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Epstein-Barr virus-associated infectious mononucleosis and risk factor analysis for complications in hospitalized children

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The characteristics of Epstein-Barr virus (EBV)-associated infectious mononucleosis (IM) in Chinese children are rarely reported. To evaluate the clinical presentations and risk factors for complications of EBV-associated IM in previously healthy children in Taiwan, hospitalized children with the diagnosis of IM due to EBV infection from January 1998 to December 2002 were enrolled. Patients had to fulfill the serologic criteria for the diagnosis of primary EBV infection [viral capsid antigen immunoglobulin M (IgM)-(+), viral capsid antigen IgG-(+), and anti-Epstein-Barr nuclear antigen (EBNA) antibody-(–) with exclusion of other concurrent infections or underlying diseases]. Ninety eight children were eligible, with 79% younger than 5 years old (mean, 4.0 ± 2.3 years). The male-to-female ratio was 2:1. Nearly all patients suffered from fever (mean duration 10.3 ± 6.0 days). Cough/rhinorrhea, tonsillopharyngitis, cervical lymphadenopathy and hepatosplenomegaly were found over half of the patients. Atypical lymphocytosis (mean, 12 ± 13%) and elevated serum aspartate aminotransferase (AST; mean, 167 ± 183 IU/L) and alanine aminotransferase (mean, 221 ± 222 IU/L) were the most striking laboratory findings. Various complications, including hematologic, hepatobiliary, central nervous system, and obstructive airway problems occurred in about 20% of patients with significantly prolonged course of hospitalization. All patients recovered uneventfully under supportive and immunomodulating management. Female gender, no signs of tonsillopharyngitis, white blood cell count ≤10,000/mm^3 and AST ≥150 IU/L were significant risk factors for the occurrence of complications. Clinicians should monitor such patients closely and give proper treatment to decrease possible morbidity or even mortality should complications occur.

Key words: Epstein-Barr virus infections, infectious mononucleosis, prognosis, risk factors

Epstein-Barr virus (EBV) is a member of the human herpesvirus family with seroprevalence over 90% in developing countries [1]. Its clinical manifestations vary in different countries, cultures and socioeconomic settings. Previous investigations revealed that in poor urban settings or developing countries, 80-100% of children were seropositive by 3 to 6 years of age; however, in economically privileged communities and developed countries, it often occurs between the ages of 10 and 30 years [2-4].

Infectious mononucleosis (IM), a benign lymphoproliferative disease, is the best-known clinical syndrome caused by EBV [5]. Unlike cases with primary EBV infection (being generally largely asymptomatic), those with IM usually suffer from prolonged fever, and a few complications such as hematologic disorders and airway obstruction causing morbidity or even mortality may occur during the course of IM due to EBV infection [6,7].

In the present study, we undertook a retrospective review and analysis of clinical manifestations, laboratory features and outcomes of hospitalized children with IM due to primary EBV infection in our institution. We also sought to determine the possible risk factors for the occurrence of complications.

Materials and Methods

Patients and case definition

We collected information retrospectively on hospitalized children who were younger than 18 years old and admitted to a private tertiary Children's Hospital with the main diagnosis of IM due to primary EBV infection between January 1998 and December 2002. The accurate

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diagnosis was proved by: (1) presence of at least 3 of the clinical symptoms of fever, tonsillopharyngitis, cervical lymphadenopathy, hepatomegaly or splenomegaly; and (2) serologic profile of primary EBV infection: presence of immunoglobulin M (IgM) antibody to EBV viral capsid antigen (VCA-IgM) and IgG antibody to EBV VCA (VCA-IgG) concurrent with absence of anti-Epstein-Barr nuclear antigen (EBNA) antibody. Complications were defined as follows: (1) hematologic problems: profound leukopenia [white blood cell (WBC) count <1500/mm^3], anemia (hemoglobin <9 g/dL) or thrombocytopenia (platelets <100,000/mm^3); (2) upper airway obstruction: presence of dyspnea or stridor; (3) liver function impairments: ascites, hypoalbuminemia (albumin <2.5 g/dL), or hyperbilirubinemia (total bilirubin >2 g/dL); or (4) other major organ involvements (i.e., central nervous system (CNS) involvement such as seizure or encephalitis) [6,7]. Patients who had major underlying diseases such as congenital heart disease, oncologic disease or immunodeficiency, or had a concurrent infection were excluded. Demographic features, clinical manifestations, laboratory data, and risk factors associated with complications among these patients were reviewed and analyzed.

