



REVIEW ARTICLE

## Atypical manifestations of Epstein–Barr virus in children: a diagnostic challenge<sup>☆</sup>



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### KEYWORDS

Epstein–Barr virus;  
Infectious mononucleosis;  
Child;  
Complications

### Abstract

**Objective:** Clarify the frequency and the pathophysiological mechanisms of the rare manifestations of Epstein–Barr virus infection.

**Sources:** Original research studies published in English between 1985 and 2015 were selected through a computer-assisted literature search (PubMed and Scopus). Computer searches used combinations of key words relating to “EBV infections” and “atypical manifestation.”

**Summary of the findings:** Epstein–Barr virus is a herpes virus responsible for a lifelong latent infection in almost every adult. The primary infection concerns mostly children and presents with the clinical syndrome of infectious mononucleosis. However, Epstein–Barr virus infection may exhibit numerous rare, atypical and threatening manifestations. It may cause secondary infections and various complications of the respiratory, cardiovascular, genitourinary, gastrointestinal, and nervous systems. Epstein–Barr virus also plays a significant role in pathogenesis of autoimmune diseases, allergies, and neoplasms, with Burkitt lymphoma as the main representative of the latter. The mechanisms of these manifestations are still unresolved. Therefore, the main suggestions are direct viral invasion and chronic immune response due to the reactivation of the latent state of the virus, or even various DNA mutations.

**Conclusions:** Physicians should be cautious about uncommon presentations of the viral infection and consider EBV as a causative agent when they encounter similar clinical pictures.

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### PALAVRAS-CHAVE

Vírus de Epstein–Barr;  
Mononucleose infecciosa;

### Manifestações atípicas do vírus de Epstein–Barr em crianças: um desafio diagnóstico

### Resumo

**Objetivo:** Esclarecimento da frequência e dos mecanismos patofisiológicos das manifestações raras da infecção por vírus de Epstein–Barr.

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## Crianças; Complicações

**Fontes:** Estudos de pesquisas originais publicados em inglês entre 1985 e 2015 foram selecionados por meio de uma busca na literatura assistida por computador (Pubmed e Scopus). As buscas no computador utilizaram combinações de palavras-chave relacionadas a “infecções por VEB” e “manifestação atípica”.

**Resumo dos achados:** O vírus de Epstein–Barr é um herpesvírus responsável por uma infecção latente vitalícia em quase todo adulto. A infecção primária ocorre principalmente em crianças e se apresenta como síndrome clínica da mononucleose infecciosa. Contudo, a infecção por vírus de Epstein–Barr pode apresentar diversas manifestações raras, atípicas e de alto risco. Ela pode causar infecções secundárias e diversas complicações dos sistemas respiratório, cardiovascular, geniturinário, gastrointestinal e nervoso. O vírus de Epstein–Barr também desempenha um papel significativo na patogênese de doenças, alergias e neoplasias autoimunes, com o linfoma de Burkitt sendo o principal representante das últimas. Os mecanismos dessas manifestações ainda não foram resolvidos. Portanto, as principais sugestões são invasão viral direta e resposta imune crônica devido à reativação do estado latente do vírus ou mesmo diversas mutações do DNA.

**Conclusões:** Os médicos devem tomar cuidado sobre apresentações incomuns de infecção viral e considerar o VEB um agente causador quando encontrarem situações clínicas semelhantes.

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## Introduction

Epstein–Barr virus (EBV) is a common infectious agent, found in approximately 95% of the world's population. Primary infection with EBV is more frequent during childhood and causes a mild infection, which usually presents with no symptoms.<sup>1</sup> However, when primary infection occurs during adolescence, it leads to infectious mononucleosis (IM) in 30–70% of cases, where up to 20% of B lymphocytes are infected with EBV.<sup>1,2</sup>

EBV is a DNA virus belonging to the herpes family, and is also known as human herpes virus 4. It is composed of a linear dsDNA genome enclosed by a capsid, which is surrounded by the tegument and a host cell membrane-derived envelope embedded with glycoproteins. EBV has a large genome, coding for 87 proteins. The functions of 72 of these proteins have been defined so far.<sup>1</sup>

