# Epidemiologic and clinical characteristics of infectious mononucleosis associated with Epstein-Barr virus infection in children in Beijing, China

**Li-Wei Gao, Zheng-De Xie, Ya-Yi Liu, Yan Wang, Kun-Ling Shen**
*Beijing, China*

***Background:*** **Infectious mononucleosis (IM) is a self-limited disease, but a few cases may have severe complications. This retrospective study was to explore the epidemiologic and clinical characteristics of IM associated with Epstein-Barr virus infection (EBV-IM) in children.**

***Methods:*** **Hospitalized patients with EBV-IM were enrolled during January 2005 to October 2008 in Beijing Children's Hospital Affiliated to Capital Medical University. All patients were divided into four groups: <1 year (group I), 1 to 3 years (group II), 3 to 6 years (group III), and ≥6 years (group IV). The epidemiology and clinical characteristics were compared among the four groups.**

***Results:*** **Totally 418 patients were enrolled, with 245 boys and 173 girls. Fever, lymphadenopathy and pharyngitis were three main manifestations of the patients. The incidences of hepatomegaly, splenomegaly and rash were higher in the patients aged below 6 years, and with age increment the incidences lowered. In contrast, the patients aged <1 year had the lowest incidence of tonsillopharyngitis. The total white blood cell count was higher in the infantile group than in the other groups (*P*=0.038). The infantile group had significantly lower levels of serum alanine aminotransferase and aspartate aminotransferase than the older groups (*P*=0.007 and *P*=0.012 respectively). The percentage of $CD4^+$ T cell subset decreased and the percentage of $CD8^+$ T cell subset increased with age increment.**

***Conclusions:*** **The incidence of EBV-IM peaked in children at age of 4 to 6 years in Northern China. Most of the patients had the classic triad of fever, lymphadenopathy and pharyngitis. Clinical symptoms, signs, laboratory findings and complications of patients varied with ages.**

***World J Pediatr 2011;7(1):45-49***

***Key words:*** **children;**
**Epstein-Barr virus;**
**infectious mononucleosis**

Original article

## Introduction

Epstein-Barr virus (EBV) is a virus of the human herpes family, discovered by electron microscopy of cells cultured from Burkitt's lymphoma tissue by Epstein and Barr in 1964.[1] It was shown to be the etiologic agent of infectious mononucleosis (IM) in 1968. Although over 90% of people are infected by this virus, most of them are asymptomatic, especially infants and children less than 6 years old. About 25%-30%[2] of primary infection in adolescents and adults result in IM which is characterized by fever, lymphadenopathy, and pharyngitis. A study[3] in 1994 revealed that in China the seroprevalence of antibodies to EBV rose rapidly between 1 and 6 years, reaching 80% by 6 years and nearly all children had seroconverted by 10 years. Chan and Tsai et al[4,5] reported the clinical characteristics of Chinese children with EBV-IM in Hong Kong and Taiwan of China in 2003 and 2005 respectively, showing the differences of infectious mononucleosis associated with Epstein-Barr virus infection (EBV-IM) between China and western countries. But the spectrum of clinical manifestations and laboratory findings of primary EBV infection is not reported systematically in the mainland of China despite early seroconversion against the virus. The present study was undertaken to investigate the epidemiologic and clinical features of a large number of children with EBV-IM in North China.

**Author Affiliations:** Department of Pulmonary and Infectious Diseases, Beijing Children's Hospital affiliated to Capital Medical University, Beijing, China (Gao LW, Shen KL); Department of Virology Laboratory, Beijing Children's Hospital affiliated to Capital Medical University, Beijing, China (Xie ZD, Liu YY, Wang Y)

**Corresponding Author:** Prof. Kun-Ling Shen, Department of Pulmonary and Infectious Diseases, Beijing Children's Hospital affiliated to Capital Medical University, Beijing 100045, China (Email: kunlingshen@hotmail.com)

doi:10.1007/s12519-011-0244-1

## Methods

### Patients

Hospitalized patients with EBV-IM less than 18 years old treated during January 2005 to October 2008 in Beijing Children's Hospital Affiliated to Capital Medical University were retrospectively reviewed. All of them had been treated with ganciclovir conventionally. They were all Chinese from North China and assigned into four age groups: <1 year (group I), 1 to 3 years (group II), 3 to 6 years (group III), and more than or equal to 6 years (group IV).

