over 12 years to describe the distribution, clinical features, complications, and outcome of EBV in Turkish children.

MATERIAL AND METHOD

The medical records of all children with primary EBV infection (<18 years of age) diagnosed in the Pediatric Hematology and Oncology Units of the Department of Pediatrics, Dr. Sami Ulus Maternity and Children Training and Research Hospital, between 2008 and 2020 were reviewed after our Institutional Review Board had approved the study. (date: 07.04.2021, no: E-21/04-145)

Medical records were reviewed, and 209 patients with primary EBV infection were retrospectively analyzed for initial clinical and laboratory findings, management, and outcome data. Patients were excluded if there was no regular follow-up or where analyses of anti-EBV-capsid antigen (CA)-IgM and anti-EBV-CA-IgG antibodies and EBNA were inadequately documented. In this study, we included 120 patients. In the study population, the following data were analyzed: age, sex, detailed physical examination findings, laboratory findings including complete blood count [white blood cell (WBC), neutrophil, lymphocyte, and platelet count, mean platelet volume (MPV), platelet distribution width (PDW), concentrations of hemoglobin (Hb)] and biochemical examinations [alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, triglycerides, lactate dehydrogenase (LDH), C-reactive protein (CRP)] and anti-EBV-capsid antigen (CA)-IgM and anti-EBV-CA-IgG antibodies and serum concentration of immunoglobulin (Ig) A, G, and M. In addition, coagulation function test [fibrinogen (Fib), activated partial thromboplastin time (APTT), prothrombin time (PT)], bone marrow aspiration findings, parvovirus, and cytomegalovirus (CMV) infection were diagnosed with immunoglobulin M antibodies or genomic DNA copy number by polymerase chain reaction (PCR). Primary EBV infection was diagnosed based on clinical manifestations, positive IgM antibody titers, and IgG antibody titers to EBV viral capsid antigens (VCA). In addition, throat culture was performed in patients presenting with tonsillopharyngitis to exclude Group A beta-hemolytic streptococci. Neutropenia was defined as an absolute neutrophil count below 1500 per µl, thrombocytopenia as platelet count $<150\times10^9$/L and lymphocytosis as lymphocyte count above or equal to 5000 per µl or at least 50% of a total white blood cell. The following criteria were used to diagnose IM in our study: i) 3 of the following clinical symptoms: Fever, angina, large cervical lymph nodes, hepatomegaly, splenomegaly; ii) Positivity for anti-EBV-capsid antigen (CA)-IgM and anti-EBV-CA-IgG antibodies.[24]

Statistical Analysis

All reagents for testing were the original reagents of the instruments. The Kolmogorov-Smirnov normality test was used to determine if the data is normally distributed.

The Mann-Whitney U test was used to compare differences in non-parametric variables (non-normally distributed data). Categorical variables were presented as a proportion and analyzed with the Chi-squared test. Continuous data were analyzed using Student's t-test. Values were expressed as n (%), the mean ± standard deviation, or median (interquartile range). Spearman correlation analysis was used for grading variable data, whereas Pearson correlation analysis was used for continuous variable data. All statistical analyses were performed using SPSS version 22.0 (IBM Corp.). $p<0.05$ was considered to indicate statistical significance.

RESULTS

Each of the 120 Turkish children had a specific serologic profile of primary EBV infection and a clinical picture of primary EBV infection. The serologic findings of all children were positive VCA IgM and/or VCA IgG. The age of the children ranged from 1 to 17 years, with a median of 5 years. The peak incidence occurred at 3 to 5 years, followed by 8 to 11 years. The male (n: 68, 57%) female ratio was 1.3:1. No seasonal or yearly variation in the frequency of primary EBV infection was detected.

Clinical Manifestations

Fifty-seven (48%) of 120 children had fever on admission. No age difference in the magnitude and duration of the febrile response was observed. Lymphadenopathy (>2 cm) and tonsillopharyngitis were detected in 105 (88%) and 69 (58%) children, respectively. Splenomegaly and hepatomegaly were present in 55 (46%) and 39 (33%) patients, respectively. Cutaneous rashes, predominantly maculopapular, were detected in 3 children (15%), of whom all patients have antibiotics before the appearance of the skin rash. Eyelid edema was detected in 13 children (11%) and palatal petechiae in 7 (6%) children.