EBV transmission is achieved with saliva it and initially infects epithelial cells in the oropharynx and nasopharynx. Afterwards, EBV enters the underlying tissues and infects B-cells. After a primary lytic infection, EBV is capable of remaining dormant in resting memory B-cells, from which it periodically reactivates. The ability of reactivation makes EBV a constant challenge to the host.<sup>1</sup>

IM is the main clinical entity caused by EBV. Diagnosis is based on clinical examination, revealing the classic triad of fever, lymphadenopathy, and pharyngitis,<sup>3</sup> and laboratory findings including the presence of atypical lymphocytosis and heterophile antibodies.<sup>2</sup> The disease is managed specifically with supportive care, since it is a self-limited infection.<sup>3</sup> However, IM has been associated with numerous early or late complications, with a range of graveness.

This review focuses on the rare manifestations of IM in children. Original research studies published in English between 1985 and 2015 were selected through a computer-assisted literature search (PubMed and Scopus). Computer

searches used combinations of key words relating to “EBV infections” and “atypical manifestation.” In addition, the reference lists of the retrieved articles helped in the search for other relevant articles, which were not found during the searching procedure. Thus, 48 studies were selected and discussed here (24 case reports, 14 reviews, five case control studies, one population-based study, two letters to editor, one cohort study, one meta-analysis). The potential factors, which may bias the findings of this review, are restriction of articles to English, together with database and citation bias.

## Secondary infections

### Acute dacryocystitis

Acute dacryocystitis is a rare complication of IM, with only five reported cases. It is defined by a painful, palpable mass in the medial canthal area, usually accompanied by fever.<sup>4</sup>

The etiology is nasal epithelial edema and lymphoid hyperplasia from IM, which cause temporary nasolacrimal duct obstruction. Colonization of lacrimal sac contents by respiratory pathogens ultimately leads to acute dacryocystitis. This complication is likely to occur in children and young adults due to the smaller nasal anatomy and unique epidemiology of EBV.<sup>4</sup>

Patients with IM and acute dacryocystitis should be treated with antibiotics; drainage of the lacrimal sac abscess may be required.<sup>4</sup>

## Respiratory complications

### Upper airway obstruction

Upper airway obstruction is a conceivably life threatening complication of IM. Significant airway obstruction affects

approximately 1–3.5% of cases. Suspicion should be raised in the presence of odynophagia, cervical lymphadenopathy, and symptoms of respiratory distress.<sup>5</sup>

IM causes inflammation of Waldeyer's ring, edema of the pharynx and epiglottis, and pseudomembrane formation in the large airways. Signs of severe upper airway obstruction are often absent during the first stages of the disease. Patients should be treated with corticosteroids, and in severe cases, acute tonsillectomy, endotracheal intubation, or tracheotomy may be mandatory in order to secure the airway.<sup>5</sup>

## Pneumonia

Pulmonary involvement is found in 5–10% of the IM cases in children. Reports of severe EBV symptomatic lung infection are rare and frequently described in immunosuppressed adults. There have been five reported cases of severe lung involvement in EBV infection in children. Three of these children suffered from respiratory distress and interstitial pneumonitis, one from bilateral lower lobe consolidation and effusion complicated by hemoptysis, and the last one from pleuropneumonia.<sup>6</sup>

The pathophysiological mechanism includes lymphocytes infected by EBV, which infiltrate the lung during acute IM. However, it is questionable whether this pulmonary involvement is the result of direct viral invasion of lung or whether it represents an immunologic reaction to the virus. It has also been suggested that EBV acts as a co-pathogen or induces a temporary immunosuppression, causing susceptibility to another infection.<sup>6</sup>

## Cardiovascular complications

### Acute myocarditis

Prevalence of EBV is estimated to be less than 1% in viral myocarditis,<sup>3</sup> while there are several anecdotal reports of heart complications from IM during the last 60 years.<sup>7</sup> EBV and CMV are associated with this pathology, particularly after heart transplantation.<sup>8</sup>