Collected information included (1) demographic features of the patients; (2) clinical features: peak temperature, fever duration, lymphadenopathy, hepatomegaly and splenomegaly, complications of the heart, and neurological and hematological findings; (3) laboratory findings: whole blood cell, liver function, cardiac enzymes, $CD4^+$ and $CD8^+$ T cells subsets, and chest X-ray.

### Diagnostic criteria of EBV IM[4,5]

We screened 438 hospitalized patients with EBV-IM, and 418 of them met the diagnostic criteria as follows: (1) presence of at least three of the following clinical manifestations: fever, tonsillopharyngitis, cervical lymphadenopathy, hepatomegaly or splenomegaly; (2) serologic profile of primary EBV infection: IgM to EBV viral capsid antigen (VCA-IgM) and IgG to EBV capsid antigen (VCA-IgG) were positive, with absence of an antibody to Epstein-Barr nuclear antigen (EBNA).

### Complications

Complications were defined as follows: (1) pneumonia: parenchymal and interstitial impairments according to X-ray; (2) thrombocytopenia: thrombocyte $<100\times10^9$/L; (3) neutropenia: neutrophil $<1.5\times10^9$/L; (4) hemophagocytic lymphohistiocytosis (HLH), with which the patient must be EBV-positive and with 5 of the 8 clinical features including fever, splenomegaly, cytopenias, hypertriglyceridemia and/or hypofibrinogenemia, hemophagocytosis in the bone marrow or spleen or lymph nodes, no evidence of malignancy, low or absent NK-cell activity, ferritin ≥500 mg/L, soluble CD25 reported by Henter et al;[6] and (5) other complications: neurological involvement such as seizure or encephalitis.

### Statistical analysis

Statistical analysis was performed with the statistical package of SPSS 11.5 for windows. Measurement data were analyzed using analysis of variance, and enumeration data by the Chi-square test. All tests were two tailed and $P<0.05$ was considered statistically significant.

## Results

### Demographic features of patients

In the 418 hospitalized patients enrolled in this study, 245 were male and 173 female, with a male-to-female ratio of 1.4:1. Their median age was 6 years, ranging from 8 months to 17 years, with the peak age of 4 to 6 years. The age distribution of these patients is shown in Fig., i.e., 1.4% (6) of the 418 patients <1 years (group I), 12.9% (54) were between 1 and 3 years (group II), 34.9% (146) patients were between 3 and 6 years (group III), and 50.7% (212) were ≥6 years (group IV).

### Clinical features

Of the 418 patients with EBV-IM, 75.6% (320) had fever, lymphadenopathy, and pharyngitis. Overall 386 (92.3%) children had fever (with temperature above 37.3°C) on admission, and the mean peak temperature was (38.6±0.7)°C (range: 37.3-41.2°C) and the mean duration of fever was (12.1±7.6) days. The incidences of tonsillopharyngitis and cervical lymphadenopathy were 83.5% (349) and 95% (397) respectively. Splenomegaly (subcostal 1-3 cm) and hepatomegaly (subcostal 1-4 cm) were seen in 47.4% (198) and 58.1% (243) of the patients, respectively. Cutaneous rashes

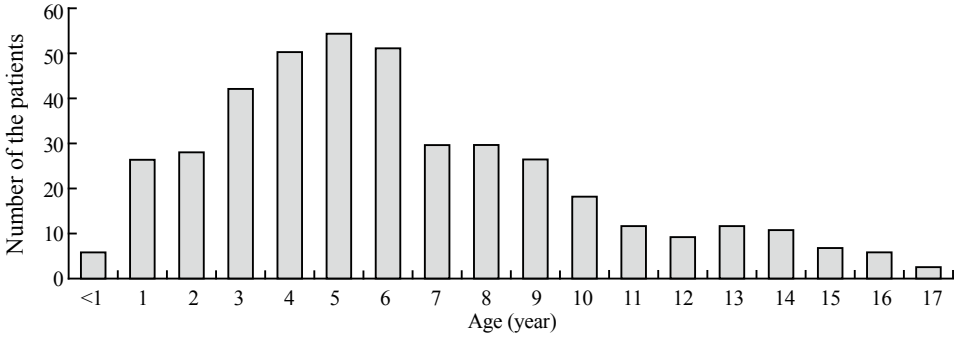


**Fig.** Age distribution of the 418 patients with infectious mononucleosis associated with Epstein-Barr virus infection.

