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Evaluation of Clinical and Laboratory Features of Epstein-Barr Virus-Associated Acute Infectious Mononucleosis in Children

Çocuklarda Epstein-Barr Virüsüyle İlişkili Akut Enfeksiyöz Mononükleozun Klinik ve Laboratuvar Özelliklerinin Değerlendirilmesi

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Objectives: The various symptoms of infectious mononucleosis associated with Epstein-Barr virus may confuse physicians in differential diagnosis. The aim of this study is to evaluate the clinical and laboratory findings of this disease in symptomatic children.

Patients and Methods: This study was retrospectively performed on 52 cases (31 boys, 21 girls; mean age 5.4±3.4 years; range 1 to 13 years) with acute Epstein-Barr virus infection. The clinical and laboratory findings were evaluated according to admission time after initial complaints (≤5/>5 days) and the age groups of the cases (≤2/>2 years).

Results: The major symptoms were fever, lymphadenopathy and tonsillopharyngitis in the classical triad. Moreover, atypical cases who had ascites, arthritis and severe abdominal pain were defined. No case had a poor prognosis. The most frequent laboratory finding was lymphocytosis. While the major symptoms were more frequent in the group "admission time ≤ 5 days", the count of atypical lymphocyte were higher in the group "admission time > 5 days". However, these differences could not be defined between age groups.

Conclusion: Infectious mononucleosis due to Epstein-Barr virus is a disease with good prognosis in children. The features of the disease may vary according to admission time, and this fact should be taken into consideration in the diagnosis.

Key Words: Infectious mononucleosis; Epstein-Barr virus; findings; prognosis; age; admission time; children.

Amaç: Epstein-Barr virüsünden kaynaklanan enfeksiyöz mononukleozun değişik semptomları, ayırıcı tanıda hekimlerin aklını karıştırabilir. Bu çalışmanın amacı semptomatik çocuklarda bu hastalışın klinik ve laboratuvar bulgularının değerlendirilmesidir.

Hastalar ve Yöntemler: Bu çalışma akut Epstein-Barr virüs eneksiyonu olan 52 olgu (31 erkek, 21 kız; ort. yaş 5.4±3.4; dağılım 1-13) üzerinde retrospektif olarak yürütüldü. Klinik ve laboratuvar bulgular, şikayetler başladıktan sonraki başvuru zamanı (≤5/>5 gün) ve yaş gruplarına (≤2/>2 yıl) göre değerlendirildi.

Bulgular: Major semptomlar klasik triadda yer alan ateş, lenfadenopati, tonsillofarenjit idi. Ayrıca asit, artrit ve şiddetli abdominal ağrıyla başvuran atipik olgular da tanımlandı. Hiçbir olguda kötü bir prognoz gözlenmedi. En sık rastlanan laboratuvar bulgu lenfositozdu. Major semptomlar başvuru zamanı ≤5 gün olan grupta daha sık iken, atipik lenfositler başvuru zamanı >5 gün olan grupta daha yüksek bulundu. Bu tür farklılıklar yaş grupları arasında saptanmadı.

Sonuç: Epstein-Barr virüsüne bağlı enfeksiyöz mononükleoz, çocuklarda iyi prognozlu bir hastalıktır. Hastalık özellikleri başvuru gününe göre değişkenlik gösterebilir, tanıda bu durum göz önüne alınmalıdır.

Anahtar sözcükler: Enfeksiyöz mononukleoz; Epstein-Barr virüsü; bulgular; prognoz; yaş; başvuru zamanı; çocuklar.

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Infectious mononucleosis (IMN) is a lymphoproliferative and an infectious disease mostly caused by Epstein-Barr virus (EBV) and rarely caused by the other viruses such as Cytomegalovirus (CMV) classified in herpes group viruses.[1-3] A classical triad after a prodromal period, such as fever, exudative tonsillopharyngitis and lymphadenopathy characterizes this disease. In addition; enanthema, eyelid edema, hepatosplenomegaly and skin eruption may also be observed. Skin eruption is usually associated with drug intake such as beta-lactam antibiotics.[1-3]

