Pediatric Mononucleosis and Epstein-Barr Virus Infection

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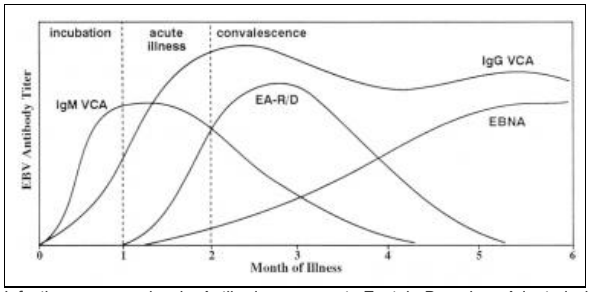
Background

Epstein-Barr virus (EBV), or human herpesvirus 4, is a gammaherpesvirus that infects more than 95% of the world's population. The most common manifestation of primary infection with this organism is acute infectious mononucleosis, a self-limited clinical syndrome that most frequently affects adolescents and young adults. Classic symptoms include sore throat, fever, and lymphadenopathy. Infection with Epstein-Barr virus in younger children is usually asymptomatic or mild. However, Epstein-Barr virus is also a human tumor virus, the first virus associated with human malignancy. Infection with Epstein-Barr virus is associated with lymphoproliferative disorders, especially in immunocompromised hosts, and is associated with various tumors, including nasopharyngeal carcinoma and Burkitt lymphoma.

See Clues in the Oral Cavity: Are You Missing the Diagnosis?, a Critical Images slideshow, to help identify the causes of abnormalities of the oral cavity.

Acute infectious mononucleosis was first described in the late 19th century as acute glandular fever, an illness consisting of lymphadenopathy, fever, hepatosplenomegaly, malaise, and abdominal discomfort in adolescents and young adults. In 1920, Sprunt and associates applied the name infectious mononucleosis to cases of spontaneously resolving acute leukemia associated with blastlike cells in the blood. Downey described the lymphocyte morphology in 1923. In 1932, Paul and Bunnell discovered that serum from symptomatic patients had antibodies that agglutinate the RBCs of unrelated species, the heterophile antibodies. This allowed enhanced diagnostic accuracy of infectious mononucleosis. The graph below demonstrates the antibody response to Epstein-Barr virus.



Infectious mononucleosis. Antibody response to Epstein-Barr virus. Adapted with permission from Johnson DH, Cunha BA. Epstein-Barr virus serology. Infect Dis Pract. 1995;19:26-27.

The search for the etiologic agent of infectious mononucleosis was unsuccessful for many years, partly because researchers did not appreciate that most primary infections are asymptomatic and that most adults are seropositive. In 1964, Epstein described the first human tumor virus when he found virus particles in a Burkitt lymphoma cell line.[1] Henle reported the relationship between acute infectious mononucleosis and Epstein-Barr virus in 1968.[2] Subsequently, a large prospective study of students at Yale University firmly established Epstein-Barr virus as the etiologic agent of infectious mononucleosis.[3]

Pathophysiology

Humans are the only known reservoir of Epstein-Barr virus. Epstein-Barr virus is present in oropharyngeal secretions and is most commonly transmitted through saliva. After initial inoculation, the virus replicates in nasopharyngeal epithelial cells. Cell lysis is associated with a release of virions, with viral spread to contiguous structures, including salivary glands and oropharyngeal lymphoid tissues. Further viral replication results in viremia, with subsequent infection of the lymphoreticular system, including the liver, spleen, and B lymphocytes in peripheral blood. Host immune response to the viral infection includes CD8+ T lymphocytes with suppressor and cytotoxic functions, the characteristic atypical lymphocytes found in the peripheral blood. The T lymphocytes are cytotoxic to the Epstein-Barr virus–infected B cells and eventually reduce the number of Epstein-Barr virus–infected B lymphocytes to less than 1 per 10^6 circulating B cells.

