

EBV as the cause of fever of unknown origin in children

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Abstract

EBV is a human herpesvirus which is ubiquitous in nature and infects most of the world population. Children mostly acquire primary EBV infection from close contact that involves exchange of oral secretions. Primary EBV infection in children may go undetected as it is often asymptomatic or is presented with atypical or partial Infectious Mononucleosis syndrome. This study aimed to highlight the role of primary EBV as a cause of Fever of Unknown Origin in childhood. Fever resulted the most common symptom of IM in 97% of children, it was of long duration and correlated with the massive lymphocytosis of primary EBV infection in children. Primary EBV infection is a potential cause of Fever of Unknown Origin in Children.

Keywords: Fever; EBV; Symptom; Lymphocytosis; FUO

1. Introduction

Epstein-Barr virus (EBV) is one of the eight known human herpesviruses which is ubiquitous in nature. EBV was discovered in 1964 by electron microscopy of suspension cultures of African Burkitt lymphoma cells [1]. Four years later, EBV was discovered to be the causative agent of infectious mononucleosis, which is its most common clinical manifestation [2]. Infectious mononucleosis was the name chosen by Sprunt and Evans to describe a syndrome that resembled an acute infectious disease accompanied by atypical large peripheral blood lymphocytes [3]. Like other herpesviruses, EBV virions have a double-stranded, linear DNA genome surrounded by a protein capsid. Initial infection occurs in the oro-pharyngeal region. The host cells of EBV are mainly lymphocytes and epithelial cells [4]. EBV infection in B cells induces the activation of their growth program and triggers the differentiation into memory B cells. Infected memory B cells are released into the peripheral circulation, their number decreases over time after the onset of symptoms of primary infection, but these cells are never eliminated entirely [5].

Children mostly acquire primary EBV infection from close contact that involves exchange of oral secretions via shared items such as toys and bottles. Aside from oral transmission, EBV has been acquired from blood, transplanted hematopoietic cells, or solid organs [6, 7, 8, 9]. Healthy people continue to shed EBV for many months after their acute infection and are potentially capable of transmitting it [10, 11]. Infectious mononucleosis most often begins insidiously, with vague malaise, followed several days later by fever, sore throat, swollen posterior cervical lymph nodes, and fatigue. Some patients experience an abrupt influenza-like onset, with fever, chills, body aches, and sore throat. Complications may be due to tissue-invasive viral disease or to immune-mediated damage. Many complications have been associated with infectious mononucleosis, but nearly all of them are uncommon or rare such as: conjunctivitis, hemophagocytic syndrome, myocarditis, neurologic diseases other than meningoencephalitis, pancreatitis, parotitis,

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pericarditis, pneumonitis, psychological disorders, and splenic rupture [12, 13]. Splenic rupture is a rare but greatly feared complication that excludes athletes from contact sports for various periods.

The aim of this study is to highlight the importance of primary EBV infection as a potential cause of Fever of Unknown Origin in children.

2. Material and methods

This study is a retrospective one. There are enrolled 107 children, 0-14 years old, diagnosed with Infectious Mononucleosis and hospitalized in the Pediatric Infectious Disease Ward in the University Hospital Center “Mother Tereza”, Tirana during a 4-years period 2015-2019.

Diagnosis was concluded based on positive immunoglobulin M (IgM) of EBV viral capsid antigen. Data are extracted from the patients clinical records.

3. Results

During a 4-years period 2015-2019 in the Pediatric Infectious Disease Ward, in the University Hospital Center “Mother Teresa”, Tirana were hospitalized 107 children diagnosed with Infectious Mononucleosis caused by EBV. In 4% of cases diagnosis on admission was Fever of Unknown Origin (Table1).