The pathophysiological progression is composed of three phases. During the first phase, destruction of the cardiomyocytes derives directly from virus-mediated lysis or indirectly from immune response with the expression of proinflammatory cytokines. During the second phase, T-cells detect the viral antigen and destroy the infected cardiac cells through cytokine or perforin secretion. In the last phase, the destroyed myocytes are replaced by diffuse fibrosis, leading to dilated ventricles and cardiac failure.<sup>8</sup>

Myocarditis, as well as other heart complications of EBV like pericarditis, might even precede clinical IM, hindering the diagnosis.<sup>7</sup>

### Atherosclerosis

The role of EBV in the pathogenesis of atherosclerosis is based on findings suggesting that EBV DNA is commonly found in atheromatous plaques. However, EBV DNA presence in

atheroma ranges from 12% to 80%, thus these findings are questionable.<sup>9</sup>

This complication regards only adults, and the possible mechanism is based on EBV-encoded enzyme deoxyuridine triphosphate nucleotidohydrolase (dUTPase). dUTPase has been shown to induce the production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and endothelial cell expression of intercellular adhesion molecule-1 (ICAM-1). Emotional and psychosocial stress is believed to deregulate immune repression of the virus, allowing its replication and the production of dUTPase. This mechanism provides an explanation for the connection between stress, EBV, and coronary artery events.<sup>10</sup> EBV-induced gene 3 (Ebi3) is also implicated in atherosclerosis.<sup>11</sup>

## Hematological complications

### Thrombocytopenia

Mild thrombocytopenia occurs in 25–50% of uncomplicated cases during the acute phase of the disease. An occasional patient may have thrombocytopenia for 8 weeks or more. In contrast, severe thrombocytopenia (platelet count  $<20 \times 10^9/L$ ) is rare, with 38 reported cases. Twenty-eight of these patients were younger than 21 years old. Two of these patients died of complications from thrombocytopenia and hemorrhage.<sup>12</sup> Although severe EBV-associated thrombocytopenia is rare, it can have life-threatening consequences. This complication should be considered in any patient with acute EBV infection and evidence of mucosal or dermal bleeding.<sup>13</sup>

It has been proposed that the pathophysiology of thrombocytopenia includes the presence of a platelet-destroying agglutinin produced in response to a viral agent–platelet bond. Other possible mechanisms include vascular damage due to the infectious agents, and hypersplenism or antibody formation in the spleen and the reticuloendothelial system.<sup>12</sup>

### Aplastic anemia

Aplastic anemia following primary EBV infection or in association with reactivation of EBV infection has been reported in 24 cases in the literature. Seventeen of these cases were children under 18 years old. However, it is likely that some cases of aplastic anemia characterized as idiopathic are, in fact, triggered by an EBV infection, since in young children EBV infection presents with atypical symptoms.<sup>14</sup>

EBV infected B-cells may provoke oligoclonal expansion of suppressor T-cells (CD8+, CD28–), which prevent autologous marrow hematopoietic cells development. EBV-associated and idiopathic aplastic anemia have similar prognosis.<sup>14</sup>

### Agranulocytosis

Mild neutropenia is a common manifestation in IM during the first weeks of illness, but agranulocytosis or severe neutropenia after IM is very rare, with only 29 cases reported.<sup>15</sup>

The pathogenesis of agranulocytosis after IM may involve decreased production or maturation of myeloid cells in the marrow, as a result of the direct effect of EBV or antibody-mediated peripheral destruction of myeloid cells. The hypothesis of maturation arrest of myeloid cells has been suggested because mature myeloid cells disappear in the patient's bone marrow. Anti-human neutrophil antigen-1a (anti-HNA-1a) and anti-HNA-1b antibodies are both associated with the pathophysiology in agranulocytosis after IM, although it is unknown whether anti-neutrophil antibodies are produced in EBV-infected B cells.<sup>15</sup>

### Lymphohistiocytosis

Hemophagocytic syndrome or hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening disease caused by a dysfunction of cytotoxic T cells and NK cells.<sup>16</sup> Incidence of HLH is estimated at one case per 800,000 people, half of which are associated with EBV. EBV-associated HLH has been observed in infants, children, and adults, but 80% of the cases occur in children of 1–14 years of age. HPS can be either primary, *i.e.*, due to an underlying genetic defect; or secondary, associated with malignancies, autoimmune diseases (macrophage activation syndrome), or infections. Infectious triggers are mainly viruses of the herpes group, with EBV being the most common.<sup>17</sup>

