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# Different clinical presentation of infectious mononucleosis in children: a retrospective analysis of 369 cases

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***Summary***

**Aim:** The aim of this study was to investigate the clinical findings and serologic test results of the patients diagnosed with Epstein-Barr virus (EBV)-induced infectious mononucleosis.

**Material and Method:** This retrospective study was performed among 369 serologically proven (positive EBV VCA IgM) infectious mononucleosis subjects out of 845 patients who were tested for EBV VCA IgM and IgG antibodies because of their suspicious clinical findings between January 2004 and December 2009. EBV VCA IgM and IgG antibodies were detected by enzyme linked immunosorbent assay (ELISA). Clinical findings of the subjects and any other diseases related to EBV in differential diagnosis were evaluated.

**Results:** The mean age of 369 subjects diagnosed with EBV infection was 94.5±58.4 months (range: 6 months -14 years). One hundred and seventy-one patients (46.4%) out of 369 were female. Symptoms and findings at the time of the first evaluation were as follows: fever longer than seven days and malaise (43.1%); fever, sore throat and cervical lymphadenopathy (33.1%); fever with maculopapulary rash (10.3%); anemia and thrombocytopenia (7.1%); elevated liver function enzymes (4.1%) and arthralgia (1.6%). The classical clinical findings of infectious mononucleosis such as fever, cervical lymphadenoathy, pharyngitis and splenomegaly were observed in 357, 155, 152 and 177 subjects, respectively (96.7%, 42%, 41.2%, 47.9% and 21.4%, respectively), while hepatomegaly and edema of the eyelids were observed in 79 and 65 subjects, respectively (21.4% and 17.6%, respectively). The mean hemoglobin level was 8.2±2.3 g/dL. The mean leukocyte count was 10.8±4.6 103/µL. The mean thrombocyte count was 168±87 103/µL. The mean C-reactive protein level was 56.6±42.5 mg/L. EBV VCA IgM and IgG antibodies were simultaneously positive in 248 subjects (67.2%) at the time of the first evaluation, while in 121 subjects (32.8%) EVB VCA Ig G antibody was detected 18.3±4.6 days after the initial diagnosis. During the follow-up, 12 (3.2%) subjects were diagnosed with EBV-related hematologic malignancies including leukemia (one acute myeloid and 3 lymphoblastic leukemia cases, 1.1%), lymphoma (five cases, 1.3%) and hemophagocytic syndrome (three cases, 0.8%).

**Conclusions:** In children, infectious mononucleosis can present with a wide range of clinical symptoms besides its classical presentation. In addition to clinical findings, serologic tests are required for definitive diagnosis. In addition, EBV VCA IgG seroconversion is necessary to rule out false positivity. In 3.2% of the cases with unexpected clinical course, EBV-related hematologic malignancies may develop. *(Turk Arch Ped 2012; 47: 187-190)*

**Key words:** Child, EBV, mononucleosis

## Introduction

The seropositivity rate against Epstein-Barr virus (EBV) in the adult age group in the general population is 90-95% in many countries (1). It has been reported that 80-86% of the adults in Turkey are seropositive against EBV (2). IN USA and England, EBV seroconversion occurs before the age of 5 in 50% of the population. This rate increases further in the second decade of life. In populations with low sosioeconomic level and in children living in crowded environments with poor hygiene, the frequency of EBV antibody in the first year of life is higher. Infections related to this virus are usually asemptomatic in the childhood and primary infection is generally asemptomatic until the age of 10. This increases the seropositivity rate in the adult age group. In socioeconomically developed countries, the frequency of primary EBV infection is higher in 15-25 age group and the probability of symptomatic course is higher. Healed infection leaves immunity (3).

Generally, the frequency of infection does not vary with seasons. However, it has been reported to be more frequent in

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spring and autumn months in studies performed in college students (4). Infectious mononucleosis is the primary infection picture and the most common clinical form in children. It is contaminated by oropharyngeal secretion and close contact including mainly kissing. The possibility of transmission of the disease by individuals with acute infectious mononucleosis is high. The virus can be isolated from saliva of these individuals for the first 18 months after the begining of infection. In addition, the virus can be isolated from the nasopharynx in 10-20% of healthy seropositive individuals (5). Cytomegalovirus, rubella, toxoplasma gondii infections and some hematologic malignancies may cause clinical findings similar to EBV infection. Therefore the diagnosis of EBV infection is very important.

In this study, we aimed to examine the clinical and laboratory findings of the patients who were referred to our clinic with different complaints and who were found to have positive EBV VCA IgM and/or IgG antibodies.