Statistics

Statistical analysis was performed by use of the Statistical Package for the Social Sciences software package (version 11.0). Mann-Whitney test and Fisher's exact test were used to analyze clinical features and laboratory findings between patients with and without complications. The cut-off points of the continuous variables with significance were calculated by receiver operating characteristic curves. The odds ratio was calculated by univariate logistic regression, and multivariate logistic regression was also performed using forward stepwise selection of the significant variables. A *p* value of less than 0.05 was considered statistically significant.

Results

Demographic features of patients with EBV-associated infectious mononucleosis

Ninety eight patients were eligible for this study. There were 65 males and 33 females, with a male-to-female ratio of 2:1. Age ranged from 1.0 to 16.0 years, with a mean of 4.0 ± 2.3 years. The age distribution of these patients is shown in Fig. 1. Seventy nine percent of patients developed infection before 5 years of age, and nearly 60% before 4 years old.

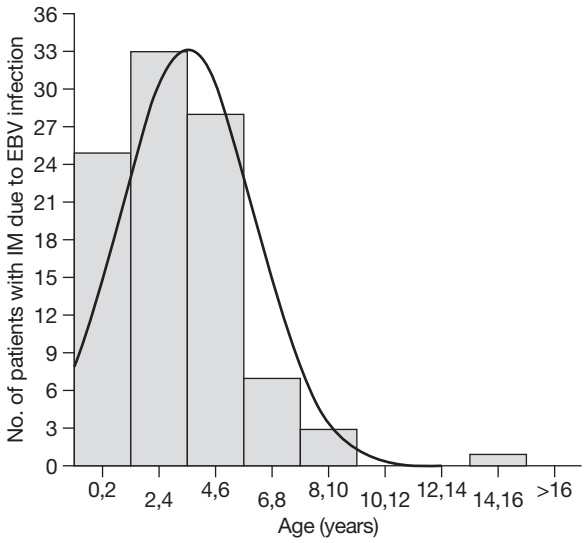

Fig. 1. Age distribution of children with infectious mononucleosis (IM) due to Epstein-Barr virus (EBV) infection.

Clinical features

The clinical features of the patients are shown in Table 1. All but 2 patients suffered from fever, with tonsillopharyngitis and hepatomegaly being the second and third most common manifestations. The duration of fever ranged from 0 to 29 days, with a mean of 10.3 ± 6.0 days; and 81.6% of patients (80/98) suffered from fever longer than 5 days. Cough/rhinorrhea, cervical lymphadenopathy, and splenomegaly also occurred frequently in our patients.

Laboratory findings

Table 2 shows the laboratory findings of the patients. The data revealed that the WBC ranged from 2600 to 35,800/mm^3 (mean, 16,261 ± 7039), with leukocytosis (WBC ≥10,000/mm^3) in 84% of the patients. The percentage of atypical lymphocytes ranged from 0 to 59% (mean, 11.6%), with significant atypical lymphocytosis (>10%) occurring in 41.8% of patients. Anemia (hemoglobulin, <9 g/dL) or thrombocytopenia (platelets, <100,000/mm^3) were noted in 14.3% of patients (14/98). Elevated serum hepatic enzymes, defined as alanine aminotransferase (ALT) ≥55 IU/L (normal range, 0-35 IU/L) and/or aspartate aminotransferase (AST) ≥55 IU/L (normal range, 0-35 IU/L), were noted in 61.2% of patients, with AST ranging from 19.0 to 1035.0 IU/L (mean, 166.6 ± 183.3) and ALT ranging from 8.0 to 1014.0 IU/L (mean, 220.9 ± 222.2).