Possible mechanism includes T cell/NK cell deregulation, which leads to increased cytokine release, resulting in activation of histiocytes followed by hemophagocytosis. Histiocytic infiltration of the reticuloendothelial system causes hepatomegaly, splenomegaly, lymphadenopathy, and pancytopenia, eventually leading to multiple organ dysfunctions.<sup>16</sup>

### Genitourinary system complications

#### Renal dysfunction

EBV infection's renal involvement varies from microscopic hematuria and mild proteinuria to acute renal failure.<sup>18</sup> Renal dysfunction in IM is infrequent, mostly self-limited, and is rarely associated with failure of renal function. Evidence of mild renal involvement may be present up to 16% in patients with IM, but severe renal failure is rare.<sup>19</sup>

Hematuria or proteinuria can be found in 2% and 18% of IM cases respectively, whereas azotemia has been reported in only eight cases. Interstitial nephritis is the most common histologic abnormality. EBV is believed to play a vital role in the pathogenesis of IgA nephropathy. Occasional case reports of nephrotic syndrome, hemolytic uremic syndrome, hepatorenal syndrome, and rhabdomyolysis in patients with IM have also appeared.<sup>18</sup> Acute renal failure, although less common, has been associated primarily with rhabdomyolysis and interstitial nephritis.<sup>19</sup>

Finally, membranous nephropathy is a result of a prolonged systemic viral proliferation and persistent antigenemia in IM patients who lack a fully competent immune system, thus leading to immune complex deposition in the kidney.<sup>19</sup>

The possibility of IM should be considered when patients present acute renal failure, particularly if other features

such as fever, hemolytic anemia, hepatitis, or thrombocytopenia are present.<sup>18</sup>

### Genital ulcers

Genital ulceration is an uncommon manifestation of primary EBV infection. Identified by the Austrian dermatologist Lipschütz as an acute disease with fever, genital ulceration, and lymphadenomegaly in young women in 1913 and called Lipschütz's ulcer, today it is attributed to EBV infection.<sup>20</sup> Forty-one cases have been reported, with the vast majority being females.<sup>21–23</sup>

Patients develop one or more large ulcers with diameter between 0.3 and 4 cm.<sup>24</sup> The EBV-associated ulcers are often quite deep and necrotic, with irregular edges, and may cause pain and urinary symptoms. The mean healing time is 18 days.<sup>20</sup>

There have been three hypotheses suggested for the pathogenesis of EBV genital ulcers. The first hypothesis includes type III hypersensitivity reaction to immune complexes produced in the acute phase of EBV infection. EBV genital ulcers could also result from cytolysis due to EBV replication in vulvar keratinocytes, along with the inflammatory response to viral agents. Finally, these ulcers might represent a type of aphthosis.<sup>23</sup>

EBV is also present elsewhere in the female genital tract; however, its pathogenic role in the cervix, uterus, fallopian tubes, and ovaries is poorly understood.<sup>22</sup>

### Gastrointestinal complications

#### Hepatitis

Cholestatic hepatitis with mild liver dysfunction has been reported in more than 90% of patients with primary EBV infection, but severe liver dysfunction or gallbladder involvement is rare.<sup>25</sup> Primary EBV infection can cause a mild self-limited hepatitis, which typically resolves without clinical importance; jaundice can be seen in 5–10% of cases. Liver function abnormalities most often occur during the second week of illness and resolve within 2–6 weeks.<sup>25</sup>

#### Acute acalculous cholecystitis

Eleven cases of acute acalculous cholecystitis (AAC) have been reported during the course of primary EBV infection, 10 of which were in children or young adults.<sup>24</sup>

The main cause of AAC is gallbladder stasis and stagnation of bile. Increased bile viscosity, gallbladder wall ischemia, and proinflammatory mediators like eicosanoid have also been implicated in the pathogenesis. Gallbladder wall thickening and sludge formation may occur during the course of viral hepatitis. Hydrops of the gallbladder may occasionally develop during IM. Whether the increased thickness of the gallbladder wall results from direct invasion of the gallbladder mucosa by EBV or whether EBV-associated cholestasis causes the gallbladder wall irritation or both is not established.<sup>24</sup>

