

Clinical manifestations and laboratory results of 61 children with infectious mononucleosis

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Abstract

Objective: To investigate the clinical manifestations of infectious mononucleosis in children of different ages.

Methods: Clinical data from pediatric patients with infectious mononucleosis admitted from May 2015 to April 2019 were retrospectively analyzed. Patients were stratified into three groups (age 1–3 years, 4–6 years, and 7–14 years) for analysis of clinical and laboratory results.

Results: Data from 61 patients (male:female ratio 1.18:1) aged 5.15 ± 2.93 years (mean \pm standard deviation; range: 1–14 years) were analyzed. Infectious mononucleosis occurred throughout the year and the main clinical manifestations were fever (98.3%), tonsillitis (100%), tonsillar white exudate (83.6%), cervical lymphadenopathy (98.3%), hepatomegaly (37.7%), splenomegaly (42.6%), eyelid edema (41.0%), and nasal obstruction (49.2%). Disease onset was most common during early childhood (37.7%) and at preschool age (37.7%). Younger children had more obvious symptoms of nasal obstruction and older children had more significant elevations of alanine aminotransferase and higher percentages of atypical lymphocytes.

Conclusion: The clinical manifestations of infectious mononucleosis in children differed by age. These associations required attention for clinical decision making.

Keywords

Epstein–Barr virus, infectious mononucleosis, age staging, clinical manifestations, laboratory results, retrospective analysis

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Introduction

Infectious mononucleosis (IM) is an acute infectious disease caused by the Epstein–Barr virus (EBV), and occurs most commonly children and adolescents. EBV is a herpesvirus that replicates primarily in B lymphocytes but can also be detected in epithelial cells of the pharynx as well as the parotid ducts. EBV is transmitted by saliva with a latency period of 4 to 8 weeks. Typical signs and symptoms of IM include fever, lymphadenopathy, and herpangina. However, clinical manifestations can be variable and also include headache, fatigue, rash, jaundice, and hepatosplenomegaly.¹ IM can also cause rarer complications such as lymphocytosis, decreased liver function, peritonsillar abscess, airway obstruction, and splenic rupture.^{2–4} The populations at risk of EBV infection differ in developed and developing countries. EBV infection is more common in infants and young children in developing countries, but more common in children and adolescents in developed countries.⁵

Sixty-one pediatric patients with infectious mononucleosis were admitted to the Department of Pediatrics, People's Hospital of Shanghai Pudong New District, Shanghai University of Medicine and Health Sciences from May 2015 to April 2019. These patients were stratified into three groups (age 1–3 years, 4–6 years, and 7–14 years). Their clinical and laboratory results were analyzed to investigate the features associated with infectious mononucleosis in children of different ages.

Materials and methods

General information

Children with diagnosed infectious mononucleosis admitted to the Department of Pediatrics of Department of Pediatrics, People's Hospital of Shanghai Pudong

New District, Shanghai University of Medicine and Health Sciences from May 2015 to April 2019 were enrolled. The patients were stratified into three groups (age 1–3 years, 4–6 years, and 7–14 years) for analysis of clinical and laboratory results. We included all immunocompetent children and adolescents (minimum age: 15 years and 3 months) with a diagnosis of IM confirmed by EBV serology [negative for anti-Epstein–Barr nuclear antigen (EBNA) IgG antibodies and positive for anti-viral capsid antigen (VCA) IgM antibodies] who presented at the People's Hospital of Shanghai Pudong New District. EBV was not treated with antibiotics in any patients. Patients diagnosed with cytomegalovirus mononucleosis or other mononucleosis-like infections were excluded. All patients were recruited from discharge diagnoses.

Diagnostic criteria

All IM patients met the diagnostic criteria of the Zhu Futang Textbook of Pediatrics (7th Edition).¹ These criteria included any three of the following symptoms: fever, pharyngitis, tonsillitis, cervical lymphadenopathy (>1 cm), hepatomegaly (age <4 years: >2 cm; age \geq 4 years: palpable), and splenomegaly (palpable). In addition, hemograms needed to show that white blood cells accounted for more than 50% of cells or had counts exceeded $5.0 \times 10^9/L$, with atypical lymphocytes accounting for more than 10% of cells or having counts exceeding $1.0 \times 10^9/L$. Finally, laboratory tests had to meet any of the following conditions: (i) VCA IgM positive; (ii) anti-VCA IgG titer increase of more than four-fold compared with paired serum; or (iii) anti-VCA IgG positive and anti-EBNA IgG negative.