were detected in 62 (14.8%) patients, predominantly maculopapular, of whom 21 did not receive antibiotics before the appearance of skin rash. Eyelid edema was detected in 48 patients (11.5%).

There were significant differences in clinical features among the four groups, such as tonsillopharygitis, hepatomegaly, splenomegaly and rash (Table 1). The incidences of hepatomegaly, splenomegaly and rash were higher in younger patients, and with age increment, the incidence became lower. In contrast, the patients in the group of <1 year had the lowest incidence of tonsillopharyngitis.

### Laboratory findings

White blood cell (WBC) count ranged from $2.4\times10^9$/L to $52.8\times10^9$/L [mean: $(13.6\pm7.4)\times10^9$/L], with leukocytosis (WBC>$10\times10^9$/L) in 67.5% (282) of the patients, and higher total WBC was more common in infants than in older children ($P$=0.038) (Table 2). Neutropenia was detected in 18 (4.3%) patients with a mean count of $(1.38\pm0.42)\times10^9$/L. The incidence of atypical-lymphocyte (>10%) was 51.9% (206/397), with no difference among the four groups ($P$=0.223). Thrombocytopenia was noted in 5.0% (21) of the 418 patients, and one of these patients presented with intracranial hemorrhage (lowest platelet count, $3.8\times10^9$/L).

Alanine aminotransferase (ALT) (normal range 0-35 IU/L) and aspartate aminotransferase (AST) (normal range 0-35 IU/L) were the two main indexes of liver dysfunction. The elevated levels of ALT and AST were noted in 48.6% (203) of the 418 patients, with the ALT level ranging from 7.0 to 12 248 IU/L (mean: 8.9±111.0) and AST ranging from 13.0 to 429 IU/L (mean: 71.1±57.8). The data revealed that serum ALT and AST values were significantly lower in infants than in children of older age groups, with increasing trend of elevated liver transaminases ($P$=0.007, 0.012) (Table 2). Creatine kinase-MB (CK-MB) rose slightly in the 4 groups and the values of CK-MB became lower with age increment, which may be related to the time of specimen collection and the number of patients in different groups. The percentages of $CD4^+$ and $CD8^+$ lymphocytes were both normal in the <1 year group. But in the group II to IV the percentage of $CD4^+$ T cell subset decreased and the percentage of $CD8^+$ T cell subset increased with age increment.

### Complications and prognosis

The total incidence of complications was 16.5% (69) in all 418 patients. The main complications included pneumonia, thrombocytopenia, neutropenia, and hematologic system problems (Table 3). Pneumonia was the most common complication found in 59

**Table 1.** Clinical features of hospitalized children with Epstein-Barr virus-associated infectious mononucleosis in age groups

| Characteristics | <1 y ($N$=6) (%) | 1-3 y ($N$=54) (%) | 3-6 y ($N$=146) (%) | >6 y ($N$=212) (%) | $P$ |
|---|---|---|---|---|---|
| Fever | 6 (100) | 47 (87.0) | 137 (93.8) | 196 (92.5) | 0.375 |
| Cervical lymphadenopathy | 5 (83.3) | 48 (88.9) | 141 (96.6) | 203 (95.8) | 0.074 |
| Tonsillopharyngitis | 1 (16.7) | 40 (74.1) | 123 (84.2) | 185 (87.3) | <0.001* |
| Hepatomegaly | 5 (83.3) | 39 (72.2) | 100 (68.5) | 98 (46.2) | <0.001 |
| Splenomegaly | 3 (50.0) | 31 (57.4) | 89 (61.0) | 75 (35.4) | <0.001 |
| Rash | 4 (66.7) | 14 (25.9) | 17 (11.6) | 27 (12.7) | <0.001† |
| Puffy eyelid | 0 (0.0) | 9 (16.7) | 19 (13.0) | 20 (9.4) | 0.345 |

$P$ values determined with the Chi-square test. *: $P$<0.001 for all of the four groups, but $P$=0.057 for the last three groups; †: $P$<0.001 for all of the four groups, but $P$=0.026 for the last three groups.