## Material and Method

The study was conducted by retrospective evaluation of 369 patients who were found to have positive EBV VCA IgM among 845 patients who presented to İstanbul Medical Faculty, General Pediatrics Outpatient Clinic between January 2004 and December 2009 and in whom EBV VCA IgM and IgG antibodies were tested. Complaints at presentation, prediagnoses and clinical and laboratory findings of the patients included in the study were recorded. Epstein-Barr virus VCA IgM and IgG antibodies were measured using ELISA (EBV VCA IgM and EBV VCA IgG, DIA.PRO Diagnostic Bioprobes Srl Via Carducci n° 27 20099 –Sesto San Giovanni. Milano-Italy). The data were analysed using SPSS 12.00 and Student's t and chi-square methods.

## Results

369 patients with positive EBV IgM antibody were determined between January 2004 and December 2009. 198 of these patients (53.4%) were male and 171 (46.4%) were female. The mean age was 94.5±58.4 months (6 months -14 years). The charactersitics of the patients are shown in Table 1. In 2009, EBV IgM antibody was found to be positive in 109 patients. EBV IgM antibody was ordered because of fever lasting for more than one week and malaise in 159 patients (43.1%), sore throat, fever and swelling in the neck in 122 patients (33.1%), maculopapular rash and fever in 38 patients (10.3%), anemia and thrombocytopenia in 26 patients (7.1%), increased transaminases in 15 patients (4.1%), arthralgia in 6 patients (1.6%) and hemophagocytic syndrome in 3 patients (0.8%). On physical examination, a body temperature of >38.5 °C was found in 357 patients (96.7%), cervical lymphadenopathy was found in 155 patients (42%), petechia in the soft palate and pharyngitis were found in 152 patients (41.2%), splenomegaly was found in 177 patients (47.9%), hepatomegaly was found in 79 patients (21.4%), edema in the eye was found in 65 patients (17.6%) and maculopapular rash and fever were found in 38 patients (10.3%).

Laboratory findings were as follows: mean Hb value: 8.2±2.3 g/dL, mean leucocyte count: 10.8±4.6 103/µL, mean platelet count: 168±87 103/µL. Reactive lymphocytosis was found in 148 patients (40.2%). Bone marrow aspiration was perfomed in 4 patients, because reactive lymphocytosis was found to be >70%. Myeloblasts were found in one of these and lymphoblasts were found in four. Three of these patients were diagnosed as acute lympoblastic leukemia (ALL) and one was diagnosed as acute myeloblastic leukemia (AML). Leukopenia was found in 21 patients (5.6%). In 15 patients (4.1%) who presented with increased transaminases, the mean value of alanine aminotransferase (ALT) was found to be 384.5±45.2 U/L and the mean value of aspartate aminotransferase (AST) was found to be 357.5±46.4 U/L. The mean CRP value was found to be 56.6±42.5 mg/L and the mean sedimentation rate was found to be 96,9±12,3 mm/h in 357 patients with fever.

In the follow-up of the patients, pathologic diagnosis was made in 5 patients (13%) who presented with servical lymphadenopathy, because lymph nodes had pathologic size. Lymphocyte-rich Hodgkin lymphoma was diagnosed in three patients and mixed cellularity Hodgkin lymphoma was diagnosed in two patients. The mean age was found to be 12.4±4.6 months in three (0,8%) patients who were diagnosed as secondary hemophagocytic syndrome. Hypertriglyceridemia (376.2±35.3 mg/dL) and increased ferritin (245±35.6 mg/L) were

**Table 1. General characteristics of the patients (n=369)**

| Characteristics | n (%) |
|---|---|
| **Age (month; mean ± SD)** | 94.5±58.4 |
| **Gender (n; % female)** | 171 (46.3) |
| **Findings at presentation** | |
| Fever (>7 days), malaise, myalgia | 159 (43.1) |
| Fever, exudative tonsillitis, cervical lymphadenopathy | 122 (33.1) |
| Fever, maculopapular rash | 38 (10.3) |
| Anemia, thrombocytopenia | 26 (7.1) |
| Increased ALT and AST | 15 (4.1) |
| Arthralgia | 6 (1.6) |
| Hemophagocytic syndrome | 3 (0.8) |
| **Physical examination findings** | |
| Splenomegaly | 177 (47.9) |
| Hepatomegaly | 79 (21.4) |
| Edema in the eyes | 65 (17.6) |
| **Other diagnoses excluding infectious mononucleosis** | |
| Hepatitis | 15 (4.1) |
| Leukemia | 4 (1.1) |
| Lymphoma | 5 (1.3) |
| Hemophagocytic syndrome | 3 (0.8) |

found in the patients with hemophagocytosis in the bone marrow. While Epstain-Barr virus VCA IgM and IgG were initilally positive in 248 patients (67.2%), only EBV VCA IgM was positive in the other 121 patients (32.8%). In these patients, EBV VCA IgG became positive averagely 18.3±4.6 days later.