Endpoints

The clinical manifestations, complications, and laboratory results of the 61 children

were retrospectively analyzed to identify differences in clinical manifestations between different age groups.

Laboratory methods

An EBV IgG ELISA kit (Abcam, Cambridge, UK) was used to detect EBV antibodies. All reagents, serum samples and controls were prepared according to the manufacturer's guidelines. Each serum sample and control was added to the 96-well plate and incubated at room temperature (RT) for at least 1 hour. After washing three times, horseradish peroxidase-conjugated secondary antibodies were added to each well. After washing, tetramethylbenzidine substrate solution was added and incubated at RT for 1 hour. The reaction was stopped and absorbance was measured as soon as possible.

Statistical methods

All statistical analyses were performed using SPSS version 25.0 software (SPSS Inc., Chicago, IL, USA). Data were compared among the three age strata. Normally distributed data were expressed as ($X \pm S$) and compared using one-way analysis of variance, while non-normally distributed data were expressed as an interquartile range and compared using non-parametric Kruskal–Wallis tests. For comparison of count data among the three groups, the χ^2 test or Fisher's exact test was used. The paired student's t-test was used to assess differences between two groups. Values of $P < 0.05$ were considered statistically significant.

Ethics

Approval was obtained from the Ethics Committee of People's Hospital of Shanghai Pudong New District, Shanghai University of Medicine and Health Sciences. Written informed consent was obtained from the patients' parents.

Results

Age associations and seasonality of IM

Of the 61 children with IM admitted from May 2015 to April 2019, 33 were boys (54.1%) and 28 were girls (45.9%), with a male:female ratio of 1.18:1. Their ages ranged from 1 year to 14 years and 8 months, with an average of 5.15 ± 2.93 years. Twenty-three children (37.7%) were 1 to 3 years old, 23 children (37.7%) were 4 to 6 years old, and 15 children (24.6%) were 7 to 14 years old. Early childhood and preschool age were the most common age groups for IM. IM developed in 16 children (26.2%) in spring, in 20 children (32.8%) in summer, in 14 children (23.0%) in autumn, and in 11 children (18.0%) in winter. Thus, IM developed throughout the year.

Clinical manifestations

The first symptoms at onset of IM were variable, with fever being the most common, occurring in 49 cases (80.3%). Other symptoms at onset included cervical lymphadenopathy in three cases (4.9%), nasal obstruction in two cases (3.3%), eyelid edema in two cases (3.3%), sore throat in two cases (3.3%), cough in two cases (3.3%), and headache in one case (1.6%).

Among the clinical manifestations of IM, fever, tonsillitis, tonsillar white exudate, and cervical lymphadenopathy were the most common and occurred in 60 (98.3%), 61 (100%), 51 (83.6%), and 60 cases (98.3%), respectively. Hepatomegaly was present in 23 cases (37.7%), splenomegaly in 26 cases (42.6%), eyelid edema in 25 cases (41.0%), rash in 13 cases (21.3%), nasal congestion in 30 cases (49.2%), and cough in 39 cases (63.9%). Fever was the most common clinical manifestation in children (only 1 of the 61 children had no fever). Body temperature fluctuated between 37.4

and 40.5°C in patients with fever. A low fever of 37.3 to 38°C was observed in three cases (5.0%), a moderate fever of 38.1 to 39°C was observed in 34 cases (56.7%), a high fever of 39.1 to 41°C was observed in 23 cases (38.3%), and fevers >41°C were not observed.

The clinical manifestations of children aged 1 to 3 years, 4 to 6 years, and 7 to 14 years were compared. There were significant differences associated with age in the frequency of nasal obstruction ($P=0.028$), sore throat ($P=0.003$), fatigue ($P=0.001$) and axillary and inguinal lymphadenopathy ($P=0.014$). No significant differences in other clinical manifestations were observed.

There was no statistical difference in treatment outcomes among the three age strata in terms of peak body temperature, days of tonsillar exudate absorption, fever duration, and duration of hospitalization (Table 1).

Laboratory tests

Among the 61 children with IM, 34 (55.7%) had $\geq 10\%$ atypical lymphocytes (sometimes up to 55%), 31 (50.8%) had elevated alanine aminotransferase, and 45 (73.8%) had elevated aspartate aminotransferase. The proportion of atypical lymphocytes ($P=0.028$) and levels of alanine aminotransferase

Table 1. Clinical manifestations of infectious mononucleosis in children of different ages.