Table 1. Clinical features of 98 hospitalized children with Epstein-Barr virus-associated infectious mononucleosis

Characteristics	Total (n = 98) No. (%)	Cases with complications (n = 19) No. (%)	Cases without complications (n = 79) No. (%)	p^a
Age (years)				
Mean ± SD	4.0 ± 2.3	3.9 ± 3.3	4.0 ± 2.1	0.336
Range	(1.0-16.0)	(1.3-16.0)	(1.0-10.1)	
Male gender	65 (66)	7 (37)	58 (73)	0.006
Period of admission (days)				
Mean ± SD	7.2 ± 5.3	9.9 ± 8.3	6.6 ± 4.0	0.028
Range	(1-40)	(2-40)	(1-32)	
Fever				
Duration (days)	96 (98)	18 (95)	78 (99)	0.352
Mean ± SD	10.3 ± 6.0	11.9 ± 7.7	9.6 ± 5.6	0.159
Range	(0-29)	(0-29)	(0-28)	
Tonsillopharyngitis	83 (85)	12 (63)	71 (90)	0.009
Hepatomegaly	77 (79)	16 (84)	61 (77)	0.756
Cough/rhinorrhea	73 (75)	13 (68)	60 (76)	0.561
Cervical lymphadenopathy	67 (68)	11 (58)	56 (71)	0.285
Splenomegaly	51 (52)	14 (74)	37 (47)	0.043
Eyelid swelling	41 (42)	6 (32)	35 (44)	0.438
Abdominal pain	14 (14)	3 (16)	11 (14)	1.000
Skin rashes	11 (11)	2 (11)	9 (11)	1.000

Abbreviation: SD = standard deviation

[a]$p<0.05$ was considered to be significant; Fisher's exact test or Mann-Whitney test used for statistical analysis.

Complications in patients with EBV-associated infectious mononucleosis

Nineteen patients (19.4%) were observed to have complications (Table 3). One of 11 children with only hematologic problems was diagnosed as having hemophagocytic syndrome (HPS), accompanied with prolonged fever, splenomegaly, and hemophagocytosis in the bone marrow. Five of the cases with EBV-associated complications had marked liver function impairment (i.e., ascites, hypoalbuminemia, and jaundice). Intravenous immunoglobulin (IVIG) was administered to 4 patients with hematologic problems with 2 lineages of cytopenia in the peripheral blood, including the patient with HPS, and the response was satisfactory. Upper airway obstruction with respiratory distress was found in 2 cases, and these patients had a good response to systemic corticosteroids. CNS involvement was also noted in 1 case with

Table 2. Laboratory findings of 98 hospitalized children with Epstein-Barr virus-associated infectious mononucleosis at admission

Characteristics	Total (n = 98) mean ± SD (range)	Cases with complications (n = 19) mean ± SD (range)	Cases without complications (n = 79) mean ± SD (range)	p^a
WBC (/mm^3)	16,261 ± 7039 (2600-35,800)	12,626 ± 8663 (2600-29,200)	17,135 ± 6349 (2700-35,800)	0.010
Segment (%)	32 ± 16 (5-82)	32 ± 19 (9-79)	32 ± 16 (5-82)	0.583
Lymphocyte (%)	46 ± 15 (10-77)	47 ± 15 (17-72)	45 ± 15 (10-77)	0.637
Monocyte (%)	7 ± 5 (0-37)	7 ± 2 (4-10)	7 ± 5 (0-37)	0.275
At-lymphocyte (%)	12 ± 13 (0-59)	10 ± 10 (0-30)	12 ± 13 (0-59)	0.812
Hemoglobin (g/dL)	11.4 ± 1.4 (6-13.8)	10.6 ± 2.3 (6-13.3)	11.6 ± 1.0 (9.1-13.8)	0.331
Platelet (10^3/mm^3)	205 ± 94 (33-577)	158 ± 129 (33-577)	216 ± 81 (109-469)	0.002
Initial AST (IU/L)	167 ± 183 (19-1035)	294 ± 274 (44-1035)	134 ± 137 (19-694)	0.001
Initial ALT (IU/L)	221 ± 222 (8-1014)	362 ± 239 (14-886)	180 ± 202 (8-1014)	0.004
CRP (mg/L)	24 ± 29 (2-145)	25 ± 26 (2-113)	24 ± 29 (2-145)	0.444

Abbreviations: SD = standard deviation; WBC = white blood cells; At-lymphocyte = atypical lymphocyte; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CRP = C-reactive protein

[a]$p<0.05$ was considered to be significant; Mann-Whitney test used for analysis.