## Discussion

The most common complaints observed in patients with infectious mononucleosis at presentation include sore throat and persistent fever. Fever of 38-39°C occurs mostly in the afternoon and even sometimes fever of 40 °C occurs. It generally persists for 10-14 days (4). In the study, fever was present in 96.7% of the patients and sore throat and lympadenopathy were present in more than 40% of the patients which constitute the most important physical examination findings. Lymphadenopathy and splenomagaly accompanying persistent fever may be present in less than half of the patients (5). In our study, splenomegaly was found with a rate of 47.9% and hepatomegaly was found with a rate of 21.4%. Periorbital edema and accompanying retroorbital pain and maculopapular rash were found with a rate of 17.6% and 10.3%, respectively, though they are not very common findings. In publications, periorbital edema which is called "Hoagland's sign" has been reported with a rate of 10-20% and maculopapular rash has been reported with a rate of 3-19% (5). The results of our study were compatible with these data. Although studies have reported that EBV infection is asymptomatic below the age of 10, the mean age in this study was 94.5±58.4 months and the patients had symptoms. Our patients had common findings of infectious mononucleosis including fever, sore throat, cervical lympadenopathy and splenomegaly as well as uncommon findings including hepatomegaly and periorbital edema.

Among laboratory findings, reactive lyumphocytosis is the most common finding. Lymphomonocytosis and 30% atypical lymphocytes develop after the second week of infection. Atypical lymphocytes called virocytes or Downey cells are basophilic cells larger than mature lymphocytes with lobulated and notched nuclei and larger cytoplasm. Atypical lymphocytes are induced cytotoxic T lymphocytes (6,7). Although the mean number of leukocytes was 10.8±4.6 103/µL in our study, reactive lymphocytosis was present in 40,2% of the patients. Therefore, EBV infection should be considered in patients with reactive lymphocytosis despite normal leukocyte count. Malignancy should be explored in patients in whom anemia and thrombocytopenia accompany reactive lymphocytosis (7,8,9). AML was associated with EBV infection in one (0.27%) of the patients with reactive lynphocytosis (>70%) and ALL was associated with EBV infection in three (0.81) in our study. In publications, leukemia associated with EBV infection has been reported with immune deficiencies in limited number of cases (8,9,10). The most distinctive finding in Epstein-Barr virus infections is lymphadenopathy. In our study, a pathologic diagnosis of Hodgkin lymphoma was made in 5 patients with larger lymphadenopathies than expected, presence of lymph nodes packet and no response to antibiotic treatment. The risk of young adult type Hodgkin lymphoma in individuals who have had infectious mononucleosis is three fold higher compared to the general population (11). However, the rate of the picture of Hodgkin lymphoma accompanied by EBV infection which was rare in publications was found with a rate of 1.3% in our study.

Hemophagocytic syndrome is a rare and life-threatening complication of EBV infection (12). It is characterized by fever, hepato-splenomegaly, pancytopenia, diffuse hemophagocytic cells in the bone marrow and disseminated intravascular coagulation. The mortality rate has been reported to be 30-40% (13,14). In our study, a diagnosis of hemophagocytic syndrome associated with EBV was made in three patiens (0.8%). In the intensive care unit, plasmapheresis, IVIG, replacement of coagulation factors and anticoagulant treatment were administered and the disease was treated.

In the early period of infection, leukopenia and normal leukocyte count may be found. In our study, leukopenia was found with a rate of 5,6%. Since the patients presented at later stages, leukocyte counts were found to be mostly normal. Thrombocytopenia observed in Epstain-Barr virus infections may be related to antiplatalet antibodies (IgG) produced against IgM (15). Thrombocytopenia was found only in 4.8% of the patients in our study.

While hepatomegaly is observed in 10-20% of Epstein-Barr virus infections, increased aminotransferase levels are observed with a rate of 80% and clinical jaundice is observed with a rate of 5% (16,17). Hepatic failure reported by Arslan et al. (18) is observed very rarely. In our study, hepatomegaly was found with a rate of 21.4% and increased transaminases in hepatitis picture was found with a rate of 4.1%. Jaundice and hepatic failure were not observed.

The most common laboratory finding used in the diagnosis is EBV VCA IgM and EBV VCA IgG antibody positivity. EBV VCA IgM positivity is valuable for diagnosis. It is important that IgG becomes positive to exclude cross reactions and false positivity (19,20). In our study, EBV VCA IgM and EBV VCA IgG antibodies were initially positive in association in more than half of the patients (67.2%), whereas only EBV VCA IgM antibody was positive in 32.8% of the patients. EBV VCA IgG antibodies became positive 2-3 weeks later in these patients. In all patients, the diagnosis of EBV infection was confirmed with clinical and hematologic findings as well as serologic findings.

Conclusively, infectious mononucleosis can cause different findings other than the classical findings in children. For a definite diagnosis EBV VCA IgM antibodies are valuable, but it is important that EBV VCA IgG becomes positive to exclude false positivity.

**Conflict of interest: None declared.**

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