Clinical manifestations	Total (n = 61)	1–3 years (n = 23)	4–6 years (n = 23)	7–14 years (n = 15)	P
Fever	60 (98.4)	23 (100.0)	23 (100.0)	14 (93.3)	0.246 ^b
Nasal obstruction	30 (49.2)	16 (65.2)	10 (43.5)	4 (26.7)	0.028 ^a
Sleep snoring	6 (9.8)	5 (21.7)	1 (4.3)	0 (0.0)	0.078 ^b
Sniffles	15 (24.5)	6 (26.1)	6 (26.1)	3 (20.0)	0.893 ^a
Cough	39 (63.9)	15 (65.2)	17 (73.9)	7 (46.7)	0.229 ^a
Pharyngalgia	21 (34.4)	3 (13.0)	8 (34.8)	10 (66.7)	0.003 ^a
Headache	5 (8.2)	0 (0.0)	2 (8.7)	3 (20.0)	0.061 ^b
Fatigue	12 (19.7)	0 (0.0)	5 (21.7)	7 (46.7)	0.001 ^b
Abdominal pain	2 (3.3)	2 (8.7)	0 (0.0)	0 (0.0)	0.334 ^b
Vomiting	6 (9.8)	3 (13.0)	1 (4.4)	2 (13.3)	0.637 ^b
Diarrhea	1 (1.6)	0 (0.0)	1 (4.3)	0 (0.0)	1.000 ^b
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Eyelid edema	25 (41.0)	9 (39.1)	10 (43.5)	6 (40.0)	0.952 ^a
Rash	13 (21.3)	7 (30.4)	2 (8.7)	4 (26.7)	0.182 ^b
Hepatomegaly	23 (37.7)	8 (34.8)	11 (47.8)	4 (26.7)	0.394 ^a
Splenomegaly	26 (42.6)	7 (30.4)	9 (39.1)	10 (66.7)	0.080 ^a
Jaundice	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Cervical lymphadenopathy	60 (98.4)	22 (95.6)	23 (100.0)	15 (100.0)	1.000 ^b
Axillary and inguinal lymphadenopathy	29 (47.5)	8 (34.8)	9 (39.1)	12 (80.0)	0.014 ^a
Enlarged tonsils	61 (100.0)	23 (100.0)	23 (100.0)	15 (100.0)	–
Tonsillar exudation	51 (83.6)	18 (78.3)	20 (86.9)	13 (86.7)	0.750 ^b
Maximum body temperature (°C)	29.2 (38.7, 39.6)	39.5 (38.7, 39.9)	39.0 (38.5, 39.3)	39.0 (38.9, 39.1)	0.193 ^c
Fever duration (days)	4.0 (3.0, 5.0)	3.0 (2.0, 4.0)	4.0 (2.0, 6.0)	3.0 (1.0, 5.0)	0.277 ^c
Duration of tonsillar exudate absorption (days)	5.0 (3.0, 5.0)	5.0 (2.0, 5.0)	5.0 (2.0, 5.0)	5.0 (4.0, 5.0)	0.822 ^c
Length of hospital stay (days)	–	10.87 ± 2.87	10.96 ± 3.08	10.67 ± 3.81	0.963 ^d

Notes: ^a χ^2 test; ^bFisher's exact test; ^cKruskal–Wallis test; ^danalysis of variance. Data are presented as number of patients (%), $X \pm S$ or median (interquartile range).

($P = 0.046$) were significantly different among the three age strata. Other indicators were not significantly different across age strata (Table 2).

Complications and comorbidities

Twenty-six (42.6%) of the 61 IM patients experienced complications. Respiratory complications were most common and occurred in 18 patients (31.1%; pneumonia, 7 patients; bronchitis, 7 patients; bacterial tonsillitis, 3 patients; and herpangina, 1 patient). Urinary complications occurred in nine patients (14.8%; microscopic hematuria, six patients; proteinuria, two patients; and urinary tract infection, one patient) and hematological complications occurred in nine patients (14.8%; thrombocytopenia, three patients; granulocytopenia, three patients; and anemia, three patients). There was one case of acute gastritis, one case of otitis media, and one case of sinusitis.

