Primary Epstein-Barr virus infection in 2-year-old children: report of 3 cases

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Some children less than four years old have Epstein-Barr virus (EBV)-induced infectious mononucleosis (IM). Because primary EBV infection in infants and young children is usually asymptomatic or subclinical, EBV infection diagnosis may not be easy among young children. To illustrate the clinical characteristics and diagnostic procedures for EBV infection in young children, the authors report herein three cases of primary EBV infection in two-year-old children with an evaluation of their initial clinical symptoms. The results showed that the common initial clinical manifestations are puffy eyelids and hepatosplenomegaly, and that these signs suggest a tentative diagnosis of IM. In conclusion, EBV capsid immunoglobulin (Ig)M antibodies and atypical lymphocytes are useful diagnostic measurements in very young children with symptoms suggestive of IM.

Key words: Epstein-Barr virus, primary infectious mononucleosis, diagnosis, children.

A large number of children less than four years old have primary Epstein-Barr virus (EBV) infection. The age of primary infection is becoming later in childhood, and the incidence in 5- to 7-year-old children was estimated as <50% in 2006[1]. Therefore, misdiagnosis is common in young children, because their clinical manifestations are usually subclinical and asymptomatic. Moreover, the intensity of the characteristic relatively atypical lymphocytosis found in peripheral blood is age-related, being less in the very young. Fortunately, measuring EBV-specific immunoglobulin (Ig)M antibodies in order to diagnose IM in early childhood does not exhibit any disparity in this age group.

Primary infection with EBV is mostly asymptomatic in young children, especially before five years of age. Infectious mononucleosis (IM) manifests in about 50% of teenagers and young adults, with fever, sore throat, generalized lymphadenopathy, frequently with hepatosplenomegaly, and lymphocytosis with characteristic atypical lymphocytes[2,3]. To diagnose EBV infection, the Paul-Bunnell-Davidsohn test is often negative, especially in young children; therefore, priority should be given to virology tests based on the detection of specific antibodies to EBV antigen[4]. To fulfill the serologic criteria for the diagnosis of primary EBV infection, children should present with viral capsid antigen (VCA) IgM positive, VCA IgG positive, and Epstein-Barr nuclear antigen-1 (EBNA-1) negative[5].

Case Reports

Case 1

A two-year-old boy was brought to our outpatient clinic because of fever and swelling of his eyelids. He was admitted to the hospital for further evaluation. His temperature was 38.8°C. He had no history of drug or food allergies and no history of trauma. His history was unremarkable and his vaccinations were current. He had traveled to the island of Bali about two weeks before being admitted.

On physical examination, the patient was alert, and his ears and nose were grossly normal, but he had periorbital edema and a slightly injected throat. There were a few pea-sized

lymph nodes on both sides of his neck. His lungs were clear on auscultation and cardiac examination was normal without any murmurs. However, his liver was palpable 2 cm below the right costal margin. Splenomegaly was also found, and both enlargements were confirmed by abdominal echography.

Laboratory data showed peripheral blood lymphocytosis (white blood cell count 15 x $10^3/\mu L$, lymphocytes 73%) with atypical lymphocytes 20%. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were increased up to 357 U/L and 314 U/L, respectively (AST, 1-9 yrs: 15-55 U/L; ALT, 1-19 yrs: 5-45 U/L). Urinalysis, electrolytes and kidney function were normal. There was no growth in blood culture. Both VCA IgM and IgG were positive and EBNA-1 was negative. Therefore, IM was confirmed and supportive treatment was given. The patient was discharged after nine hospitalization days.

Case 2

A 13-month-old boy had productive cough for three weeks. He was treated as acute bronchiolitis in an outpatient clinic for one week, but coughing and intermittent fever persisted. Therefore, he was admitted to the hospital for further evaluation and management.

The patient had been admitted to the hospital previously with a diagnosis of acute bronchiolitis at the age of six months. During the current admission, the patient was alert but ill-looking. Ears and nose were grossly normal. Puffy eyelids and slightly injected throat were noted. No neck lymphadenopathy was found. His chest was expanded and symmetrical, and coarse breathing sounds with fine rales were audible. Bronchopneumonia was confirmed by a plain chest film. Heart sounds were regular and without murmur. Liver and spleen were palpable, and hepatosplenomegaly was confirmed by abdominal echography.