In the developing and underdeveloped countries, Epstein-Barr virus-induced IMN (EBV-IMN) is generally asymptomatic in infants.[1-3] The symptoms of acute EBV-IMN are much more manifested in older children or young adults. The symptoms may be various; even this disease may lead to death.[1-3] Thrombocytopenia, agranulocytosis, hemolytic anaemia, hemophagocytic syndrome, orchitis, myocarditis, nephritis, nephrotic syndrome, hepatitis, arthritis, spleen rupture and gastrointestinal disturbances may accompany to EBV-IMN.[3-7] Rarely, the central nervous system may be involved, and aseptic meningitis, encephalitis or Guillain-Barré Syndrome may occur.[4,8] Moreover, EBV-IMN may be associated with malignancies such as nasopharyngeal carcinoma, lymphoma, and X-linked lymphoproliferative syndrome (Duncan's syndrome).[3,4]

Sometimes, the various symptoms associated with EBV-IMN may confuse physicians in the differential diagnosis. The specific and non-specific findings of this disease should be known to prevent misdiagnosis and unnecessary therapy. The aim of this study is to evaluate clinical and laboratory features of EBV-IMN, and to overview clinical presentation, laboratory findings and the prognosis of the disease in children.

PATIENTS AND METHODS

The medical records of 52 children (31 boys, 21 girls; mean age 5.4±3.4 years; range 1 to 13 years) hospitalized in the Pediatric Infection Unit at Trakya University Hospital with the diagnosis of EBV-IMN from 1996 to 2004 were evaluated, retrospectively. Epstein-Barr virus infectious mononucleosis was diagnosed by physical examination and serological methods; positive EBV-Viral capsit antigen immunoglobuline-M antibody (EBV-VCA-IgM) and Monospot latex test (Meridian Diagnostics, Inc., Cincinnati, Ohio, USA). Moreover, anti-CMV-IgM assay was used for differential diagnosis. An immunofluorescent assay (Zeus Scientific, Inc., Raritan, NJ, USA) was used for the detection of EBV-VCA-IgM and anti-CMV-IgM titres. A reaction at a dilution ≥1:10 was accepted as positive.

The groups were classified according to age and admission time of the cases. These groups were defined as ≤2 and >2 years according to ages; ≤5 and >5 days according to admission times. In the classifications, 2nd age was selected as a cut-off age for infancy period. And also, 5th admission day was selected as a cut-off day, because the mean admission time was five days.

The data concerning the following parameters were derived from the patient's medical records such as age, gender, seasonal feature, clinical complaints and signs, laboratory findings; white blood cell (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin (Hb), platelet (Plt), blood smear, serum liver enzymes; alanine aminotransferase (ALP) and aspartate aminotransferase (AST) and alkaline phosphatase (ALP) and viral serology and admission time after the initial complaints.

In the evaluation of the laboratory parameters, leukocytosis was defined as >15.000 cells/mm^3 under five years and >10.000 cells/mm^3 for older than five years. Also, normal ranges of the other laboratory parameters were defined according to reference values.[9] Moreover the following values were accepted as; low Hb: <12 mg/dl, high ESR: >20 mm/hour, high CRP: >8 mg/L, high liver transaminases: >50 U/L for ALT and >55 U/L for ALT.[9]

All statistical analyses were performed using Minitab Release-13 for Windows. Recognized statistical processes were applied. Cases were classified according to age and admission time to the hospital; chi-square (when the expected value was <5, Fisher's exact chi-square test was used) and Mann-Whitney U tests were used to

compare the groups. A value of $p<0.05$ was statistically significant.

RESULTS

In this study, we evaluated the data of 52 patients, who had positive EBV-VCA-IgM results. Thirteen cases (25%) were equal or younger than two years of age, while 39 cases (75%) were older.

Seasonal features

Twenty-one cases (40.4%) in spring, 14 cases (26.9%) in summer, six cases (11.5%) in autumn, 11 cases (21.2%) in winter had applied to the hospital. Mean hospital admission time of the patients after initial complaints was 5.2±5.3 (2-30) days. All patients were hospitalized for differential diagnosis and symptomatic therapy.