Of the 61 hospitalized children with IM, 8 (13.1%) had *M. pneumoniae* infection and 7 (11.5%) had cytomegalovirus infection.

Discussion

EBV infects B cells, which can subsequently activate cytotoxic T cells. EBV-infected B cells and atypical lymphocytes resulting from EBV infection may lead to histopathological changes in several organs of the body.³

Primary symptomatic EBV infection is common in China. Epidemiological surveys have shown that the proportion of children and adolescents who have experienced EBV infection approaches 90% with age. The proportion of EBV-experienced children aged 5 to 9 years in developing countries has reached more than 90%, with most infected during infancy. By contrast, the proportion of EBV-experienced children aged 5 to 9 years in developed countries such as Western Europe and North America is only 50%.⁴⁻⁷ Previous studies have shown that IM most commonly occurs in Chinese preschool children, consistent with the high proportion of EBV-infected children in developing countries and their associated hygiene and medical conditions.⁸ In addition, Devkota et al.⁹ speculated that children aged 6 months to

Table 2. Laboratory test results of children of different ages with infectious mononucleosis.

Clinical manifestations	1-3 years (n = 23)	4-6 years (n = 23)	7-14 years (n = 15)	P
Leukocytes ($\times 10^9/L$)	16.95 \pm 5.48	13.64 \pm 4.84	16.87 \pm 6.52	0.088 ^d
Neutrophils (%)	25.87 \pm 10.88	24.53 \pm 7.76	23.97 \pm 12.27	0.834 ^d
Lymphocytes (%)	62.0 (56.0, 66.0)	60.7 (57.6, 74.4)	48.0 (36.0, 63.0)	0.048 ^c
Platelets ($\times 10^{12}/L$)	203.0 (137.0, 222.0)	216.0 (158.0, 240.0)	180.0 (134.0, 244.0)	0.518 ^c
Hemoglobin (g/L)	124.30 \pm 9.60	126.87 \pm 15.81	128.93 \pm 10.05	0.523 ^d
C-reactive protein (mg/L)	7.9 (4.0, 11.0)	5.0 (3.0, 9.0)	4.5 (2.0, 12.1)	0.448 ^c
Atypical lymphocytes (%)	10.0 (4.0, 16.0)	7.0 (2.0, 18.0)	17.0 (13.0, 35.0)	0.028 ^c
Alanine aminotransferase (U/L)	25.0 (16.0, 118.0)	35.0 (26.0, 90.0)	82.0 (36.0, 236.0)	0.046 ^c
Alanine aminotransferase (U/L)	51.0 (37.0, 91.0)	48.0 (40.0, 80.0)	97.0 (46.0, 159.0)	0.105 ^c
Glutamyl transpeptidase (U/L)	14.6 (9.4, 62.8)	24.0 (14.0, 53.0)	40.1 (24.9, 94.7)	0.113 ^c
Total bilirubin ($\mu\text{mol}/L$)	4.6 (3.9, 6.2)	4.4 (3.4, 5.7)	5.5 (4.6, 7.9)	0.147 ^c
Direct bilirubin ($\mu\text{mol}/L$)	1.9 (1.0, 2.6)	1.4 (1.1, 2.4)	2.1 (1.7, 3.5)	0.270 ^c
Urea nitrogen (mmol/L)	3.25 \pm 0.75	3.27 \pm 1.07	2.83 \pm 0.78	0.264 ^d
Uric acid (mmol/L)	256.46 \pm 96.22	312.57 \pm 90.21	276.47 \pm 62.89	0.096 ^d

Notes: ^cKruskal-Wallis test; ^danalysis of variance. Data are presented as $X \pm S$ or median (interquartile range).

1 year were at high risk of infection based on epidemiological data on pediatric EBV obtained from 2014 to 2017 in China. In the present study, we found that early childhood and preschool age were the two high-risk periods for IM, accounting for 75.4% of the 61 hospitalized children described here; 37.7% of children with IM were 1 to 3 years old, suggesting that IM is also very common in young children. This finding was consistent with some recent domestic reports.¹⁰⁻¹²