Primary infection with Epstein-Barr virus is followed by latent infection, a

characteristic of herpesviruses. After acute Epstein-Barr virus infection, latently infected lymphocytes and epithelial cells persist and are immortalized. In vivo, this allows perpetuation of infection, while, in vitro, immortalized cell lines are established. During latent infection, the virus is present in the lymphocytes and oropharyngeal epithelial cells as episomes in the nucleus. These episomes rarely integrate into the cell genome but do replicate with cell division and are passed to subsequent generations of cells. The rate of viral reactivation within the population of latently infected cells is low. Epithelial cells are the primary source of new virus in latently infected individuals, infecting B cells as they circulate through the oropharynx.

Two strains, labeled EBV-1 and EBV-2 (also known as type A and type B), are observed. Although the genes expressed during latent infection have some differences, the acute illnesses caused by the 2 strains are apparently identical. Both strains are prevalent throughout the world and can simultaneously infect the same person.

Knowledge of the structure of Epstein-Barr virus and of which proteins are expressed during different stages of its life cycle is required to understand the laboratory tests used to determine if an individual has primary acute, convalescent, latent, or reactivation infection. A mature infectious viral particle, which may be present in the cytoplasm of an epithelial cell, consists of a nucleoid, a capsid, and an envelope. The nucleoid contains linear double-stranded viral DNA. It is surrounded by the capsid, an icosahedral constructed of capsomers, which are tubular protein subunits. An envelope derived either from the outer membrane or the nuclear membrane of the host cell encloses the capsid and nucleoid (ie, the nucleocapsid). The envelope also contains viral proteins that were constructed and placed in the host cell membrane before viral assembly began.

To initiate cellular infection, a viral particle attaches via its major outer envelope glycoprotein (ie, gp350/220) to the Epstein-Barr virus receptor CD21 on a B lymphocyte. The binding site on epithelial cells also may be CD21, but this has not been confirmed. One in vitro model has shown EBV infection of CD21-negative polarized epithelial cells can occur with the assistance of EBV-infected memory B cells. Epstein-Barr virus is then internalized into cytoplasmic vesicles. After fusion of virus envelope with the vesicle membrane, the nucleocapsid is released into the cytoplasm. The nucleocapsid dissolves, the genome is transported to the cell nucleus, and the linear genome then circularizes, forming an episome. The cell may then proceed with either lytic infection with release of infectious virus or latent infection of the host cell. B lymphocytes with latent infection undergo growth transformation.

Lytic infection occurs early after primary inoculation. As a result of lytic infection in oral epithelial cells, Epstein-Barr virus can be found in the saliva for the first 12-18 months after acquisition. Thereafter, epithelial cells and lymphocytes are latently infected, with a few spontaneously converting, leading to viral replication, host cell lysis and death, and release of mature virions. Thus, the virus can be isolated from oral secretions of 20-30% of healthy latently infected individuals at any time.

During latent infection, cell proteins are expressed in 1 of 3 patterns. Type I latency, associated with Burkitt lymphoma, is characterized by expression of only Epstein-Barr virus–encoded RNAs, Epstein-Barr early regions (EBERs), and Epstein-Barr nuclear antigen 1 (EBNA1). Type II latency, associated with nasopharyngeal carcinoma, is characterized by expression of 3 latent membrane proteins (LMP1, LMP2A, LMP2B), plus EBERs and EBNA1. Type III latency is a pattern generally only found in healthy cells with latent infection. All 3 latency patterns can be seen in healthy individuals because the association with neoplastic changes is not absolute. In addition to the EBERs and EBNA1 expressed in type I latency, other nuclear antigens (including EBNA2, EBNA3A, EBNA3B, EBNA3C, and LMP) are expressed in type III latency. As mentioned above, spontaneous reactivation can occur in latently infected cells, leading to viral shedding.