Clinical findings

According to anamnesis, the initial complaints of the disease were fever and upper airway symptoms such as cough, rhinitis, etc. in all of the cases. The major clinical findings were determined as lymphadenopathy, tonsillopharyngitis and fever at the admission. Lymphadenopathy in 49 cases (94.2%), tonsillopharyngitis in 46 cases (88.5%) and fever in 44 cases (84.6%) were found. Moreover, while the classical triad consisting of fever, lymphadenopathy and tonsillopharyngitis was defined in 41 cases (78.8%), atypical findings as peroral enanthema in 26 cases (50.0%), hepatomegaly in 31 cases (59.6%), splenomegaly in 40 cases (76.9%), skin rash in seven cases (13.5%) and eyelid edema without nephrologic disorders in seven cases (13.5%) were determined.

In all of the cases, body temperature had altered between 38 and 39 °C. In the cases with tonsillopharyngitis, the sore throat was accompanied by marked tonsillar enlargement and exudates. Lymphadenopathy was generalized but had manifested in the regions of anterior cervical and submandibular nodes.

Twenty-two cases (23.1%) had received antibiotherapy without throat cultures before admission time. The antibiotics were given to the patient by the peripheral practitioners. These antibiotics were penicillins (8 cases), cephalosporins (3 cases) and macrolids (1 case). Skin rashes were maculopapular and were defined in seven cases who had received penicillins.

The atypical findings such as ascites, arthritis and severe abdominal pain-like acute abdomen were defined in five cases (10.1%). Ascites which was minimal and transudative was determined in three cases. The cases with ascites had suffered from hepatitis and gastrointestinal dis-

Table 1. The clinical findings according to age and admission time groups

	Age groups				Admission time groups			
	≤2 years (n=13)		>2 years (n=39)		≤5 days (n=40)		>5 days (n=12)	
	n	%	n	%	n	%	n	%
Fever	12	92.3	32	82.1	38	95.0*	6	50.0
Tonsillopharyngitis	11	84.6	35	89.7	38	95.0*	8	66.7
Lymphadenopathy	12	92.3	37	94.9	37	92.5	12	100.0
Classic triad[#]	11	84.6	30	76.9	35	87.5*	6	50.0
Hepatomegaly	10	76.9	21	53.8	24	60.0	7	58.3
Splenomegaly	10	76.9	30	76.9	30	75.0	10	83.3
Peroral enanthema	6	46.2	20	51.3	22	55.0	4	33.3
Skin rash	2	15.4	5	12.8	7	17.5	–	–
Eyelid edema	1	7.7	6	15.4	6	15.0	1	8.3
Ascites	–	–	3	7.7	2	5.0	1	8.3
Arthritis	–	–	1	2.6	–	–	1	8.3
Severe abdominal pain	–	–	1	2.6	–	–	1	8.3

[#]: Clasical triad: the combination of fever, tonsillopharyngitis and lymphadenopathy; *: $p<0.05$.

Table 2. The laboratory findings according to age and admission time groups

	Age groups				Admission time groups			
	≤2 years (n=13)		>2 years (n=39)		≤5 days (n=40)		>5 days (n=12)	
	Mean±SD	Min-Max.	Mean±SD	Min-Max.	Mean±SD	Min-Max.	Mean±SD	Min-Max.
Serum ALT (U/L)	57±53	12-225	86±69	11-205	59±51	12-200	83±76	11-225
Serum AST (U/L)	47±33	18-168	54±36	20-110	43±27	18-100	66±47	20-168
Serum ALP (U/L)	361±104	158-562	333±104	180-539	363±90	180-539	324±141	158-562
Lymphocyte count (/mm^3)	6102±2913	1710-13838	7961±1872	4165-10240	6640±2613	2160-12636	6214±3459	1710-13838
Neutrophil count (/mm^3)	4269±1413	1458-7830	5072±1597	1560-7735	4550±1349	1560-7120	4159±1890	1458-7830
Atypical lymp.(%)	7±3	5-14	6±2	5-12	6±2	5-14	9±3^{+*}	5-14
Monocytes (%)	5±2	4-15	6±2	4-10	5±2	4-10	6±4	4-15
ESR (mm/h)	22±9	10-50	25±12	11-50	22±9	10-50	25±14	12-50
CRP (mg/L)	16±15.0	6-65	14±11	6-35	15.8±15.2	6-65	15.1±10.9	6-37
Hb (g/dl)	12.0±0.5	10.6-12.6	11.6±0.5	10.6-12.1	11.7±0.5	10.9-12.6	11.7±0.7	10.6-12.5

ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; Hb: Hemoglobin; ALT: Alanin aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphates; $^{+}$: p<0.0001.

turbances. Each of the atypical findings such as arthritis and severe abdominal pain had been observed in separate cases. Reactive arthritis had involved a single joint (right ankle). An acute abdomen-like clinic with severe abdominal pain had occurred due to mesentery lymphadenitis. At the admission-time none of the cases with atypical features had fever. They had generalized microlymphadenopathy and tonsillopharyngitis.