Table 3. Complications of Epstein-Barr virus-associated infectious mononucleosis in 19 hospitalized children

Complications	Frequency No. (%)
Hematologic disorders only	11/98 (11.2)
Anemia only (hemoglobin <9 g/dL)	3/98 (3.1)
Thrombocytopenia only (platelet $<10^5/mm^3$)	7/98 (7.1)
Combined anemia and thrombocytopenia (1 case is a patient of HPS)	1/98 (1.0)
Hepatic dysfunction[a]	5/98 (5.1)
Hepatic dysfunction only	2/98 (2.0)
Combined hepatic dysfunction and hematologic disorders	3/98 (3.1)
Anemia only and hepatic dysfunction	1/98 (1.0)
Anemia, thrombocytopenia and hepatic dysfunction	2/98 (2.0)
Upper airway obstruction	2/98 (2.0)
Central nervous system disorders[b]	1/98 (1.0)

Abbreviation: HPS = hemophagocytic syndrome

[a]Definition of hepatic dysfunction: hyperbilirubinemia (total bilirubin >2 mg/dL); ascites; hypoalbuminemia (albumin <2.5 g/dL).

[b]Definition of central nervous system disorders: seizure disorders or signs of encephalopathy (i.e., conscious disturbance, behavior or personality changes).

EBV-associated complications, with the presentations of seizure and conscious disturbance. All children with complications gradually recovered without long-term sequelae via supportive care, and anti-inflammatory agent or immunomodulating therapy.

We compared the clinical manifestations between patients with and without complications (Table 1), and found that male gender and signs of tonsillopharyngitis were less frequently associated with complications (p=0.006, p=0.009); In addition, longer periods of admission and splenomegaly were more frequent (p=0.028, p=0.043) in patients with complications. In an analysis of laboratory data (Table 2), WBC count and platelet count were significantly lower (p=0.010 and p=0.002, respectively), and AST and ALT levels were significantly higher (p=0.001 and p=0.004, respectively) in cases with complications. The cut-off points of the above continuous variables were calculated by receiver operating characteristic curves.

Table 4 shows the results of univariate logistic regression analysis of the clinical and laboratory findings for the occurrence of complications in patients with EBV-associated IM. Female gender, no signs of tonsillopharyngitis, splenomegaly and admission ≥10 days were significantly associated with complications. WBC count ≤10,000/mm^3, platelet count ≤150,000/mm^3 and AST ≥150 IU/L or ALT ≥150 IU/L were also significantly found in patients with complications.

Stepwise multivariate logistic regression analyses were performed to assess the risk factors for the complications in patients with EBV-associated IM (Table 5). In stepwise multivariate logistic regression analyses of clinical findings with control of age parameter, female gender and no signs of tonsillopharyngitis were significant risk factors for the occurrence of complications. Length of admission ≥10 days was excluded because we considered it as a consequence of complications, and thus not a valid risk factor. In the analysis of laboratory findings, lower platelet count was not included in the regression model because this finding may also be a result of complications. Multiple logistic regression analysis with control of parameters including age, gender, and signs of tonsillopharyngitis showed that WBC count ≤10,000/mm^3 and AST ≥150 IU/L were significant risk factors for the occurrence of complications.

Table 4. Univariate logistic regression analysis for the presence of complications in patients with Epstein-Barr virus-associated infectious mononucleosis

Characteristic	Odds ratio (95% CI)	p[a]
Clinical findings		
Female gender	4.73 (1.64-13.63)	0.004
Duration of admission ≥10 days	6.81 (1.95-23.77)	0.003
Tonsillopharyngitis	0.19 (0.06-0.63)	0.007
Splenomegaly	3.18 (1.04-9.67)	0.042
Laboratory findings		
WBC count ≤10,000/mm^3	13.52 (3.97-46.08)	<0.001
Platelet ≤150,000/mm^3	7.31 (2.46-21.72)	<0.001
Initial AST ≥150 IU/L	5.64 (1.76-18.12)	0.004
Initial ALT ≥150 IU/L	7.09 (1.43-35.15)	0.017

Abbreviations: CI = confidence interval; WBC = white blood cell; AST = aspartate aminotransferase; ALT = alanine aminotransferase

[a]p<0.05 was considered to be significant.