A Danish study used data from a cohort of 2,823,583 Danish children born between 1971 and 2011 to study familial aggregation of infectious mononucleosis (IM). The study found evidence of familial aggregation of IM that warrants genome-wide association studies on IM disease etiology, especially to examine commonalities with causal pathways in other Epstein-Barr virus-related diseases.[4]

Epidemiology

Frequency

United States

Epstein-Barr virus is not a reportable infection, and the exact frequency of symptomatic primary infection is not known. By age 5 years, approximately 50% of the US population is infected. During childhood, primary infection is usually asymptomatic or associated with mild elevation of liver function test findings. Epstein-Barr virus infection acquired during adolescence is asymptomatic or associated with the syndrome of acute infectious mononucleosis.

The incidence of acute infectious mononucleosis was approximately 45 cases per 100,000 population per year in the early 1970s, with the highest incidence in individuals aged 15-24 years. However, changes in economic status may have changed both the age of initial infection and the incidence of infectious mononucleosis since the large epidemiologic studies were completed. In lower

socioeconomic groups, Epstein-Barr virus infection is more common, occurs at an earlier age, and is less likely to be associated with acute infectious mononucleosis.

Roommates of students with primary Epstein-Barr virus infection develop seroconversion at the same rate as the general population of college students.

Approximately 90% of the US population is infected with Epstein-Barr virus by age 25 years.

Epstein-Barr virus infection does not occur in epidemics and has relatively low transmissibility.

International

Epstein-Barr virus infection occurs with the same frequency and symptomatology in the developed nations of the world as in the United States.

Epstein-Barr virus is more frequently acquired in childhood in underdeveloped nations, and, therefore, the syndrome of acute infectious mononucleosis is unusual in these nations.

In Africa, the virus is associated with endemic Burkitt lymphoma in the setting of co-infection with *Plasmodium falciparum*.[2]

High numbers of Epstein-Barr virus episomes are found in the cells of undifferentiated or poorly differentiated nasopharyngeal carcinoma. This is the most common tumor in adult men in southern China and is also common in North American Inuits and North African whites.

Mortality/Morbidity

Most primary Epstein-Barr virus infections are asymptomatic. It is perhaps the most common reason for fever of unknown origin in young children and can present with fever in isolation or in the context of lymphadenopathy, fatigue, or nonspecific malaise.

Death is unusual in immunocompetent patients with acute infectious mononucleosis but may occur due to neurologic complications, upper airway obstruction, or splenic rupture.

Epstein-Barr virus infection is linked with numerous tumors. Endemic Burkitt lymphoma, the most common tumor of childhood in Africa, is associated with Epstein-Barr virus and malaria. Infection with *P falciparum* malaria stimulates polyclonal B-cell proliferation with Epstein-Barr virus infection and impairs the T-lymphocyte response to Epstein-Barr virus, apparently contributing to tumor pathogenesis.

In Asia, Epstein-Barr virus infection is related to development of nasopharyngeal carcinoma. Predisposing factors include a diet rich in nitrosamines, salted fish, Chinese race, and the HLA-A2 haplotype. Most non-Hodgkin lymphomas are associated with Epstein-Barr virus, and evidence of the Epstein-Barr virus genome is demonstrable in many of these tumors.

Epstein-Barr virus is also associated with Hodgkin lymphoma, in which the Epstein-Barr virus genome is present in the Reed-Sternberg cell. The EBNA1 protein interferes with tumor growth factor–beta signaling by downregulating *Smad2*; this interference with tumor-suppressor functions may contribute to tumor formation.[5] In addition, the same protein may play a role in immune evasion via recruitment of regulatory T-helper cells.[6] The precise mechanism by which Epstein-Barr virus may contribute to tumor pathogenesis are uncertain; some authors suggest that interleukin-10 may be linked to immune evasion, whereas others suggest it is linked to recovery.

Epstein-Barr virus infection in patients who are immunocompromised is associated with several syndromes and proliferative disorders.