Laboratory findings showed peripheral blood lymphocytosis (white blood cell count 15 x $10^3/\mu L$, lymphocytes 65%) with atypical lymphocytes 17%. Abnormal liver enzymes were also noted: AST 45 U/L, ALT 26 U/L, and lactate dehydrogenase (LDH) 1406 U/L (LDH, 1-9 yrs: 150-500 U/L). The VCA IgM and IgG were positive, and EBNA-1 was negative. Thus, IM complicated with pneumonia was confirmed and empirical antibiotic was given. The patient was discharged after one week of hospitalization.

Case 3

A two-year-old girl had lethargy and fever up to 38.5°C for four days. This was followed by bilateral puffy eyelids the next day, and she was admitted to the hospital via emergency service.

She had no history of drug allergy, no recent travel, and her vaccinations were on schedule. On physical examination, she was alert and well developed. The patient's ears and nose were grossly normal, but periorbital edema and a mild throat infection were noted. Multiple pea-sized lymph nodes were palpable over the submandibular and occipital area. Her chest was symmetrical with clear breath sounds. Heart sounds were regular without murmur. The liver was palpable 3 cm below the right costal margin, and the spleen was palpable 1.5 cm below the left costal margin. Hepatosplenomegaly was confirmed by abdominal echography. Moreover, she had peripheral blood lymphocytosis (white blood cell count 12 x $10^3/\mu L$, lymphocytes 80%) with atypical lymphocytes 22%. Serologic tests were positive for VCA IgM and IgG and negative for EBNA-1. IM was diagnosed, supportive treatment was given, and the patient was discharged on the 5^{th} hospitalization day.

Discussion

Epstein-Barr virus is a gamma-herpes virus that generally spreads to and between young children through salivary contact. It causes clinical illness only when primary infection is delayed until adolescence or beyond, when an intense immunopathological reaction leads to the symptoms of IM in roughly 50% of infections[6]. The spectrum of clinical manifestations associated with EBV infection is large and continues to expand, including increasing atypical presentation[2]. An unexpected finding was the large number of young children with this disease, who were less than four years old and always asymptomatic[7,8]. However, there are geographic variations in occurrence. Most of the children in Asia and in other

developing countries are infected before one year of age (>90% of 5- to 9-year-old children are infected), while the age of primary infection is delayed in Western countries (50% of 5- to 9-year-old children are infected). Furthermore, the age of primary infection continues to extend to later in life[1].

Infectious mononucleosis (IM) is the prototypical manifestation of primary infection with EBV[9]. Its peak incidence occurs in adolescents and young adults 15 to 19 years of age[10]. The clinical picture of IM includes fever, pharyngitis, malaise, fatigue, lymphadenopathy, and splenomegaly with atypical lymphocytosis; however, it is often asymptomatic or subclinical in the younger age group. Cheng et al.[11] found that the younger age group (<3 years) had a higher monocyte count, lower occurrence of hepatitis, and lower ALT and AST than the older age group. They also suggested that quantitative real-time polymerase chain reaction (PCR) of EBV DNA is useful for diagnosing and monitoring EBV-associated IM in younger children[11].

The rate of heterophil antibody responses appears to increase progressively with advancing age from infancy up to four years, after which the rates approach values similar to those reported in young adult patients[12]. VCA IgM is the most reliable serological marker of primary EBV infection, although it can be detected in only limited cases in children. Moreover, two peaks were found in an age-distribution graph of VCA IgM-positive specimens. Boys outnumbered girls in children up to three years of age, and vice versa in those 15 to 25 years old[13]. Serodiagnosis by a combination of ELISA for early antigen (EA) IgM and EBNA-1 IgG was more easily detected in infants and young children, and it was more sensitive than immunofluorescence methods[14]. The presence of VCA IgG in the absence of VCA IgM and EBNA-1 IgG antibodies makes classifying EBV infection more difficult, because this serological picture can be seen in past infections when EBNA-1 IgG did not appear or was lost, or in acute infections with early disappearance or delayed onset of VCA IgM[15]. De Paschale et al.[15] also stated that the presence of isolated VCA IgG was usually associated with past infection, particularly in adults, but it may be present in about one-third of children.

An atypical lymphocytosis of at least 20% or atypical lymphocytosis of at least 10% plus lymphocytosis of at least 50% strongly supports the diagnosis of IM[16]. Clinically, for diagnosis of primary EBV infection, patients should fulfill the serologic criteria that VCA IgM and IgG are positive and EBNA-1 is negative[5].

In our cases, puffy eyelids and hepatosplenomegaly were the most common initial symptoms, while throat infection, lymphadenopathy and skin rash were not obviously present. The serological findings and peripheral blood analysis did meet the IM diagnostic criteria. The liver enzymes ALT, AST and LDH may be increased. Finally, it should be kept in mind that CMV infection might mimic EBV-induced IM in the youngest.

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