Recovery in all reported cases was excellent without any surgical treatment. Clinicians should be aware that AAC may

complicate IM, thus avoiding unnecessary invasive surgery and antibiotic therapy.<sup>24</sup>

### Acute liver failure

Acute EBV infection is a rare cause of acute liver failure (ALF) in young adults, but the available data are insufficient and there are not reports for children. As demonstrated by an 1887 patient cohort study, EBV is responsible for only 0.21% of ALF cases. Most cases occur post-transplantation or are associated with immunodeficiency syndromes.<sup>26</sup> Since EBV is a ubiquitous virus and lacks a specific treatment, there is a significant risk for children who are EBV negative before liver transplantation to be infected by an adult EBV positive liver. Rising EBV titers should be approached with reduction of immunosuppression.<sup>27</sup> It is questionable if the pathophysiology of EBV-related ALF is due to a generalized host immune response to EBV antigens or increased viral replication.<sup>26</sup>

### Splenic rupture

Splenomegaly is a common complication of IM and of other infectious conditions. It is frequently self-limited. Spontaneous splenic rupture, however, is a rare manifestation of IM, estimated at 0.1–0.5% of IM cases.<sup>28</sup> Most of reported splenic ruptures occurred within 3 weeks after IM diagnosis, but rupture appears to occur even after 7 weeks.<sup>17</sup>

EBV infection is believed to damage the splenic architecture by invading the spleen with lymphocytes and atypical lymphoid cells. This infiltration weakens the fibrous support system of the spleen and the splenic capsule becomes thinner, promoting the rupture. The rupture may occur following a minor trauma or spontaneously. The spontaneous rupture is hypothesized to be a result of either an acute increase in portal venous pressure caused by Valsalva maneuver or the compression of the enlarged spleen by the contracted diaphragm or the abdominal wall.<sup>28</sup>

Most cases report full resolution of hematoma from 4 weeks up to 1 year. There is evidence supporting that the spleen can retain full function while maintaining a low risk for repeat rupture even after parenchymal disruption. Thus, non-operative management of splenic rupture during IM, in a stable trauma patient, appears to be the treatment of choice, when also considering the risks following a splenectomy.<sup>28</sup>

Since splenic rupture is more frequent within 3 weeks of the infection onset, it is suggested that patients should refrain from sports for a minimum 3 weeks or once clinical symptoms and findings are resolved.<sup>17</sup>

## Neurological complications

### Facial nerve palsy

There have been only 14 cases of EBV-associated facial nerve palsy (FNP). Of these, 36% of the cases were bilateral, although bilateral FNP among FNP patients ranges from 0.3% to 2%. Otitis media caused by EBV may transmit the infection to the facial nerve leading to this type of FNP,

since it was recognized in two of these cases. Another possible explanation is the direct viral invasion or immunological response to EBV by the central nervous system. The mean age of these patients compared to non-EBV-associated FNP patients was much lower. This is associated with increased incidence of EBV infection during childhood.<sup>29</sup>

EBV infection should be suspected in patients with FNP, especially when it is bilateral, even when systemic manifestations of EBV infection are absent. These patients do not require any special treatment.<sup>30</sup>

### Guillain–Barre syndrome

There have been several case reports since 1947 reporting EBV infection to precede Guillain–Barre syndrome (GBS). It has also been reported that EBV is responsible for 10% of GBS cases. However, the criteria used in these reports are questionable, since EBV is ubiquitous.<sup>31</sup> The excess risk of GBS in the 2 months following EBV infection is believed to be 20-fold.<sup>32</sup>