Table 1 Diagnosis on admission

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Angina	3	2.8	2.8	2.8
	Bacteremia	1	0.9	0.9	3.7
	Pneumonia	1	0.9	0.9	4.7
	Periorbital cellulitis	1	0.9	0.9	5.6
	Fever of Unknown Origin	4	3.7	3.7	9.3
	Hepatitis	7	6.5	6.5	15.9
	Viral infection	20	18.7	18.7	34.6
	Lymphadenitis	9	8.4	8.4	43.0
	Lymphadenopathy	8	7.5	7.5	50.5
	Infectious Mononucleosis	19	17.8	17.8	68.2
	Septicemia	2	1.9	1.9	70.1
	Hystiocytosis	1	0.9	0.9	71.0
	Leishmania visceralis	2	1.9	1.9	72.9
	Upper respiratory infection	22	20.6	20.6	93.5
	Bacterial Tonsillitis	7	6.5	6.5	100.0
	Total	107	100.0	100.0	

Fever was the first symptom in 84% of children followed by lymphadenitis in 11% of cases, fatigue in 2% of cases and rash, palpebral edema and cough in 1% of children respectively (Figure 1).

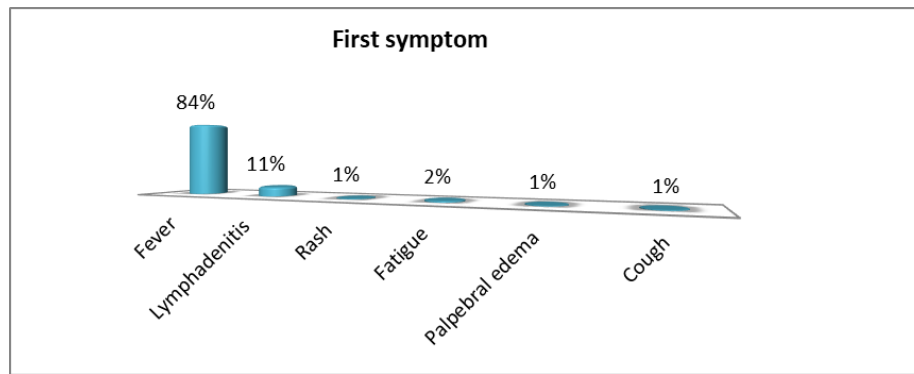


Figure 1 First symptom of IM

Fever was the most common symptom, 97% of children had fever, 63% had sore throat, 20% of children had breathing difficulty, 21% had fatigue, 12% had abdominal pain, 9% vomiting and 6% of children had diarrhea (Figure 2).

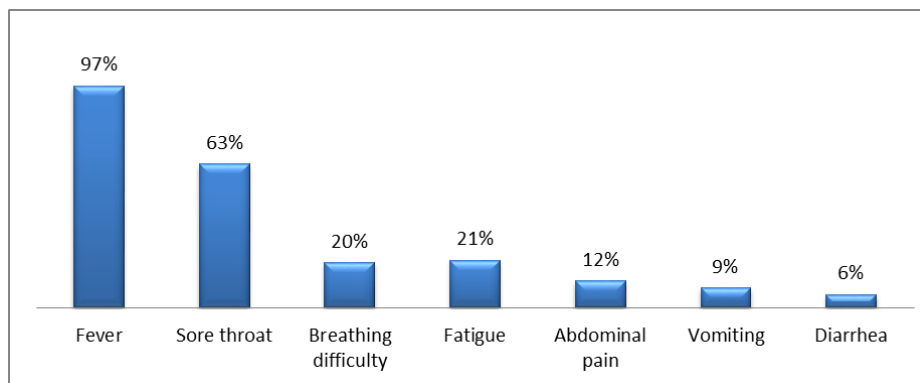


Figure 2 Symptoms of IM

The median days with fever were 7.8 days ranging from 0 day to 20 days (Figure 3).

