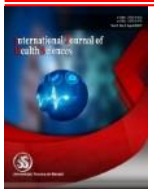

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Manifestations of EBV Infection in Children

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Abstract

The Epstein-Barr virus (EBV) is one of the most common viruses in humans. It was discovered in 1964, by electron microscopy, in the cultured cells from Burkitt Lymphoma. The primary EBV infection frequently presents as infectious mononucleosis, a clinical syndrome characterized by fever, sore throat, swollen posterior cervical lymph nodes, and fatigue. This study was conducted to explore the characteristics of EBV infection in children. In this sample of 107 hospitalized children who resulted in primary EBV infection, the most common symptoms and signs were fever, pharyngitis, and lymphadenopathy. The most affected age was 2-6 years old, and 40% of children presented with infectious mononucleosis. EBV infection in children often presents with symptoms that are indistinguishable from other childhood infections.

Contents

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1 Introduction

The Epstein-Barr virus (EBV), or Human Herpes Virus 4, is ubiquitous in nature and one of the most common viruses in humans. It was discovered in 1964 by Sir Michael Anthony Epstein and Yvonne Barr in collaboration with Bert Achong (Epstein et al., 1964). Virus particles were identified by electron microscopy in the cultured cells from Burkitt Lymphoma, and the results were published in *The Lancet* in 1964 by Epstein, Achong, and Barr (Miller, 2006). In 1967, a technician in their laboratory developed mononucleosis, and in the serum sample taken from him, there were detected antibodies to the virus. Four years after the virus detection, in 1968, it was discovered that EBV could directly immortalize B cells after infection (Henle et al., 1968).

Like other herpesviruses, EBV virions have a double-stranded, linear DNA genome surrounded by a protein capsid, which is covered by an envelope containing both lipids and glycoproteins, which are essential to infection of the host cell (Kieff & Rickinson, 2007; Epstein et al., 1965). The primary route of transmission is through saliva, so the primary infection occurs in the oral compartment. EBV infects both B cells and epithelial cells; the mechanisms to enter these cells are different. After the infection with EBV, the virus executes some or all of its repertoire of gene expression programs to establish a persistent infection. The lytic cycle produces large numbers of virions to infect other B-lymphocytes within the host (Odumade et al., 2011).

The primary EBV infection frequently presents as infectious mononucleosis, a clinical syndrome characterized by fever, sore throat, swollen posterior cervical lymph nodes, and fatigue. In the majority of cases, primary EBV infections cause no serious consequences from lifelong infection. However, EBV has a well-established oncogenic potential, which under some circumstances can be life-threatening. Furthermore, EBV infection has been implicated in the pathogenesis of various autoimmune diseases, such as multiple sclerosis (Munz et al., 2009).

This study aims to explore the clinical manifestations and hematologic findings that follow EBV infection in children.

2 Materials and Methods

This is a retrospective study of 107 children hospitalized in the Pediatric Unit of the University Hospital Center “Mother Tereza” in Tirana, Albania. Children were 0-14 years old. EBV infection was determined by detection of IgM antibodies to the early antigen VCA (viral capsid antigen), and absence of IgG antibodies to the latent antigen EBNA, which is the antibody profile of acute primary EBV infection. The parameters studied were: age, gender, symptoms, clinical findings, and hematological findings. Pearson Correlation was performed to measure the similarity or correlation between variables. Spearmen correlation was performed to describe the relationship between two variables in non-normally distributed continuous data.

3 Results and Discussions

Children in the age group 2-6 years old resulted in the most affected with acute primary EBV infection, 56 (52%) cases. The second most affected was the age-group 6-14 years old, 35 (33%) cases, and the least affected was the age-group 0-2 years old, 16 (15%) cases. The median age was 4.74 (DS $\pm$2.776). (Fig.1) Male was the most affected gender, 70 (65%) cases, and females, 37(35%) cases.