Individuals with Duncan syndrome (ie, X-linked lymphoproliferative syndrome) may develop fatal primary Epstein-Barr virus infection due to a defect in the immune response to Epstein-Barr virus (poor anti-EBNA responses). The defective gene is the signaling lymphocyte activation molecule (SLAM)–associated protein (*SAP*) and is found on the X chromosome. Boys with Duncan syndrome often develop fatal massive hepatitis, hemophagocytosis, or a disseminated lymphoproliferative disorder triggered by primary Epstein-Barr virus infection. The median age of presentation is 2.5 years, with a median survival of 33 days. Survivors of the initial infection develop B-cell lymphoma or hypogammaglobulinemia and usually die by age 10 years. In children with Duncan Syndrome, the paucity of normal class-switched mature B cells means the virus instead establishes itself in nonswitched memory B cells (as opposed to naive or transitional B cells).[7]

Other congenital immunodeficiencies are associated with the development of Epstein-Barr virus–associated lymphoproliferative disorders. These include ataxia-telangiectasia, Chédiak-Higashi syndrome, Wiskott-Aldrich syndrome, and common variable immunodeficiency.

Posttransplant lymphoproliferative disorder (PTLD) is a potentially fatal lymphoproliferative syndrome associated with Epstein-Barr virus and monoclonal or polyclonal expansion of B cells. It occurs in patients after organ transplantation, particularly after heart transplantation, and usually responds to decreased immune

suppression.

Epstein-Barr virus–associated lymphomas occur in patients with secondary immunodeficiencies (eg, after cancer chemotherapy). Unfortunately, these tumors do not respond to decreased immunosuppression.

In patients with AIDS, Epstein-Barr virus is associated with hairy leukoplakia, leiomyosarcoma, CNS lymphoma, and lymphoid interstitial pneumonitis in children. However, only approximately one half of acquired immunodeficiency syndrome (AIDS)-associated Burkitt lymphomas contain Epstein-Barr virus genomes, which suggests a more complex interaction between chronic human immunodeficiency virus (HIV) infection and immune system defects. Acyclovir has been shown to have some potential benefit in treating patients with AIDS-associated Epstein-Barr virus disease.

Hemophagocytic lymphohistiocytosis (HLH) is an immune activation syndrome that can be triggered by EBV infection, especially in immunocompromised patients. HLH can also be triggered by other infections,[8] and inherited HLH exists as well, which typically presents at a very young age.

HLH is characterized by multiorgan dysfunction and cytopenias, and laboratory findings that overlap with severe EBV infection and leukemia. Typical presentations are fever, hepatosplenomegaly, rash, and pancytopenia. Various laboratory findings are suggestive of HLH, including high ferritin, high triglycerides, and low fibrinogen, as well as cytopenia in at least 2 cell lines. The most specific serologic marker is high levels of soluble interleukin 2 receptor. Low natural killer cell number and activity is also a sensitive marker for HLH.

Race

Epstein-Barr virus infection has no racial predilection; however, HLA-A2 haplotypes, which are more common in people of Chinese origin, are associated with a predisposition for nasopharyngeal carcinoma. The risk associated with HLA-A2 haplotypes is higher than any environmental risk posed by diet. First-generation US immigrants of Chinese origin have a higher risk for nasopharyngeal carcinoma.[9]

Large epidemiologic studies performed in the 1970s revealed that acute infectious mononucleosis was 30 times more likely to occur in whites than in African Americans. However, this correlated with lower social economic status and earlier asymptomatic infection in African Americans and, therefore, did not reflect a true racial difference.

Sex

The incidence of infectious mononucleosis is the same in men and women, although the peak incidence occurs 2 years earlier in females.

Postinfectious fatigue is more common in females.[10, 11]

Age

Epstein-Barr virus infection usually occurs during infancy or childhood and remains latent through life.

In developed nations, infection may not occur until adolescence or adulthood, and approximately 50% of adolescents who acquire Epstein-Barr virus develop the infectious mononucleosis syndrome.

Acute infectious mononucleosis has been reported in middle-aged and elderly adults; these individuals are usually heterophile antibody negative.

Clinical Presentation

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