Fever, herpangina, and lymphadenopathy were the most common clinical manifestations in children with IM, followed by hepatosplenomegaly and eyelid edema. These findings were also consistent with those of domestic reports.^{13,14} However, the initial symptoms of IM were variable. In our study, 80.3% of children had fever at symptom onset, but some also had cervical lymphadenopathy, nasal congestion, eyelid edema, and sore throat at onset. The clinical manifestations of IM lack specificity. Because some patients may have atypical manifestations, pediatricians should pay careful attention during physical examination and differential diagnosis so as to avoid missed diagnoses.¹⁵ In this study, 41.0% of children developed eyelid edema, and two patients consulted physicians with eyelid edema as the first symptom of IM. The prevalence of eyelid edema was similar in the infant, preschool and school-age groups. Some studies have suggested that eyelid edema is associated with compression of enlarged lymph nodes in the neck leading to impaired venous lymphatic backflow.¹⁶ In this study, the 25 children with IM and eyelid edema had normal renal function, and only one patient had transient microscopic hematuria. To exclude renal lesions, eyelid edema has been regarded as one of the characteristic manifestations and major clinical presentations of IM, and is included as one of the diagnostic clinical criteria in the 8th edition of the Zhu Futang Textbook

of Pediatrics. The incidence of nasal obstruction was significantly higher in 1- to 3-year-old children than in the school-aged group at around 65.2%. Moreover, five (21.7%) children had symptoms of snoring, suggesting that the infant group was more likely to have manifestations of respiratory obstruction. Some scholars believe that nasal obstruction and snoring are caused by soft tissue hypertrophy and inflammatory edema around the nasal cavity, pharynx, and tonsils.¹⁷ Thus, symptoms of airway obstruction such as nasal obstruction and snoring may be of clinical significance in the early diagnosis of IM.

In this study, hepatomegaly (37.7%) and splenomegaly (42.6%) were common clinical signs of IM, and splenomegaly was more common in school-age children. During physical examination, hepatic and splenic palpation often misses a subset of children with hepatosplenomegaly.¹⁸

Hepatic impairment (50.8%) was the most common complication of IM and was more common in older children. Most of the liver damage in IM results from crowding and necrosis caused by cytotoxic T cells. Abnormal liver function was observed in 10 of 15 school-age children (66.7%), and alanine aminotransferase was elevated to a greater extent than in the infant and preschool age groups, consistent with domestic reports.^{2,19} In our study, the 13 cases with elevated glutamyl transferase were all children with impaired liver function. After EBV infects cells, free radicals generated by lipid peroxidation produce toxic effects, which lead to hepatocyte damage and can also cause lymphadenopathy and hepatosplenomegaly through massive activation of B lymphocytes.²⁰ Some scholars also believe that EBV activates cellular immunity, and that the infiltration of proliferating abnormal lymphocytes, plasma cells, and neutrophils into the periphery of the central veins and hepatic lobules results in hepatocyte

damage.²¹ In this study, only two (3.2%) patients showed elevated total bilirubin and four (6.5%) patients showed elevated direct bilirubin. No cases of jaundice were observed.^{6,22}

Children born prematurely (gestational age ≤ 32 weeks) may have unusual profiles of atypical lymphocytes. In this study, 55.7% of IM patients had elevated numbers atypical lymphocytes, in agreement with data from China and abroad.^{2,23} The proportion of atypical lymphocytes was higher in school-age children than in preschool age children and infant. Nearly half of preschool age children and infants had $<10\%$ of atypical lymphocytes. Atypical lymphocytes generally appear 3 days after IM onset, peak 7 to 10 days after onset, and last for 2 to 8 weeks. Other infections such as cytomegalovirus infection, infectious hepatitis, and rubella may also lead to elevated numbers of atypical lymphocytes. Thus, etiological diagnosis must be made in combination with clinical and auxiliary examinations.

Our study also had some limitations. There was some uncertainty associated with children's physical condition and parents' willingness to cooperate, which may have introduced errors in our results. Moreover, the clinical samples used in this study had small volumes, preventing additional analyses. Because of inter-individual differences in the immune systems and genetic factors in each child, IM does not always produce significant clinical characteristics. IM may depend on whether the patient is allergic. In this study, the influence of allergy on IM was evaluated. In future studies, we will further explore the clinical characteristics of IM to provide a reliable medical basis for improving the quality of life in children.

Conclusions

We found that some of the clinical features of EBV infection differed by age. Most

subjects aged 0 to 6 years presented with nasal congestion, while those aged 7 to 14 years more often presented with fatigue and axillary and inguinal lymphadenopathy, combined with atypical lymphocytosis and elevated alanine aminotransferase. Our results suggest that some clinical manifestations of EBV-associated IM in children are associated with age.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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