### Encephalitis

The incidence of EBV encephalitis is less than 0.5%, but it may be increased to 7.3% among children who are hospitalized with IM.<sup>33</sup> Fatalities occur in 0.1–1% of these cases.<sup>2</sup> EBV encephalitis commonly presents with confusion, decreased level of consciousness, fever, and epileptic seizures. The manifestations of EBV encephalitis may exist before, during, or even after the symptoms of IM.<sup>34</sup> However, most patients with EBV encephalitis do not show typical symptoms of IM; therefore, EBV should be considered a possible cause of acute childhood encephalitis, regardless the presence of IM symptoms.<sup>33</sup> EBV encephalitis prognosis may vary from complete recovery to death.<sup>34</sup>

EBV encephalitis involves a wide diversity of locations in central nervous system, with the cerebellum, cerebral hemisphere, and basal ganglia as the most frequent. Patients with isolated brain stem involvement are characterized by the highest mortality, whereas patients with thalamic involvement were recognized with the most consequences. Isolated cortical involvement and involvement of spinal cord were associated with excellent prognosis.<sup>34</sup>

The pathogenesis of EBV-induced neurologic injury has not been elucidated, although it is suggested that immunologic mechanisms are mostly responsible rather than increased viral replication.<sup>33</sup>

### Alice in Wonderland syndrome

Alice in Wonderland syndrome (AIWS) is characterized by metamorphopsia, the self-reported presence of somatosensory alteration, such as distortion in the perception of size and shape of a patient's body and illusions of changes in the size, distance, form, even colors or spatial relationships of objects.<sup>35</sup> The illusions and hallucinations are similar to the strange incidents that Alice experienced in Lewis Carroll's "Alice's Adventures in Wonderland."<sup>36</sup>

AIWS is primarily described in patients with epilepsy or migraine and drug abusers, and has rarely been described in



association with EBV and other viral infections.<sup>35</sup> Four cases with AIWS secondary to IM have been reported, including two adolescents, a 9½ year-old boy and a 7-year-old girl with EBV encephalopathy.<sup>36,37</sup>

Metamorphopsia may precede onset or follow the resolution of all clinical signs and symptoms. The duration of the visual illusion ranges between 2 weeks and 7 months, but with complete recovery in all described cases.<sup>35</sup>

AIWS diagnosis may be complicated if the visual disturbances precede the classic symptoms of IM or if IM follows a subclinical course.<sup>38</sup> Therefore, patients compatible with AIWS symptoms should be suspected for EBV infection.<sup>35</sup>

## Psychiatric complications

### Psychotic episodes

Several studies suggest a link between early-life infection and adult schizophrenia and increased prevalence of EBV in the latter. EBV is a known neurotropic infectious agent, since it is a member of the Herpesviridae family. The human brain continues to develop through childhood and early adulthood, thus infection during this period, especially with neurotropic agents, could potentially increase the risk of neurological abnormalities.<sup>39</sup>

Possible pathophysiological mechanisms include inflammatory cytokines affecting the brain after the activation of the innate immune system. Early-life infection harms microglia, distorting neuronal survival and functioning. It is also believed that there is a connection between genetic psychosis background and vulnerability to infection.<sup>39</sup>

### Fatigue

IM is a specific and strong risk factor for the development of fatigue, subsequently. However, it is possible that doctors are biased, thus overestimating the prevalence of post-IM fatigue compared to that of other viral infections. Conversely, doctors may not record fatigue after IM, considering it as an expected sequel of any viral infection. Fatigue is a subjective symptom and so is difficult to calculate as a feature of the illness. Possible risk markers for fatigue after IM are female sex, premorbid mood disorder, lack of physical fitness, inactivity, and illness perception. These markers may be used to target prevention strategies and explore etiological mechanisms.<sup>40</sup>

### Depression

The association between infectious agents and depression has been controversial. Early clinical studies supported an association of raised antibody titers against HSV and EBV with depression. However, opposing results have also been reported that reveal no significant association between antibodies to HSV, influenza, or neurotropic viruses with depression. Findings suggest that smaller sample-sized studies tend to produce negative results, and identifying a significant association between EBV infection and depression may require a sufficiently large sample size.<sup>41</sup>

## Autoimmunity

The major environmental risk factors for systemic autoimmune diseases are infections.<sup>1</sup> EBV has been suggested to be associated with autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus, multiple sclerosis (MS), inflammatory bowel diseases, autoimmune thyroiditis, insulin-dependent diabetes mellitus, Sjögren's syndrome, autoimmune liver diseases, systemic sclerosis, and myasthenia gravis.<sup>42</sup>

