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Childhood infectious mononucleosis

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Abstract

Epstein-Barr virus (EBV) is a human herpesvirus that is ubiquitous in nature, and most of the world population is infected by it. Infectious Mononucleosis (IM) is the most common clinical syndrome caused by EBV. This study was conducted to valuate epidemiological and clinical features of Infectious Mononucleosis caused by EBV in children. In it were enrolled 107 children 0-14 years old hospitalized with the diagnosis of Infectious Mononucleosis. Children ranged from 8-months old to 12.5years old, median age was 4.74 years. Fever was the most prominent feature in 97% of cases followed by lymphadenitis and pharyngitis in 79% and 78% of cases. Hepatitis was found in 55% of children. Classic syndrome of Infectious Mononucleosis was more prevalent in older children. Conclusively the probability of developing Infectious Mononucleosis after primary EBV infection correlates with age, young children are often moderately ill, presenting with atypical or partial Infective Mononucleosis syndrome.

Keywords: Infectious Mononucleosis; Children; Fever; Pharyngitis; Lymphadenitis

1. Introduction

Epstein-Barr virus (EBV) is a gamma-herpesvirus, 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 linked conclusively to Infectious Mononucleosis (IM), which is its most common clinical manifestation [2]. EBV virions have a double-stranded, linear DNA genome, which is composed approximately of 100 well known and described genes, that is surrounded by a protein capsid. The glycoproteins that lie between the capsid and the envelope are important for cell tropism, host range, and receptor recognition [3]. Primary infection occurs in the oral region, epithelial cells and lymphocytes serve as host cells of EBV. EBV attaches to B cells by binding of the viral gp350 protein to CD21 on B cells [4]. An important consequence of EBV infection in B cells is that they are induced to activate their growth program and trigger differentiation into memory B cells, then infected memory B cells are released into the peripheral circulation. The number of infected B cells decreases over time after the onset of symptoms of primary infection, but these cells are never eliminated entirely [5].

A potent innate and adaptive immune response occurs during primary EBV infection, although it controls infection, does not eliminate it, so the virus persists for the lifetime of the infected individual. After acquire of the infectious virus to oral secretions, it takes 5 to 7 weeks for the primary EBV infection to manifest itself as infectious mononucleosis. The innate immune system is an important first line of defense against viral infections, and EBV stimulates a strong type I interferon (IFN) response early after infection. Another prominent inflammatory cytokine is IFN-γ, which is produced by activated T cells and NK cells. IFN-γ is thought to be important for control of EBV infection and reactivation. However, high levels of IFN-γ likely contribute to the symptoms experienced during infectious mononucleosis, as this cytokine is

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known to cause headache, fatigue, and fever [6]. The immunosuppressive cytokines IL-10 and transforming growth factor beta (TGF-β) are also detected in the sera of infectious mononucleosis patients. During acute infectious mononucleosis, both viral and host forms of IL-10 are detected in sera [7]. Host IL-10 is produced by monocytes and lymphocytes, functions to suppress T-cell proliferation and cytokine production, and can inhibit IFN-γ production from T cells [8]. IL-10 counteracts the pathogenic effects of IFN-γ during infectious mononucleosis, the highest levels of IL-10 were observed in patients with shorter durations of symptoms [9]. NK cells are another important component of the immune response and are thought to play a key role in regulating chronic viral infections, their number increases during infectious mononucleosis [10].

Both humoral and cellular immune responses are generated in EBV infection. The humoral or antibody response is critical in diagnosing infectious mononucleosis, and the cellular response (particularly the CD8 T-cell response) is critical for controlling viral replication but may also contribute to the severe symptoms of infectious mononucleosis. Both CD4 and CD8 T cells make a robust response to EBV antigens. Early in infection, CD8 T cells specific for lytic antigens tend to dominate the response, while CD4 and CD8 T cells specific for latent antigens do not show such a large burst but persist for life [11]. The massive lymphocytosis in the blood that characterizes infectious mononucleosis consist largely of CD8 T cells specific for EBV lytic antigens. This large adaptive immune response is thought to be responsible for the major symptoms of infectious mononucleosis [12]. As other herpesviruses EBV develops latency, and oral viral shedding of the virus can persist for months and recurs intermittently for years in most healthy individuals.

Aim

This study aimed to value epidemiological and clinical features of Infectious Mononucleosis caused by EBV in children.

2. Material and methods

This is a retrospective study. In it are enrolled 107 children, 0-14 years old, hospitalized with Infectious Mononucleosis, in the Pediatric Infectious Disease Ward in the University Hospital Center "Mother Tereza", Tirana during 2015-2019.

Diagnosis was concluded based on positive immunoglobulin M (IgM) of EBV viral capsid antigen. Data are extracted from the patients clinical records. Parameters studied are age, gender, clinical findings: fever, pharyngitis, lymphadenitis, splenomegaly, hepatitis.