According to the clinical findings, although there was no significant difference between age groups (p>0.05), there was significant difference between admission time groups (p<0.05) (Table 1). The classical triad and the findings such as fever, tonsillopharyngitis were more often in the group who applied to the hospital in the first five days than the other group.

Laboratory findings

The laboratory parameter values were as follows: The WBC count; 10998±3272 (5280-18200)/mm^3, the absolute lymphocyte count; 6539±2802 (1710-13838)/mm^3, absolute neutrophil count; 4458±1482 (1458-7830)/mm^3, Plt count 275413±98199 (163000-591000)/mm^3, Hb level 11.7±0.5 (10.6-12.6) gr/dl.

The most frequent laboratory finding lymphocytosis determined in 47 (90.4%) cases was accompanied by atypical lymphocytes and monocytosis. Lymphocyte count was normal in five cases. While one case (1.9%) had neutrophilia and four cases (7.7%) had neutropenia, neutrophil counts were normal in 47 cases (90.4%). Moreover, in blood spread, the mean values of percentage rates of atypical lymphocytes and monocytes were found as 7±3 (5-14) and 5±2 (4-15), respectively.

The acute phase reactants; mean ESR and CRP levels were determined as 23±10 (10-50) mm/hr and 16±14 (6-65) mg/L, respectively. High ESR and high CRP levels were defined in 13 cases (25%) and 25 cases (48.1%), respectively. No cases had any bacterial infection, also microbiological cultures (throat, blood and urine) were sterile.

The serum liver transaminases were found mildly or moderately elevated in 14 cases (26.9%). Mean ALT and AST levels were determined as 64±58 (11-225) U/L and 48±33 (18-168) U/L, respectively. In addition, mean ALP level was 354±104 (158 –562) U/L.

Among laboratory findings, only the percentage of atypical lymphocytes were higher in the group "admission time > 5 days" than the other group (p<0.0001), (Table 2). Otherwise, according to the laboratory findings, there was no significant difference between age groups, (p>0.05), (Table 2).

The serological tests, such as EBV-VCA-IgM, anti-CMV-IgM, and Monospot latex test had been done for diagnosis and differential diagnosis. Interestingly, anti-CMV-IgM was positive

in six cases (11.5%) together with EBV-VCA-IgM (+). In these cases, CMV-DNA-PCR tests were negative.

Monospot latex tests were found to be positive in 19 cases (36,5%). The mean age of the cases with positive Monospot latex tests were 8±3 (4-13) years. The admission times were ≤5 days in 12 cases (63.2%) and >5 days in seven cases (36.8%). According to the results of Monospot latex tests, while there was a significant difference between age groups (p=0.004), no significant difference was determined between admission time groups.

Complications and therapy

The complications such as artritis, ascites, hepatitis and mesentery lymphadenitis were observed in some patients. However, there were neither any complications nor severe progress or death seen in all of the cases. We applied symptomatic therapy for all of the cases. No case received antiviral therapy.

DISCUSSION

Epstein-Barr virus infectious mononucleosis is a very common disease in the world's population. The occurrence-age of this disease changes according to socio-economic condition of the countries. In the developing and underdeveloped countries, seroprevalence of EBV-IMN is upper 95% in adults, 60% in children.[2,3,10,11] This syndrome is rarely apparent in children <4 years of age because it is usually asymptomatic in early childhood, and the symptoms manifest much more in adolescent and young adults.[1-3] Chan et al.[12] reported that the peak incidence occurred at two to four years old followed by five to nine years old and no sexual difference. In our study, the mean age of the cases with symptomatic IMN was 5.4 years. The percentage of the cases older than two years was 79.2%. Sexual difference was not detected.