One of the main mechanisms of how infections may cause autoimmunity is molecular mimicry. It is believed that sequence or structural similarities between microbial and self-antigens cross-react with B-cells, T-cells, and antibodies. Such examples are anti-citrullinated protein antibodies in RA and autoantibodies against  $\alpha$ B-crystallin in MS.<sup>42</sup>

An additional theory is referred to as bystander activation. In this case, the inflammatory background of an infection promotes activation or expansion of previously activated, autoreactive lymphocytes. Activation and expansion of autoreactive T-cells are known to occur due to the virus-induced severe local inflammation and intense local cytokine production.<sup>1</sup> EBV proteins involved in immune evasion and suppression of apoptosis of transformed infected lymphocytes are likely to result in loss of tolerance and development of autoimmunity.<sup>42</sup>

It has been suggested that raised serum titers of antibodies against EBV in autoimmune diseases could be the result of polyspecific B-cell activation. In response to polyclonal stimuli, memory B-cells proliferate and differentiate into plasma cells; this may depict a natural mechanism for the perpetuation of a lifelong serological immunity.<sup>42</sup>

Another hypothesis is the accumulation of T-cells, due to EBV frequent reactivation. EBV specific CD8+ T-cells are enriched in or near the diseased organs of patients with RA and MS, and they also accumulate in synovial fluid from patients with psoriatic arthritis, osteoarthritis, and Reiter's syndrome. This could reflect a local immune response against EBV in the diseased organs.<sup>42</sup>

After many years of viral, immunological, and epidemiological research, it is still debated whether EBV is a causative agent of these autoimmune entities.<sup>42</sup>

## Allergies

### Hypersensitivity to mosquito bites

This disease has appeared mostly in Japanese children. More than 50 cases of hypersensitivity to mosquito bites (HMB) have been reported in Japan, and there are several reports of cases in Taiwan and Mexico. HMB is identified by intense local skin symptoms, which comprise bulla, erythema, and ulceration or scarring, and systemic symptoms such as lymphadenopathy, high fever, and hepatosplenomegaly.<sup>43</sup>

CD4+ T cells from HMB patients react to specific mosquito salivary gland extracts. These T cells induce the reactivation of latent EBV infection in NK cells. EBV-carrying NK cells in HMB patients overexpress surface Fas ligand (Fas L) and the enhanced Fas L might be related to tissue damage, such as excessive skin lesions at mosquito bite sites and liver dysfunction. It has been suggested that these patients show

increased expression of viral oncogene LMP1 in EBV-infected NK cells, and the mosquito antigen also increases the expression and induces NK cell proliferation. LMP1 activates various signaling pathways during transformation, including PI3 kinase, Rac, NF- $\kappa$ B, and reactive oxygen signaling.<sup>43</sup>

Epidemiological observations suggest the possibility of endemic development of HMB, as a result of the patient's genetic background or the impact of multiple environmental factors.<sup>43</sup>

## Neoplasms

It is estimated that each year EBV is responsible for 84,000 cases of gastric carcinomas, 78,000 cases of nasopharyngeal carcinoma, and 28,000 cases of Hodgkin lymphoma. It is notable that the risk of EBV-positive Hodgkin lymphoma culminates at 4 years after IM, while it decreases to normal after 10 years. Each year there are over 6000 cases of EBV associated Burkitt lymphoma (BL) in less developed countries. The prevalence of BL in central Africa is 20 cases per 100,000 in children between the ages of 5 and 9 years.<sup>44</sup>

EBV is also associated with malignancies in immunocompromised patients. EBV lymphoma, for example, is the second most common malignancy developing after organ transplantation, because of the respective immunodeficiency.<sup>44</sup>

The most relevant children's neoplasm derived from EBV is Burkitt lymphoma.<sup>45</sup> Denis Burkitt observed a form of BL, endemic BL, which is most commonly seen in regions of sub-Saharan Africa. Regions of endemic BL have a very high frequency of disease, roughly 5–10 cases per 100,000 children. Viral genomes can be found in nearly 100% of endemic BL tumors.<sup>46</sup>