3. Results

During 2015-2019 in the Pediatric Infectious Disease Ward in the University Hospital Center "Mother Teresa", Tirana were hospitalized 107 children aged 0-14 years old with the diagnosis of Infectious Mononucleosis caused by EBV. Males were 65% of them and females 35%. Median age was 4.74 years ranging from 8 months old to 12.5 years old. 67% of children were younger than 6 years old and 33% of children were older than 6 years old. In the age distribution chart the peak was at the age interval 2-3 years old and gradually lowers with advancing of the age (Tab.1, Fig.1).

Table 1 Epidemiological data

Male	70 (65%)
Female	37 (35%)
Age M (SD)	4.74(+/-2.776)
0-6 years	72 (67%)
6-14 years	35 (33%)

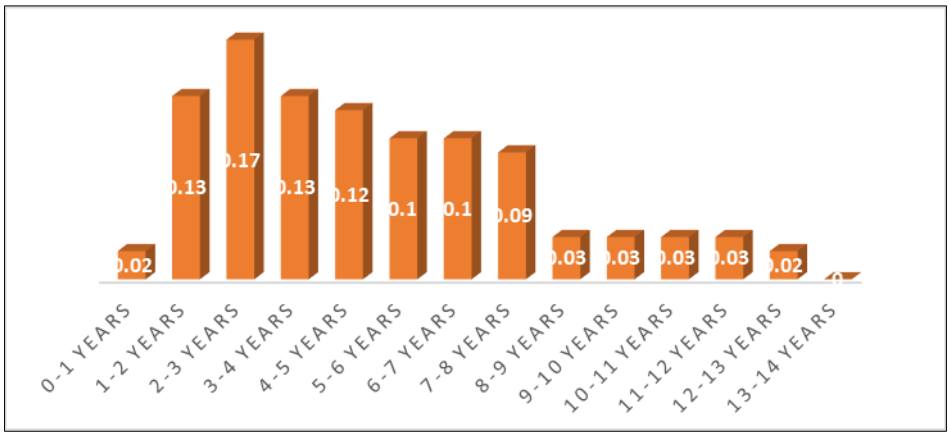

Figure 1 Age distribution chart

From the clinical features studies fever is the most frequent found in 97% of cases, lymphadenitis was present in 79% of cases, pharyngitis was present in 78% of cases, hepatomegaly was found in 25% of cases and splenomegaly was found in 36% of cases (Fig.2).

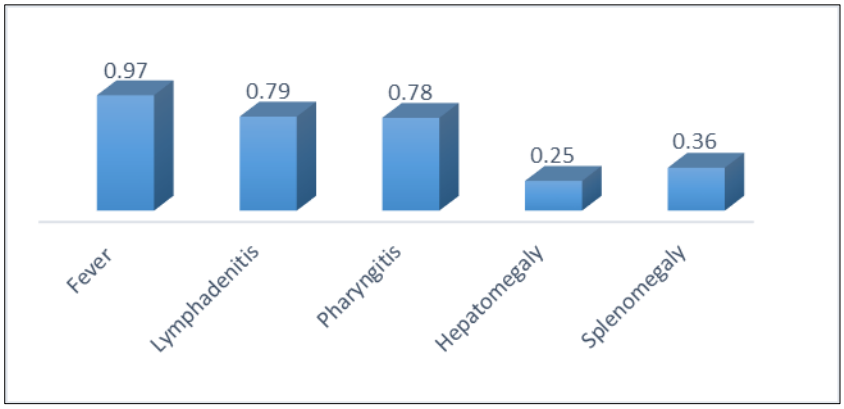

Figure 2 Clinical features

30% of Fevers were of high degree >40°C, 57% of Fevers were between 38.5°C-40°C, and 13% of Fevers were of low grade <38.5°C. The median duration of fever was 9 days.

59 children (55%), had hepatitis (elevated amino transferases). The percentage of children with hepatitis increased with age, 80% of children aged 6-14 years old had hepatitis, 45% of children between 2-6 years old had hepatitis, and 37% of children between 0-2 years old had hepatitis (Fig.3).

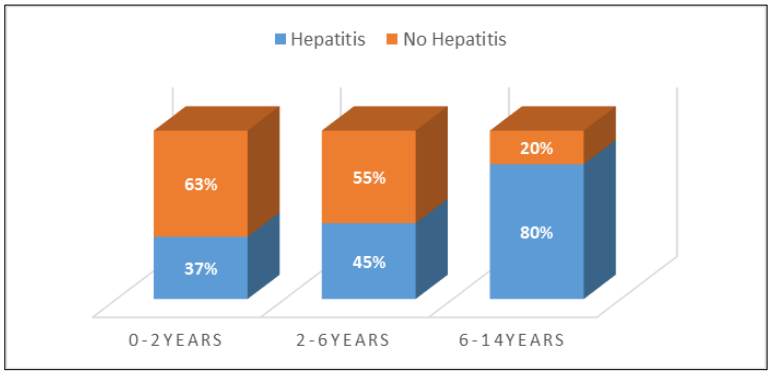

Figure 3 Hepatitis cases.