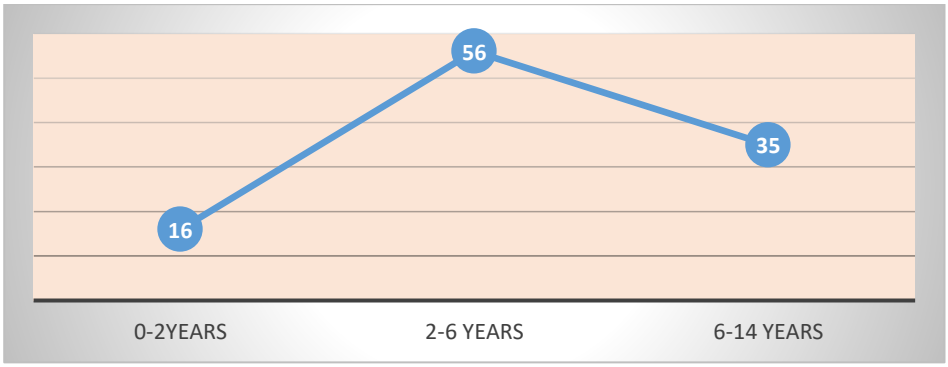

Figure 1. Age distribution chart

Hospitalized children with acute primary EBV infection showed a wide range of suspected diagnoses upon admission. Those ranged from Fever of Unknown Origin (4) to Orbital Cellulitis (1), Pneumonia (2), Sepsis (5), Infectious Mononucleosis (39), Hepatitis (7), Fever Without Focus (20), Tonsillitis (10), Lymphadenitis (17), and Leishmania Visceralis (2). (Fig.2).

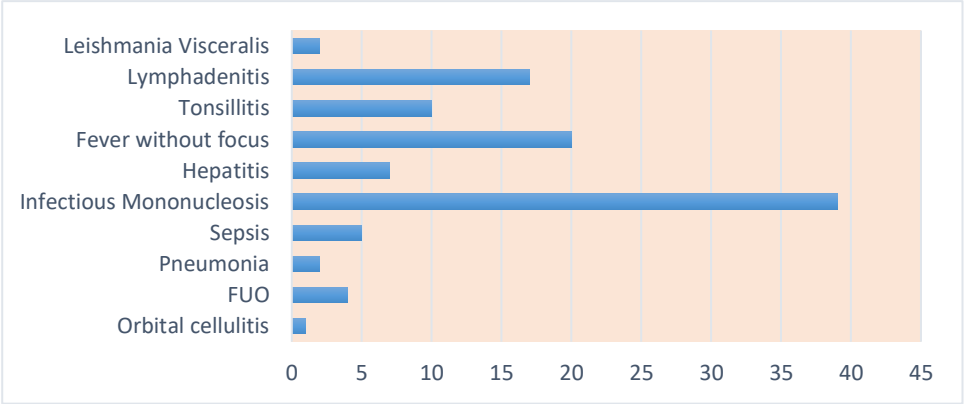

Figure 2. Diagnosis on the admission chart

Fever was the most consistent symptom, found in 97% of cases, followed by sore throat in 63% of cases. Difficulty in breathing was present in 205 of the children, and fatigue was reported in 21% of them. The least common symptoms were: abdominal pain reported in 12% of cases, vomiting in 9% and diarrhea was reported in 6% of children. (Fig.3)

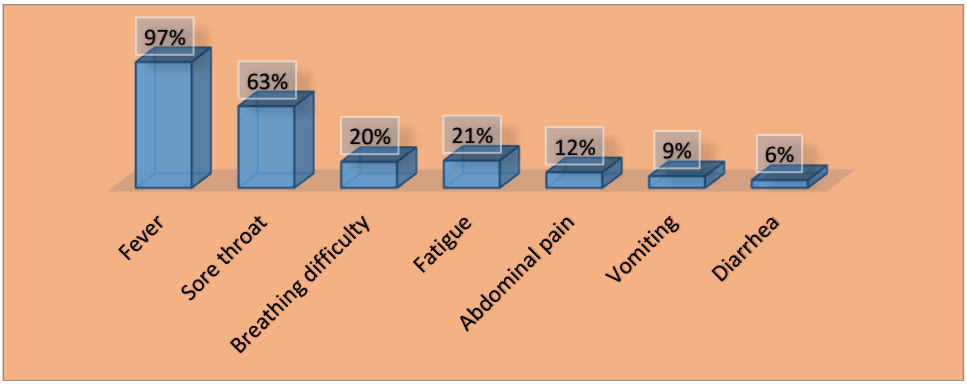

Figure 3. Symptoms distribution chart

The most common clinical sign was cervical lymphadenitis, which was present in 79% of children; generalized lymphadenitis was found in 24% of children. Pharyngitis was observed in 78% of children, the exudative form was observed in 46% of them. Spleen enlargement was found in 36% of cases, and liver enlargement was found in 25%. Rash was observed in 15% of children who had taken antibiotics. The least common clinical finding was palpebral edema in 6% of children. (Fig.4)