BL occurs worldwide at a much lower incidence in a form known as sporadic BL, which is also seen primarily in children, but has a lower association with EBV infection. Sporadic BL varies from 15% to 85% of viral tumors.<sup>46</sup>

The contribution of EBV to the pathogenesis of BL is similarly enigmatic. EBV leads to the development of transformed but not malignant lymphoblastoid cell lines (LCLs), by activating the proliferation of B cells. LCLs are responsible for the expression of numerous EBV-encoded latency proteins, many of which modulate key regulatory pathways such as PI3K and NF- $\kappa$ B, which have been solidly linked to cancer. In the absence of functional T cells or during continuous antigen presence, EBV-induced LCLs grow unhindered.<sup>47</sup> EBV also inhibits the apoptosis of premalignant tumor cells, allowing transforming events to occur.<sup>1</sup> The final steps of the oncogenic pathway are the translocations in MYC and TCF-3 genes. These are the most common mutations caused by EBV, which lead to the production of oncogenic transcription factors in BL.<sup>47</sup>

## X-linked lymphoproliferative disease

Primary EBV infection in boys with X-linked lymphoproliferative disease (XLPD) leads to fulminant, often even fatal disease. In addition, the condition predisposes to considerably elevated incidence of lymphomas.<sup>48</sup>

Mutation or deletion of the SH2D1A gene causes lack of functional signaling lymphocytic activation molecule

(SLAM)-associated protein (SAP), which regulates T-cell apoptosis. The lack of SAP results in uncontrolled proliferation of CD8+ T-lymphocytes leading to XLPD. T-cell apoptosis, which is also inefficient in the IM mostly due to the Epstein–Barr virus nuclear antigen anti-apoptotic function, enhances the effects of SAP absence.<sup>48</sup>

## Discussion

EBV infects virtually everyone by adulthood, and a lifelong latency is maintained. It infects children silently, whereas the majority of adolescents develop IM when infected.<sup>17</sup> On rare occasions the symptoms of IM may persist in a chronic or recurrent form, and fatal IM occurs rarely. Depending on the type and degree of immune deficiency and the time the EBV infection occurs in the life cycle, various atypical outcomes can occur.<sup>1</sup>

These manifestations may be acute, such as genital ulcers and acute dacryocystitis,<sup>4,20</sup> or delayed, such as autoimmunity and atherosclerosis.<sup>10,42</sup> Some of them may be relatively benign like fatigue, allergies, and FNP<sup>13,30,43</sup> and others may be life-threatening, like splenic rupture and ALF.<sup>17</sup> The remaining EBV complications include myocarditis, renal dysfunction, hepatitis, and AAC,<sup>8,19,24,25</sup> as well as several hematological, neurological, and respiratory entities.<sup>16</sup> Although these manifestations are quite rare, physicians and especially pediatricians should be aware of such cases in order to avoid unnecessary treatment and procedures, since IM would be easily treated only with supportive care.<sup>17,24</sup> When similar signs and symptoms to the aforementioned are present, the differential diagnosis should include EBV as a causative agent. The patient's history is of great importance and may provide the first indications for the appropriate diagnosis. Individualization and optimization of the patient's follow-up would also aid in preventing and treating possible complications.<sup>3</sup> In other words, knowledge of these scenarios would be beneficial for both the child's health and the treatment cost, hence improving medical practice.

It is notable that there are many open questions regarding the mentioned manifestations and further studies are needed to elucidate the role of the immunological mechanism of EBV on various target organs.<sup>42</sup> The full understanding of these mechanisms and the correlation between EBV and the pathological entities will assist in the treatment and prevention of severe morbidity.

Nonetheless, the immune system is critical in preventing the progression of EBV disease, since the immunological status of the patient plays a crucial role in the subsequent development of pathologies.<sup>1</sup> As life expectancy increases and as more manipulations of the immune system are achieved, more unusual manifestations of EBV infection will appear, which will be a diagnostic challenge in the future.

## Conflicts of interest

The authors declare no conflicts of interest.

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