Table 5. Multivariate stepwise logistic regression analyses of risk factors for the presence of complications in patients with Epstein-Barr virus-associated infectious mononucleosis

Characteristic	Odds ratio (95% CI)	p^a
Clinical findings	(Odds ratio with control of age)	
Female gender	4.40 (1.44-13.49)	0.010
Duration of admission ≥10 days	Not selected	
Tonsillopharyngitis	0.23 (0.07-0.82)	0.023
Splenomegaly	Not selected	
Laboratory findings	(Odds ratio with control of age, gender and signs of tonsillopharyngitis)	
WBC count ≤10,000/mm^3	8.30 (1.82-37.83)	0.006
Platelet ≤150,000/mm^3	Not selected	
Initial AST ≥150 IU/L	4.86 (1.21-19.55)	0.026
Initial ALT ≥150 IU/L	Not selected	

Abbreviations: CI = confidence interval; WBC = white blood cell; AST = aspartate aminotransferase; ALT = alanine aminotransferase
[a] $p<0.05$ was considered to be significant.

Discussion

Our study revealed that EBV-associated IM mainly affected preschool male children, with about 80% of children being younger than 5 years old. This result was in agreement with previous observations of primary EBV infection in children in Taiwan reported by Wu et al [8]. However, in developed or industrialized countries such as the United States or European countries, primary EBV infection often affects adolescents or young adults [2,4]. The cause of the difference in age distribution of primary EBV infection is unclear. The denseness of population and poor public hygiene status of northern Taiwan may partly contribute to this difference.

IM usually includes a constellation of symptoms/signs, such as prolonged fever, tonsillitis, cervical lymphadenopathy, splenomegaly, and hepatomegaly [9], which were also found in our patients. Prolonged fever was especially prevalent with a mean of 10.3 ± 6.0 days and 81.6% of patients longer than 5 days. The result was also in correlation with previous studies in Taiwan reported by Wu et al, which showed that over half of the febrile children of primary EBV infection suffered from fever for more than 1 week [8]. This phenomenon is consistent with the finding that prolonged generalized strong immune reactions to target organs frequently occur in IM due to primary EBV infections. Therefore, if hospitalized children suffer from prolonged fever of unknown origin, IM due to primary EBV infection must be taken into consideration in the differential diagnosis. Accompanying symptoms and signs, especially involvement of lymphoid organs, could alert clinicians to the suspicion of EBV-associated IM.

Significant atypical lymphocytosis (>10%) was present in 41.8% of patients, which was similar to the findings in Krabbe et al's report [9]. The atypical cells are mature T lymphocytes that have been antigenically activated. Although atypical lymphocytosis may be seen in many of the infections causing lymphocytosis, the highest degree of atypical lymphocytes is most often seen in EBV infection [10]. The atypical lymphocytosis finding in peripheral blood could be supportive of EBV infection. Mild, transient elevations of hepatic aminotransferases with hepatomegaly are common and usually asymptomatic in patients with EBV-associated IM [10]. One study reported that the prevalence of elevated aminotransferase was about 50-80% [7]. Such findings were also seen in our series, with 61.2% of the children having elevated hepatic aminotransferases. The cause of hepatic inflammation may be due to the lymphocytic infiltration of the liver and proliferation of Kupffer cells [7].