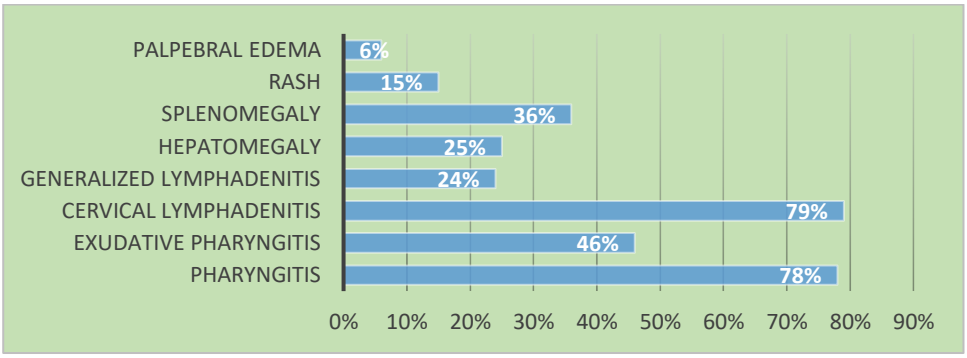

Figure 4. Clinical signs distribution chart

White blood cells (Leukocytes) were increased in 75% of cases. 25% of children had a leukocyte count over 20,000 cells/ml. (Fig.5)

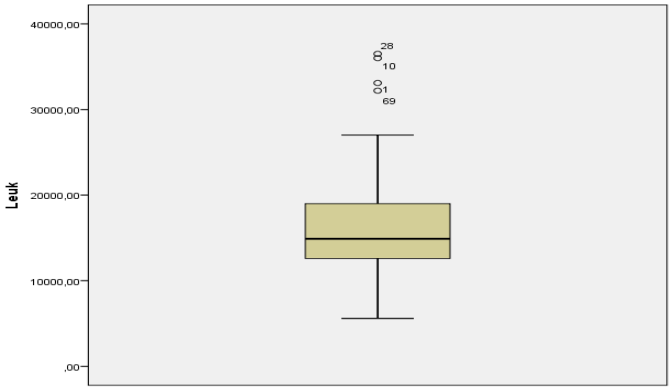

Figure 5. White blood cells distribution chart

Spearman Correlation test did not find a strong connection between leukocytes and lymphocytes, Spearman correlation coefficient r= 0,224, confidence level p>0.02 (Sig. (2-tailed)) (Fig. 6)

Correlations

			Leuk	Limf
Spearman's rho	Leuk	Correlation Coefficient	1,000	,224*
		Sig. (2-tailed)	.	,021
		N	107	107
	Limf	Correlation Coefficient	,224*	1,000
		Sig. (2-tailed)	,021	.
		N	107	107

Figure 6. Spearman correlation between leukocytes and lymphocytes

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

A weak reversed correlation was found between two variables, age and leukocyte count; the Spearman coefficient is small and negative, r = -0.291 and p =0.002. Younger children have higher leukocyte counts. (Fig.7)

Correlations

		Age	Leuk	Lymph	Thrombocyt
Age	Correlation Coefficient	1,000	-,291**	-,099	-,128
	Sig. (2-tailed)	.	,002	,311	,207
	N	107	107	107	99
	Correlation Coefficient	,150	,101	,203*	-,068

**. Correlation is significant at the 0.01 level (2-tailed).

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

Figure 7. Spearman correlation between age and leukocytes

Elevation in liver aminotransferases (ALT/AST) was found in 59(53%) of children.
A statistically significant correlation between the age of the children and generalized lymphadenopathy was detected by Chi-Square Test p=0,001, χ^2 (2)= 33,128. (Fig. 8)
Generalized lymphadenopathy was more prevalent in older children (6-14 years old). Whereas cervical lymphadenopathy was more prevalent in the age-group 2-6 years old. (Fig. 9).

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	33,128[a]	12	,001
Likelihood Ratio	39,080	12	,000
N of Valid Cases	107		

Figure 8. Correlation between age and generalized lymphadenopathy

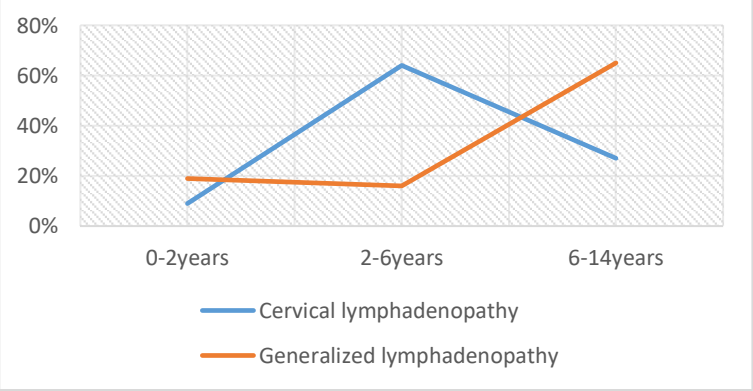

Figure 9. Distribution of lymphadenopathy

Discussion

Epstein-Barr virus is widely spread in nature and is highly efficient as it infects over 95% of the world's population. EBV is not a notifiable infection, and most of the children infected are not hospitalized; consequently, the exact incidence is unknown. However, it is estimated that approximately 50% of the US population and other developed countries are infected by the age of 5 years, and approximately 90% of the population is seropositive for EBV by the age of 25 years (Dowd et al., 2013; Crawford et al., 2006). The seroprevalence varies by geographic location, primary infection occurs at a young age in developing countries, due to overcrowded living conditions, and at a later age in more industrialized countries (Odumade et al., 2011).