**Table 2.** Laboratory findings (mean±SD) of the patients in the four age groups

| Characteristics | <1 y | 1-3 y | 3-6 y | >6 y | $P$ |
|---|---|---|---|---|---|
| WBC ($10^9$/L) | 16.4±12.4 | 14.6±8.1 | 14.5±7.9 | 12.5±6.6 | 0.038 |
| Lymphocyte (%) | 58.2±17.8 | 64.6±14.4 | 61.7±12.9 | 60.7±14.9 | 0.324 |
| PLT ($10^9$/L) | 270.2±123 | 225.8±114.7 | 221.4±83.6 | 221.9±95.7 | 0.660 |
| Atypical-lymphocyte (%) | 12.2±10.5 | 11.6±11.9 | 11.5±10.8 | 14.1±13.7 | 0.223 |
| ALT (IU/L) | 67.7±35.6 | 96.1±58.5 | 64.3±38.3 | 104.7±68.7 | 0.007 |
| AST (IU/L) | 49.0±12.1 | 70.9±43.0 | 59.8±34.7 | 79.5±53.6 | 0.012 |
| CK-MB (IU/L) | 20.9±7.5 | 15.5±6.9 | 12.3±6.2 | 9.5±3.7 | <0.001 |
| $CD4^+$ (%) | 37.4±11.0 | 24.7±9.0 | 19.5±9.7 | 19.3±12.0 | 0.002 |
| $CD8^+$ (%) | 28.2±6.3 | 46.9±14.4 | 57.3±17.0 | 56.7±16.2 | <0.001 |
| $CD4^+/CD8^+$ | 1.4±0.4 | 0.6±0.4 | 0.4±0.3 | 0.4±0.3 | 0.032 |

$P$ values determined with ANOVA. WBC: white blood cell; PLT: platelet; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK-MB: creatine kinase-MB.

**Table 3.** Complications of patients with Epstein-Barr virus-associated infectious mononucleosis in the four age groups

| Complications | Total frequency (%) | <1 y (*N*=6) (%) | 1-3 y (*N*=54) (%) | 3-6 y (*N*=146) (%) | ≥6 y (*N*=212) (%) | *P* |
|---|---|---|---|---|---|---|
| Pneumonia | 59 (14.1) | | | | | |
| Parenchyma | 49 (11.7) | 3 (50.0) | 9 (16.7) | 22 (15.1) | 15 (7.1) | 0.001* |
| Interstitium | 13 (3.1) | 0 (0.0) | 3 (5.6) | 6 (4.1) | 4 (1.9) | 0.428 |
| Thrombocytopenia | 21 (5.0) | 1 (16.7) | 6 (11.1) | 3 (2.1) | 11 (5.2) | 0.035 |
| Neutropenia | 18 (4.3) | 0 (0.0) | 3 (5.6) | 5 (3.4) | 10 (4.7) | 0.893 |
| Hemophagocytic syndrome | 3 (1.3) | 2 (33.3) | 1 (1.9) | 0 (0.0) | 0 (0.0) | - |

*P* values determined with the Chi-square test. *: *P*=0.001 for all of the four groups, but *P*=0.024 for the last three groups.

(14.1%) of the 418 patients, including the pathological changes of lung parenchyma and interstitium. The incidence of pneumonia with parenchymal damage decreased with age increment. Among the patients with pneumonia, 16.9% (10/59) were infected with streptococcus concurrently. Three patients were complicated with HLH with an age of 11 months, 2 years and 3 years respectively, and manifested with prolonged fever, hepatosplenomegaly, pancytopenia and hemophagocytosis in the bone marrow. One patient involved in the central nervous system and presented seizure and conscious disturbance. All of the patients were treated with supportive therapy and antiviral medication, such as ganciclovir. More than 98% (410/418) of the patients were benign and self-limited, but 8 patients were discharged against the doctors' advice. Intravenous immunoglobulin and corticosteroids were administered to 3 patients with HLH, with satisfactory results.