Nineteen patients (19.4%) with EBV-associated IM in our series experienced complications, including hematologic issues, hepatic dysfunctions, upper airway obstructions, and CNS involvement. Anemia with hemoglobin <9 g/dL occurred in 7.1% of our patients, which was more prevalent than the reports of Whitelaw et al [11] and Gelati et al [12]. They found that approximately 3% of cases with primary EBV infection experienced autoimmune hemolytic anemia, which occurred usually during the first 2 weeks of illness, lasting for less than 1 month. Thrombocytopenia with platelets <10^5 mm^3 occurred in 10.2% of our patients, a much lower-prevalence than in the studies of Carter [13] and Cantow and Kostinas [14]. They reported that 25-50% of patients developed thrombocytopenia during the second and third week of illness. Both hypersplenism and antiplatelet antibody may have contributed to thrombocytopenia [15]. The causes

of the difference in prevalence of anemia or thrombocytopenia between our study (age less than 18 years) and others (all ages) might include different study population, different definitions of thrombocytopenia and anemia, and variations among different races. One of our patients was diagnosed with HPS, which was reported to attack healthy young children in Taiwan with evidence of active EBV infection in most cases [16]. This is probably associated with a defect in immune regulation and abnormal T-cell function [17,18]. Moreover, the clinical course could be fulminating with mortality rates of 40% for immunocompromised and 20% for immunocompetent patients [19]. Fortunately, the patient with HPS in our series recovered uneventfully after IVIG treatment.

Few studies have been performed in search of risk factors for the occurrence of complications [7,9]. Female gender, duration of hospitalization ≥10 days, no signs of tonsillopharyngitis, and splenomegaly were significantly associated with the occurrence of complications in the univariate logistic regression model. In multiple logistic regression model with control of age parameter, female gender and no signs of tonsillopharyngitis were the clinical factors most significantly related to the occurrence of complications. We attempted to discover if the age of female patients with complications (mean, 4.4 ± 3.9 years; range, 1.5 to 16.0) was different from those without complications (mean, 4.6 ± 2.0 years; range, 1.0 to 9.0) or male patients with complications (mean, 3.0 ± 1.5 years; range, 1.3 to 5.0). The results showed that both comparisons were insignificant (p=0.202 and p=0.552, respectively). Thus, we found no definite explanation as to why female gender was frequently found in patients with complications, and further studies need to be conducted in the future. It was also difficult to explain why no sign of tonsillopharyngitis was a significant risk factor for complications. One possible theory is that patients without signs of tonsillopharyngitis might not have the first-line body protection for viral infections, and this could allow the virus to spread more easily and to cause complications. In the analysis of laboratory findings, WBC count ≤10,000/mm^3 and AST ≥150 IU/L were significant risk factors for complications in the regression model, with control of parameters including age, gender and signs of tonsillopharyngitis. This means that a stronger degree of body immune response and organ involvements might occur during the infection. Thus, close monitoring should be done for any possible complications in patients with the above manifestations during hospitalization.

Treatment of EBV-associated syndromes is largely supportive and symptomatic [3,6,7,11]. There is little benefit of antiviral treatment for EBV-associated syndromes [20-24]. However, the applications of systemic corticosteroid, IVIG or further advanced immunomodulating therapy were recommended in life-threatening or complication events [7]. Systemic corticosteroid is a potent anti-inflammatory and immunosuppressive agent and may hasten resolution of some complications, especially upper airway obstruction and possibly immune-mediated anemia and thrombocytopenia [7,11,25]. IVIG or etoposide is effective in reversing the process of lymphohistiocytic dysregulation resulting from virus infection and probably controlling active virus replication in certain cases through immunomodulation [16]. In our series, 4 patients with 2 lineages of cytopenia had good responses to IVIG therapy, including the patient with HPS. Systemic corticosteroids also demonstrated a beneficial effect on obstructive inflammatory tonsillitis. Fortunately, all children with complications were responsive to systemic corticosteroids and/or IVIG and had a favorable prognosis without long-term sequelae or mortality. The prognosis of primary EBV infection without complications was relatively good under supportive and symptomatic care.

In conclusion, EBV-associated IM in hospitalized children in Taiwan mainly affected preschool males with favorite prognosis. However, various complications still occurred in about 20% of the patients and significantly prolonged the course of hospitalization. Female gender, no signs of tonsillopharyngitis, WBC count ≤10,000/mm^3 and AST ≥150 IU/L were significant risk factors for the occurrence of complications. Clinicians should take proper action to decrease any possible morbidity or mortality if complications occur during the clinical course.

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