In the presenting study, approximately 70% of the children were younger than 6 years. The most affected age group was 2-6 years old; during these years, children frequently attended day-care facilities. Young children most likely acquire primary EBV infection from close contact that involves exchange of oral secretions via shared items such as toys, bottles, and other objects. In young children, primary infection is usually asymptomatic or causes an acute illness that is often not recognized as being due to EBV (Odumade et al., 2011). In adolescents and young adults there are presented asymptomatic forms too; however, primary EBV infection frequently presents as infectious mononucleosis. In this study, only 40% of cases were suspected to have Infectious Mononucleosis on admission; the majority were suspected of other acute infections of the child, which ranged from Fever of Unknown Origin, fever without Focus, to Leishmania Visceralis, Sepsis, Orbital cellulitis, Tonsillitis, Pneumonia, and lymphadenitis (Cots et al., 2015). This wide range of diagnoses on admission reflects the nonspecific presentation of EBV infection in children. The majority of children were males; however, EBV has no gender predilection (Dunmire et al., 2018).

EBV infection elicits a potent innate and adaptive immune response. This response aims to control the infection, but does not eliminate it; the virus escapes the immune system and persists for a lifetime. The penetration of the virus in B lymphocytes and epithelial cells in the oral compartment initiates a robust immune response. This immune response is thought to be the cause of the most common clinical findings of EBV infection: pharyngitis and cervical lymphadenitis. These common signs were present in approximately 80% of the children enrolled in the study. The innate immune system is an important first-line defense against EBV infection. It induces a strong type I interferon (IFN) response early after infection. The inflammatory cytokines, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and IL-1β are found in increased levels in tonsillar tissue from patients with infectious mononucleosis (Foss et al., 1994). IFN-γ has an important role in controlling EBV infection and reactivation (Ebrahimi et al., 2001; Lee et al., 2009). These high levels of IFN-γ likely contribute to the symptoms experienced during infectious mononucleosis, as this cytokine is known to cause headache, fatigue, and fever (Schiller et al., 1990). NK cells are an important component of the immune response and play a key role in regulating chronic viral infections (Lanier, 2008). NK cell numbers increase during infectious mononucleosis; their numbers are associated inversely with disease severity (Tomkinson et al., 1987; Williams et al., 2005; Zhang et al., 2007).

The adaptive immune response to EBV, both humoral and cellular immune responses, is well studied. The humoral or antibody response is essential in diagnosing EBV infection, and the cellular response, particularly the CD8 T-cell response, is critical for controlling viral replication and also is responsible for the severe symptoms of infectious mononucleosis (Hislop et al., 2007). In the presented study was found that EBV induced a cellular immune response; 75% of children had increased white blood cells, most of them were lymphocytes, and consequently, a positive correlation was found between leukocyte and lymphocyte count, while applying the Spearman correlation test. Statistical tests also revealed that younger children had higher white blood cells. Lymph nodes and the lymphatic system are part of the adaptive immune system; they are major sites of lymphocytes and include B and T cells. The robust adaptive immune response results in the lymph nodes' enlargement, which was found in approximately 80% of children. Cervical lymphadenopathy predominated in younger children, whereas generalized lymphadenopathy predominated in older children (Wemel et al., 2017).

4 Conclusion

EBV infection is prevalent in children. The most affected are young children, 2-6 years old. Fever, pharyngitis, and lymphadenitis are the most common signs. In the majority of children, infection is non-specific, with symptoms and signs of a common viral infection. However, children may develop the clinical syndrome of infectious mononucleosis.

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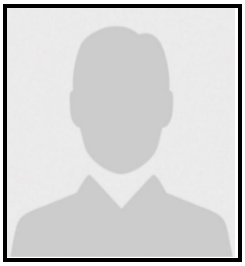

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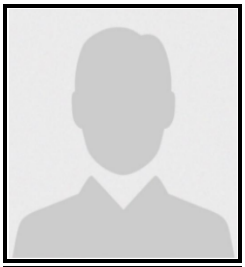

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