Laboratory Findings

Laboratory characteristics of the cases are presented in **Table 1**. Anemia was detected in 13 (11%) children. Mild and severe neutropenia was detected in 12 (10%) and 1 (0.8%) children, respectively. Mild thrombocytopenia without bleeding complications was present in 10 (8%) children with a mean platelet count of 250×10^9/L $\pm113\times10^9$/L. Seven patients presented with acute idiopathic thrombocytopenia (lowest platelet count, 2×10^9/L). Leukocytosis and lymphocytosis were detected in 68 (57%) and 73 (61%) children, respectively. ALT and AST values were elevated in 55 of 120 (46%) of all children.

Table 1: Laboratory characteristics of the cases.

	Mean±SD	Minimum-maximum
Hemoglobin (g/dl)	12.2±1.1	8-15
Mean corpuscular volume (fl)	78.1±5.6	54-89
White blood cell count (per µl)	12,554±6,656	3,600-40,750
Neutrophil count (per µl)	3,633±2,849	40-23,0000
Lymphocyte count (per µl)	6,644±3,963	1,730-25,850
Monocyte count (per µl)	1,003±1,051	140-8,760
Platelets (x109/L)	250±113	2-573
Alanine aminotransferase (U/L)	103±132	6-661
Aspartate aminotransferase (U/L)	97±110	21-569
Immune globulin M (mg/dl)	148±69	51-333
Immune globulin G (mg/dl)	1095±388	499-2280
Immune globulin A (mg/dl)	117±80	6.4-417

Complications

EBV-associated HLH was seen in a 13-year-old male patient. At the time of diagnosis, EBV PCR 12.555 copy was detected. Steroid and IVIG treatment was given and could be controlled by only steroid and IVIG treatment without any need for chemotherapy. Transient macroscopic hematuria was present early in the disease course in one child. The associated diseases at the time of diagnosis are given in **Table 2**. Large diffuse cell lymphoma developed in 0.8% (n:1) patients. In the patient whose EBNA became positive following primary EBV infection, lymphoma developed with EBV reactivation three years later.

Table 2: The associated diseases at the time of diagnosis.

Associated diseases	n	Duration of a EBNA positivity (month, mean (min-max))	Long-term complication
Selective IgA deficiency	2	1	No
Transient IgA deficiency	2	3.5 (1-6)	No
Transient hypogammaglobulinemia	2	8 (6-10)	No
Juvenile idiopathic arthritis	1	2	No
Autoimmun thyroiditis	1	4	No
Hemophagocytic lymphohistiocytosis	1	1	No

DISCUSSION

EBV affects more than 95% of the world's population. Infection with EBV in developing countries usually occurs during infancy and early childhood. In central Africa, almost all children are affected by 3 yr of age. On the contrary, two waves of primary EBV infection in childhood from 1 to 6 years and 10 years were observed in the Western communities.[25] Approximately 30% of infections occur during adolescence and young adulthood and are usually more symptomatic among more affluent populations in industrialized countries. EBV infections presented at all ages, from infants to adolescents, in our series of 120 children. The peak incidence occurred at 3 to 5 years, followed by 8 to 11 years.

The peak incidence of EBV infections in our patients was similar to the results of previous studies in Western communities, suggesting that there is no significant variation in EBV infections presentation among different ethnic populations. Hematological complications usually include anemia, thrombocytopenia, neutropenia, and lymphocytosis. Severe thrombocytopenia ($<20\times10^9$/L) is rare, while mild thrombocytopenia ($<100\text{-}150\times10^9$/L) occurs in 25-50% of patients. The mechanism involved in thrombocytopenia has been reported to occur as a result of increased peripheral destruction due to antiplatelet antibodies and splenomegaly with a normal or increased megakaryocyte count in the bone marrow. Neutropenia to less than 1,500 neutrophils per µl, typically lasting only a few days to 2 weeks, occurs in approximately 3% of cases.[9] The pathogenesis of neutropenia after EBV infection may involve decreased production or maturation of myeloid cells in the bone marrow, as a result of the direct effect of EBV or antibody-mediated peripheral destruction of myeloid cells. Anti-human neutrophil antigen-1a (anti-HNA-1a) and anti-HNA-1b antibodies are both associated with the pathophysiology in neutropenia after EBV infection, although it is unknown whether anti-neutrophil antibodies are produced in EBV-infected B cells. Autoimmune hemolytic anemia is a rare complication.