67 children (63%), had the classic presentation of Infectious Mononucleosis with fever, pharyngitis and lymphadenitis. Whereas 40 children (37%), had 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 had the classic form, and 26% of them had atypical presentation. 43% of children 0-6 years old had atypical presentation, whereas 57% of them had classic form of Infectious Mononucleosis (Fig.4).

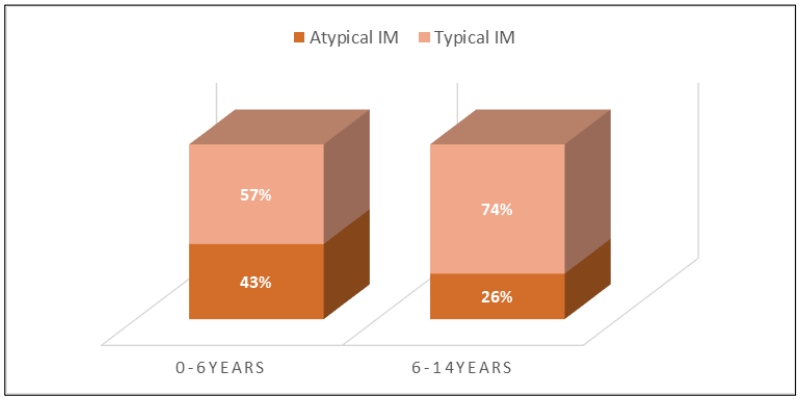

Figure 4 Clinical syndromes of Infectious Mononucleosis

4. Discussion

EBV infection is not a reportable disease, so its true prevalence is not known. The sero-prevalence of EBV varies widely by geographic location, developed countries carry a lower burden of sero-prevalence than the developing ones. Primary EBV infection occurs at a younger age among persons from lower versus higher socioeconomic backgrounds [13, 14]. Most of the children (67%) in this study were younger than 6 years old. The age of the children hospitalized with the diagnose of Infectious Mononucleosis in this study, ranged from 8 months old to 12.5 years old, literally it can be found in any age. The crowed living conditions in kindergartens and the process of sharing toys, bottles and utensils, and close contact put younger children in higher risk to contact the virus than the older ones. The peak age of the children with Infectious Mononucleosis, in this study was between 2-3 years old which correlates with the first year the children attend kindergarten.

Fever was the most significant symptom in the children hospitalized with Infectious Mononucleosis, found present in 97% of them. Fever was of high grade in almost one third of children, it was greater than 40°C, with a median duration of 9 days, which is longer than other childhood viral infections. Pharyngitis and lymphadenitis which are both signs that define Infectious Mononucleosis were found in 78% and 79% of children respectively. Hepatitis, confirmed by abnormal liver function, which is often present and is considered as part of acute disease rather than a complication, in this study was found in only 55% of children. However it was mild and subclinical and none of the children developed jaundice. The presence of hepatitis increased with age, 80% of children older than 6 years had abnormal liver function.

Most of the hospitalized children with Infectious Mononucleosis (63%) presented with full-blown syndrome (fever, pharyngitis, lymphadenitis), the remainder (37%) had partial syndrome of Infectious Mononucleosis. Typical syndrome of Infectious Mononucleosis was more common in older children, 74% of children over 6 years presented with the full clinical features of fever, pharyngitis, lymphadenitis. Whereas most of the children younger than 6 years of age presented with a partial (atypical) syndrome.

The risk of developing infectious mononucleosis after primary EBV infection correlates with the age of the patient [15]. Younger children are usually asymptomatic or moderately ill, with a partial infectious mononucleosis syndrome, although classic infectious mononucleosis can occur in this age group [16]. Primary EBV infection among adolescents and young adults may also be asymptomatic, but at least half of them develop full-blown infectious mononucleosis. It was proposed that adults acquire a higher viral dose than children do through salivary contact [17]. This higher viral dose would initiate a larger CD8 T-cell response, which would cause the symptoms of infectious mononucleosis through production of inflammatory cytokines. Another possible explanation is that preexisting immunity to other viruses which cross-reacts with EBV, the heterologous immunity, could provide a robust CD8 T-cell response to primary EBV [18]. This could explain why adolescents and adults tend to experience infectious mononucleosis, while children are largely asymptomatic, as adults are likely to have broader immune experience in general.

Primary EBV infection can be diagnosed with certainty only by performing the appropriate laboratory tests. Children who are mildly ill are unlikely to be identified because either their parents do not seek medical assistance or EBV infection is not considered in the differential diagnosis. Children with a typical infectious mononucleosis syndrome are still a diagnostic challenge because their signs and symptoms are not very sensitive or specific for EBV infection.

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. The probability of developing Infectious Mononucleosis after primary EBV infection correlates with the age of the patient. Young children are often moderately ill presenting with atypical or a partial Infectious Mononucleosis syndrome. However typical Infectious Mononucleosis syndrome can occur at any age.

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

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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