No relation between IMN and seasons is reported.[2] In our study, 21 cases (40.4%) applied to the hospital on springtime but it was not significant.

The classic triad of IMN characterized by fever, tonsillopharyngitis and lymphadenopathy may be seen in 80% of the symptomatic cases. The other usual clinical findings of IMN are hepatomegaly (10-30%) and splenomegaly (50%). Some cases may have eyelid edema without renal involement. Moreover, there may be skin rash associated with drugs such as penicillin and their derivatives.[3-5] In our study, classic triad was observed at 78.8% of the cases. Hepatomegaly and splenomegaly rates were 59.6% and 76.9%, respectively. In addition, eyelid edema and skin rash were determined in 13.5% of the cases.

Though liver transaminases may increase in some cases, symptomatic hepatitis and jaundice are rare in IMN.[1-4] Chan et al.[12] reported that the older cases had high liver transaminase and hepatobiliary symptoms. In this study, high liver transaminase levels were determined in 26.9% of the cases but none had symptomatic acute hepatitis. Moreover, no statistical difference was determined between age groups.

The complications of EBV-IMN are rare in children, but atypical cases accompanied by these complications may be observed.[4,13] The clinical findings such as arthritis, ascites and acute abdomen, as detected in our cases, had been determined in few numbers of cases in the other reports.[14-18] In our cases arthritis was due to infection so called reactive, ascites was associated with hepatitis, and acute abdomen-like severe abdominal pain had occurred due to mesentery lymphadenitis. Our atypical cases with complications had good prognosis and improved as typical cases.

The diagnosis of EBV-IMN was done with both the clinical findings and laboratory findings, which were positive specific antibody tests and heterophile antibody tests. Specific antibody tests of EBV are VCA-IgM, VCA-IgG, Diffuse Straining Component and Cytoplasmic Restricted Component of Early Antigen (EA-D and EA-R), and EBV-determined Nuclear Antigen (EBNA).[1-3] The detection of EBV-VCA-IgM is generally sufficient for the diagnosis of acute EBV-IMN.[3] Recently, a real-time polymerase chain reaction (PCR) assays are being used for diagnosing of symptomatic EBV infection and for monitoring the viral load.[19,20] However, the PCR-test is more sensitive in the first few days

of illness, and specific antibody tests may be more sensitive than PCR in thereafter period.[19] Moreover, EBV-DNA PCR-technique can not be used routinely because it is very expensive.

Heterophile antibody tests associated with EBV-IMN are Paul-Bunnell and Monospot tests. Monospot latex test is the most valuable and useful test in the heterophile antibody tests.[21] These tests are elevated after approximately four weeks from the beginning of incubation period. The incubation period of EBV-IMN is not clear in children and heterophile antibody tests are mostly false-negative before four years of age.[3,19] In our study, we evaluated the cases who had EBV-VCA-IgM positive for acute infection diagnosis. Also, the Monospot latex tests was determined positive in 36.5% of the cases, Moreover, the ages of cases detected positive Monospot latex tests were ≥4 years.

The main laboratory finding of the cases with IMN is usually leukocytosis and lymphocytosis accompanied with atypical lymphocytes. Atypical lymphocyte rate is usually over 10% in blood smear.[1-3] In this study, the mean rate of atypical lymphocytes was determined as 7%, this rate had varied according to the admission time to the hospital. The primary laboratory findings were leukocytosis and lymphocytosis, similarly. Moreover, high ESR and high CRP levels were observed in some cases. These findings might be due to acute EBV-IMN or secondary bacterial infections, nevertheless we couldn't determine any bacterial infection evidence.

Surprisingly, in our study, anti CMV-IgM was determined positive in six cases together with positivity of EBV-VCA-IgM. We approved that these results were false-positive. Some researchers reported that this is because of either co-infection or false-positive results.[15,22]

We aimed to argue the features of typical and atypical cases with IMN in this study. In conclusion, EBV-IMN is a disease with good prognosis, even it has atypical findings in children. The clinical and laboratory findings of EBV-IMN may change according to admission day; however, this disease, which involves reticuloendothelial system, should be considered and investigated by specific diagnostic tests in each infection. Thus, misdiagnosis and unnecessary treatment of the disease can be prevented.

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