## Discussion

IM is a benign lymphoproliferative disease caused by EBV.[1] In developed countries, it often occurs in adolescents and young adults between 10 and 30 years of age.[7] But in the present study the peak incidence occurred at age of 4 to 6 years, which is consistent with that in Chinese children with EBV-IM reported by Chan and Tsai.[4,5] These differences may be related to life style, population density, and levels of hygiene.[8] In this study, EBV-IM occurred all over the year and peaked in autumn, but the incidence of EBV-IM decreased from 2005 to 2008, which may be due to the socioeconomic development and the improvement of living standard in China.

IM is recognized as the typical clinical syndrome of primary EBV infection, which presents with fever, pharyngitis, cervical adenopathy, and other various manifestations.[9,10] In our study, 75.6% of the patients with EBV-IM presented with fever, lymphadenopathy, and pharyngitis, which are consistent with the reported results from China and other countries.[11] Previous studies[4,5] have reported that clinical manifestations varied in different age groups, and in this study the incidences of hepatomegaly, splenomegaly and rash were higher in the infantile group than in the older groups, while tonsillopharyngitis showed an incidence conversely.

WBC in all of the patients with EBV-IM was raised, and the higher total WBC was more common in infants than in older children. The appearence of atypical lymphocytes in peripheral blood is another feature of patients with EBV-IM.[12] Although the atypical lymphocyte may be seen in many infectious diseases in peripheral blood, it could be supportive of EBV infection, especially in western countries.[5] In this study, however, the incidence of significant atypical lymphocytosis (>10%) was only 51.9%, which is similar to that (41.8%) reported by Tsai et al.[5] Because there is no difference in the incidence of atypical lymphocyte among the 4 groups, the diagnostic value of atypical lymphocyte finding in peripheral blood in patients less than 6 years old is limited. ALT and AST are the main indexes of liver dysfunction and the mean levels of ALT and AST are significantly increased from infants to adolescents.[13] In our study, infants had significantly lower serum ALT and AST levels than children of older age, even though hepatomegaly and splenomegaly were more common in younger children. This may be relevant to the mature degree of immune system.[14] A previous study[15] reported that CK-MB in older children rose significantly, but in the present study, it increased slightly and became lower with age increasing. It may be relevant to the number of patients in different groups and the younger patients with EBV-HLH which can cause multi-organ damage such as heart injury.

Primary EBV infection targets B cells and is accompanied by a prominent reactive expansion of T cells, especially $CD8^+$ T-cell subset. In the present study, the frequency of $CD8^+$ T-cell subset elevated obviously, and $CD8^+$ T-cell subset was higher in older than in younger children. This may be related to the degree of maturity of the immune system in children and can explain why liver function impairments are more common in older children. Williams et al[16] also

indicated that the variability in clinical features of IM directly related to the level of T cell activation, which, in turn, related to the number of EBV-infected B cells in the circulation.

Even though the majority of patients with EBV-IM documented a benign, self-limiting course and favorable prognosis, the incidence of complications in our study was 16.5%, similar to that reported by Chan and Tsai. But a previous study[17] on children in the mainland of China revealed that the incidence of complications can reach 80%. In the present study, pneumonia was the most common complication, and others such as thrombocytopenia, neutropenia, hematologic system problems and neurologic complications were also seen. The incidences of pneumonia with parenchymal damage and thrombocytopenia were higher in young children, and decreased with age increment in contrast to previous studies of Zhao et al[18] and Grotto et al[19] which showed parenchymal damage and thrombocytopenia were more common in older children. It may be due to the age of the patients, in which young infants predominated.

In conclusion, hospitalized patients with EBV-IM in Northern China were mainly preschool children, especially those between 4 and 6 years old. Most of the patients had fever, lymphadenopathy and pharyngitis. Clinical symptoms, signs, laboratory findings and complications of patients varied with age, but the prognosis is favorable. We should pay much attention to the severe cases and their follow-up in the future practice.