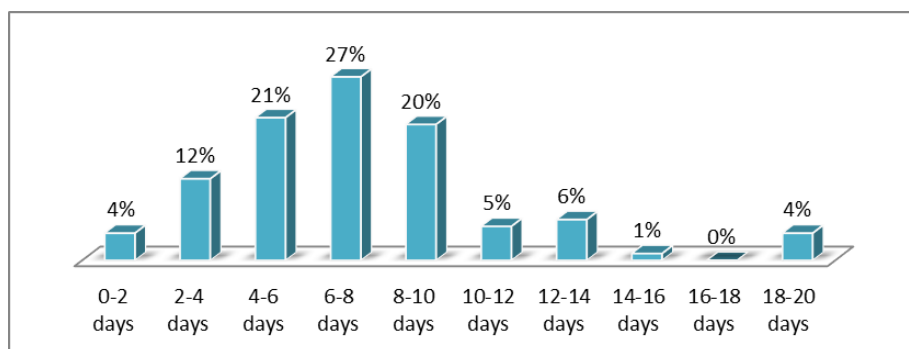


Figure 3 Days with fever in IM

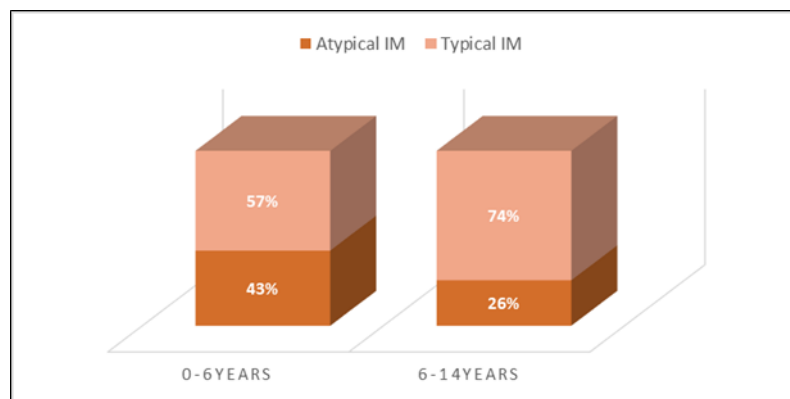
From the correlation analysis was detected an association between variables days with fever and values of lymphocytes. The association was of small and medium magnitude, in positive direction and of statistical significance. Pearson Correlation between the variable days with fever and the values of lymphocytes is positive of small magnitude and statistically significant $r=0.239$ $p=0.035$ (Table 2).

Table 2 Pearson Correlation

		Lymphocytes
Days with fever	Pearson Correlation	0,239*
	Sig. (2-tailed)	0.035
	Sum of Squares and Cross-products	756.385
	Covariance	9.823
	N	78

*. Correlation is significant at the 0.05 level (2-tailed).

According to clinical presentation forms, 67 children (63%) showed the classic presentation of Infectious Mononucleosis with fever, pharyngitis and lymphadenitis. Whereas 40 children (37%), manifested atypical presentation with a partial clinical syndrome of Infectious Mononucleosis. Typical syndrome of Infectious Mononucleosis was more common in older children, 74% of children 6-14 years old manifested the classic form, and 26% of them showed atypical presentation. 43% of children 0-6 years old showed atypical presentation, whereas 57% of them manifested classic form of Infectious Mononucleosis (Figure 4).

**Figure 4** Clinical presentations of IM

4. Discussion

Fever is the most old and prominent feature of disease in humans since antiquity. It was described since 2000 years ago by Celcius as one of the four cardinals signs of inflammation. At the same time Hippocrates noted that fever was beneficial, so till now fever is considered to be an adaptive compensatory defense mechanism leading to immune activation, and improving host survival in response to foreign invasions. However when it reaches high degrees and is prolonged in duration causes deleterious effects such as direct cellular damage, local and systemic effects. Fever is the most presenting complaint in children and the most common reason for pediatric medical consultations worldwide. A persistently febrile child lacking an obvious source of fever inflicts great distress in parents and clinical pediatricians.