Primary EBV infection causes hemolytic anemia in approximately 3% of patients.[1,8,10] In our study, severe thrombocytopenia developed in 7 (6%) patients, hemolytic anemia developed in 1 (0.8%) patient, and neutropenia developed in 13 (11%) patients. Patients with

thrombocytopenia showed improvement after IVIG, while patients with hemolytic anemia and neutropenia recovered spontaneously. Our results were consistent with the literature.

EBV is considered the major cause of severe cases of virus-associated hemophagocytic syndrome. In previous studies, the most frequent reason for HLH was infections and the most common infectious agent was EBV. In these studies, HLH was triggered by EBV in 1/3-3/4 of the patients.[21-22,26]

The initial treatment for HLH aims to calm down the hyperactivated immune system and remedy hypercytokinemia. Some studies showed that secondary HLH might be controlled by only steroid and IVIG treatment without any need for etoposide. Similarly, in our study, HLH in a patient could be controlled by only steroid and IVIG treatment without any need for chemotherapy. Early recognition and initiation of HLH-directed therapy are important for patient survival.[27-28]

The genetic, environmental, and infectious processes, especially viral infections, appear to play a role in the etiology of rheumatic disease in children. Epstein–Barr virus is the most commonly emphasized viral agent that facilitates rheumatic diseases. Clinical and laboratory investigations have revealed that EBV triggers the development of SLE, RA, but only a limited number of published reports regarding the occurrence of EBV infection in patients with JIA and autoimmune thyroiditis.[29,30] One of our patients was diagnosed with primary EBV with JIA and another with autoimmune thyroiditis. There are different kinds of literature on whether EBV infection increases JIA frequency. EBV infection can significantly induce an immune disorder leading to an uncontrolled inflammatory process that results in JIA symptoms. The previous study observed a significantly higher level of EBV antibodies in children with autoimmune thyroid disease (study group) (n=34) than in a control group (P=0.008), suggesting that EBV infection might play a role in the pathogenesis of autoimmune thyroid disease in children. Another study further investigated this phenomenon and showed three cases with newly diagnosed autoimmune thyroid disease and primary EBV infection.[24] Notably, further studies are needed to explain the role of the immunological mechanism of EBV on various target organs.[31-32]

Selective IgA deficiency and hypogammaglobulinemia are the common immunodeficiency syndrome. The clinical and laboratory features variability suggests that IgA deficiency and hypogammaglobulinemia have multiple causes. Acquired deficiency of IgA and hypogammaglobulinemia have been linked to some drugs and infections. An infectious cause has been suggested by reports of IgA deficiency in some children with EBV.

In our study, two patients with transient IgA deficiency, two patients with selective IgA deficiency, and two patients transient hypogammaglobulinemia temporally related to an EBV infection. Thus EBV infection should be considered in the differential diagnosis of acquired IgA deficiency.[32-34]

EBV is associated with 1% of global cancers, mostly lymphomas and carcinomas; approximately 140.000 people die of EBV-associated cancers each year.[11,12] In agreement with our study, A Scandinavian study observed in 2003 an increased risk of EBV-positive HL in young adults, with an odds ratio (OR) of 2.7 [95% confidence interval (CI): 1.2 to 6.0], and a median incubation period of 4.1 years with a peak risk after 2.1 years after primary infection.[20] In later years, A British study showed similar results in two different cohorts.[35] EBV-positive DLBCL seems to affect primarily elderly patients. Studies on children are limited. In our study, large diffuse cell lymphoma developed in 0.8% (n: 1) patients. In the patient whose EBNA became positive following primary EBV infection, lymphoma developed with EBV reactivation three years later.

CONCLUSION

The prognosis for infectious mononucleosis is excellent, although various acute complications may occur. However, severe complications are very rare, and most of the complications resolve spontaneously without certain therapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Ankara Sami Ulus Training and Research Hospital at the University of Health Sciences Ethics Committee. (date:07.04.2021, no:E-21/04-145)

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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