**Funding:** This study was supported by the Science and Technology Project of Bejing, China (Z0005190042511).
**Ethical approval:** This study was approved by the Ethics Committee of Beijing Children's Hospital, China.
**Competing interest:** None declared.
**Contributors:** Gao LW designed the study, performed the experiment and wrote the paper. Xie ZD and Shen KL supervised the study and revised the paper. Liu YY and Wang Y collected part of specimens and helped to do the experiment.

## References

1 Cohen JI. Epstein-Barr virus infection. N Engl J Med 2000;343:481-492.
2 Hallee TJ, Evans AS, Niederman JC, Brooks CM, Voegtly H. Infectious mononucleosis at the United States Military Academy. A prospective study of a single class over four years. Yale J Biol Med 1974;47:182-195.
3 Kangro HO, Osman HK, Lau YL, Heath RB, Yeung CY, Ng MH. Seroprevalence of antibodies to human herpesviruses in England and Hong Kong. J Med Virol 1994;43:91-96.
4 Chan CW, Chiang AK, Chan KH, Lau AS. Epstein-Barr virus-associated infectious mononucleosis in Chinese children. Pediatr Infect Dis J 2003;22:974-978.
5 Tsai MH, Hsu CY, Yen MH, Yan DC, Chiu CH, Huang YC, et al. Epstein-Barr virus-associated infectious mononucleosis and risk factor analysis for complications in hospitalized children. J Microbiol Immunol Infect 2005;38:255-261.
6 Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-131.
7 Moffat LE. Infectious mononucleosis. Prim Care Update Ob Gyns 2001;8:73-77.
8 Papesch M, Watkins R. Epstein-Barr virus infectious mononucleosis. Clin Otolaryngol Allied Sci 2001;26:3-8.
9 Williams H, Crawford DH. Epstein-Barr virus: the impact of scientific advances on clinical practice. Blood 2006;107:862-864.
10 Balfour HH Jr, Holman CJ, Hokanson KM, Lelonek MM, Giesbrecht JE, White DR, et al. A prospective clinical study of Epstein-Barr virus and host interactions during acute infectious mononucleosis. J Infect Dis 2005;192:1505-1512.
11 Cheng CC, Chang LY, Shao PL, Lee PI, Chen JM, Lu CY, et al. Clinical manifestations and quantitative analysis of virus load in Taiwanese children with Epstein-Barr virus-associated infectious mononucleosis. J Microbiol Immunol Infect 2007;40:216-221.
12 Hu L, Yang J, Cui T, Xing H, Cai P. Diagnosis of infectious mononucleosis by combined detection of atypical lymphocytes and transaminase. J Huazhong Univ Sci Technolog Med Sci 2006;26:384-385.
13 Doğan I, Ergün M, Cindoruk M, Unal S. Acute hepatitis induced by Epstein-Barr virus infection: a case report. Turk J Gastroenterol 2007;18:119-121.
14 Celtik C, Kucukugu Y, Balci DB, Oner N, Duran R, Karasalihoglu S. Evaluation of clinical and laboratory features of Epstein-Barr virus-associated acute infectious mononucleosis in children. Trakay Univ Tip Fak Derg 2008;25:221-227.
15 Ishikawa T, Zhu BL, Li DR, Zhao D, Maeda H. Epstein-Barr virus myocarditis as a cause of sudden death: two autopsy cases. Int J Legal Med 2005;119:231-235.
16 Williams H, Macsween K, McAulay K, Higgins C, Harrison N, Swerdlow A, et al. Analysis of immune activation and clinical events in acute infectious mononucleosis. J Infect Dis 2004;190:63-71.
17 Jenson HB. Acute complications of Epstein-Barr virus infectious mononucleosis. Curr Opin Pediatr 2000;12:263-268.
18 Zhao F, Peng H, Zeng B. Clinical analysis of infectious mononucleosis children with different ages. Clin J General Pract 2008;6:1133-1134.
19 Grotto I, Mimouni D, Huerta M, Mimouni M, Cohen D, Robin G, et al. Clinical and laboratory presentation of EBV positive infectious mononucleosis in young adults. Epidemiol Infect 2003;131:683-689.

*Received February 26, 2010*
*Accepted after revision June 7, 2010*