Fever of Unknown Origin (FUO) in adults was defined by Petersdorf and Besson in 1961 as a state of febrile illness for more than three weeks with a body temperature greater than 38.3°C on several occasions and uncertain diagnosis after one week of study in hospital [14]. The definition of FUO in children varies from 1 - 3 weeks. Even with modern advances in medicine, FUO remains a challenge and it may be a symptom of approximately 200 described cases [15, 16]. Classical FUO is subdivided in four main etiological categories: infections, malignancies, non-infectious inflammatory diseases (NIID) and miscellaneous conditions [17]. Infections were the leading cause for classical FUO in most published studies, accounting for approximately one third of all cases: abscesses, endocarditis, tuberculosis, and complicated urinary tract infections dominate the group of infection-related FUO, regardless of the age of the patient. Geography is also an important factor in the etiology base of FUO, as in developing countries the percentage of infections is much higher than in developed countries, while for neoplasms and NIID it is the opposite [18,19].

A potent innate and adaptive immune response is inflicted during primary EBV infection, which controls infection but does not eliminate it, and the virus persists for lifetime. Many inflammatory cytokines are detected in blood during

primary EBV infection, the most prominent among these is IFN- γ . IFN- γ is produced by activated T cells and NK cells, and despite being important of controlling EBV infection and reactivation, it is known to contribute to the symptoms experienced during infectious mononucleosis, as this cytokine causes headache, fatigue, and fever [20]. Both CD4 and CD8 T cells make a robust response to EBV antigens, and the massive lymphocytosis in the blood that characterizes infectious mononucleosis is thought to consist largely of CD8 T cells specific for EBV lytic antigens [21]. This large adaptive immune response is another component responsible for the major symptoms of infectious mononucleosis, as disease severity correlated more closely with lymphocytosis than with viral load [22].

Fever is the most prominent symptom of Infectious Mononucleosis(IM) in children, it was present in 97% of children enrolled in the study. Compared to other viral infections of childhood fever in IM is of longer duration, in the presenting study it ranged from 1 day to 20 days and the mean duration of fever was 7.8 days. In 4% of cases the admission diagnosis was Fever of Unknown Origin (FUO), in which fever lasted approximately 3 weeks (20 days). Fever was also the first symptom in 84% of children in this study. There was found a statistically significant correlation between the duration of fever and lymphocytosis $r=0.239$ $p=0.035$ which means that higher levels of lymphocytes are associated with longer duration of fever. So the massive lymphocytosis in blood after primary EBV infection is a major factor that contribute to the prolongation of fever and the severity of the disease.

Primary EBV infection in children may go undetected as it is often asymptomatic or is presented with atypical or partial Infectious Mononucleosis syndrome. In the presenting study 37% of children presented with atypical (partial) IM. In children younger than 6-years old 43% of cases presented as atypical IM, whereas in children older than 6-years 26% of cases presented as atypical IM. It is obvious that the risk of developing IM after primary EBV infection correlates with the age of the patient. Young children are usually moderately ill, often presenting with atypical or partial IM. Although classic IM can occur at any age. The table of diagnosis on admission was wide on a considerable grade, which is another indicator that reflects the different clinical pictures with which primary EBV infection is manifested in childhood. Children with atypical IM are a diagnostic challenge because their signs and symptoms are not very sensitive or specific for EBV infection, so a high index of suspicion should be maintained while valuing a child with prolonged fever without an obvious focus.

5. Conclusion

In the early childhood, primary infection of EBV is usually asymptomatic or produce an acute illness that is not distinguishable from other acute illnesses of childhood. Fever is the most common symptom of EBV infection in children. Its duration is much longer than in most other viral infections of childhood. Primary EBV infection is a potential cause of Fever of Unknown Origin in Children.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

Authors declare no conflict of interest.

Statement of ethical approval

The present research work does not contain any studies performed on animals/humans subjects by any of the authors.

Statement of informed consent

Informed Consent was taken from the parents of hospitalized children included in the study, for using the data of their medical records, providing anonymity.

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