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Review Article

Heterophile Antibody Positive Infectious Mononucleosis by Epstein Barr Virus (EBV) - A Short Review

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Abstract

Epstein Barr virus (EBV) is a member of the herpes virus family under the subfamily gamma *Herpesviridae* with lymphoproliferative potential growing abundantly in lymphoid tissue. Infectious mononucleosis (IM), is an acute self-limited illness usually seen in nonimmune young adults following primary infection with the EB virus, EBV has been found as the most common etiological agent of heterophile positive IM. Intimate oral contact, as in kissing, appears to be the predominant mode of transmission. This accounts for infectious mononucleosis being called the `kissing disease'. The atypical mononuclear cells in IM are not virus infected B lymphocytes but lymphoblasts derived from T cells reactive to the virus infection. The blood picture may sometimes resemble lymphocytic leukemia. The original serologic test for infectious mononucleosis, the Paul-Bunnell test, detected heterophile antibodies by agglutination of sheep or horse red blood cells. The Paul Bunnell antibody develops early during the course of infectious mononucleosis, and disappears within about two months. These tests are now available in convenient latex agglutination or solid phase immunoassay form.

Keywords: EBV; Kissing Disease; Atypical Mononuclear Cells; Paul-Bunnell Test; Heterophile Antibodies

Introduction

Epstein Barr virus (EBV), also known as human herpesvirus 4, is a member of the herpes virus family under the subfamily gamma *Herpesviridae*. EB virus is a DNA virus with a toroid shaped protein core that is wrapped with DNA, a nucleocapsid with 162 capsomers, a protein tegument between the nucleocapsid and the envelope. The outer envelope is coded with glycoprotein spikes [1]. In 1958, Burkitt described an unusual lymphoma in children in certain parts of Africa. Based on epidemiology, Burkitt hypothesized that this lymphoma may be caused by a mosquito born virus.

Several attempts have been made to isolate viruses from such tumours. This has led to the isolation of many viruses, apparently 'passenger viruses' from lymphoma cells which does not have any malignant potential. Epstein, Barr and Achong in 1964, isolated a new type of herpesvirus, named the EB virus, specifically affecting cells of the B lymphocyte lineage [2]. Only human and some subhuman primate B cells have receptors (CD 21 molecules) for the virus. EBV infected B cells are transformed so that they become capable of continuous growth *in vitro*. It is one of the most common viruses affecting humans of all ages. EBV can cause infectious mononucleosis and other illnesses. EBV is closely related to viruses present in Old World nonhuman primates, including EBV-like viruses of chimpanzees and rhesus monkeys. For example, the rhesus monkey virus and EBV share similar sequences and genetic organization, and they maintain persistent infection in the oropharynx and in B cells [3]. Thus, EBV probably evolved from a nonhuman-primate virus. In the 1980s, EBV was found to be associated with non-Hodgkin's lymphoma and oral hairy leukoplakia in patients with the acquired immunodeficiency syndrome (AIDS) [4,5]. In 1970 EB virus DNA was detected in tissues from various malignancies including anaplastic nasopharyngeal carcinoma and Burkitt's lymphoma [6]. Later on EB virus DNA has been found in tissues from other cancers, such as T-cell lymphomas and Hodgkin's and Non-Hodgkin's disease [7,8]. Infectious mononucleosis (IM), is an acute self-limited illness usually seen in nonimmune young adults fol-

lowing primary infection with the EB virus, EBV has been found as the most common etiological agent of heterophile positive IM. The atypical mononuclear cells in IM are not virus infected B lymphocytes but lymphoblasts derived from T cells reactive to the virus infection. The blood picture may sometimes resemble lymphocytic leukemia. Two major EB virus types have been detected in humans: EBV-1 and EBV-2 (also known as types A and B). EBV-1 and EBV-2 differ in the sequence of the genes that code for the EBV nuclear antigens [9]. EBV-2 immortalizes B cells less efficiently than EBV-1 *in vitro*, and the viability of EBV-2-infected lymphoblastoid cell lines is less than that of EBV-1-infected lines [10].

Epidemiology

The Epstein Barr (EB) virus is ubiquitous in human populations of all age groups. As with other herpes viruses, infection with the EB virus leads to latency, periodic reactivation and lifelong persistence. Each individual get infected with EBV at least once in a life time. The EB virus antibodies are present in about 95 per cent of adults and children. In the overcrowded developing countries like India, the EB virus infection occurs in infancy and childhood, when it is usually asymptomatic. In the affluent countries, primary infection is often delayed till adolescence and early adulthood, when it may lead to infectious mononucleosis. In countries with high standards of hygiene a considerable number of people do not become infected as young children, the percentage of each age group remaining free from infection [11]. The source of infection is usually the saliva of infected persons who shed the virus in oropharyngeal secretions for months following primary infection and intermittently thereafter. The EB virus is not highly contagious and droplets and aerosols are not efficient in transmitting infection. It has been clear that virus in the buccal fluid is the main source of transmission of the infection in the population, by droplets and casually contaminated objects in the case of young children, and by direct salivary transfer during kissing among the sexually active people [12]. Intimate oral contact, as in kissing, appears to be the predominant mode of transmission. This accounts for infectious mononucleosis being called the `kissing disease'. Infection may also follow blood or marrow transfusion but these are rare events. Routine screening of these products for EBV are not recommended. Those who miss the clinically silent natural primary infection in early childhood are likely sooner or later, to undergo delayed primary infection. Although 50 percent of such delayed infections are symptom free, as in childhood, the other 50 percent are accompanied by disease: classic infectious mononucleosis (IM) [13]. EBV infection leads development of both cell mediated immunity and humoral immunity to the virus particle. Primary infection in early childhood is almost always symptom-free and leads only to the generation of antibodies to the viral and virus-determined antigens and to the development of specific cytotoxic T lymphocytes [14]. Cell mediated and humoral immunological responses are maintained continuously thereafter throughout the life. Whenever the host's immunity is compromised, the virus undergo periodic re-activation and exacerbation of the disease. These are responsible for keeping the lifelong EBV infection in check. The EB virus persists as a latent infection in a few circulating B lymphocytes [15]. EBV is shed into the buccal fluid in readily detectable amounts in about 20 percent of those who have been infected with or without symptoms. In small amounts from time to time, the virus has also been detected in other body fluids and genital secretions including urine [16].

Pathogenesis

Following the entry of virus in through respiratory route, the virus gain access to the pharyngeal epithelial cells through CR 2 (or CD 21) receptors. It multiplies locally, invades the bloodstream and infects B lymphocytes in which two types of changes are produced. In most cases, the virus becomes latent inside the lymphocytes, which become transformed or 'immortalised' so that they become capable of indefinite growth *in vitro*. They are polyclonally activated to produce many kinds of immunoglobulins. The heterophile sheep erythrocyte agglutinin seen characteristically in infectious mononucleosis is an example of such polyclonal activation. A second type of effect, shown by a few infected B cells is lytic infection, with cell death and release of mature progeny virions. The mononucleosis represents a polyclonal transformation of infected B lymphocytes. EB virus antigens are expressed on the surface of infected B cells. The atypical lymphocytes seen in blood smears in infectious mononucleosis are T lymphocytes. Intermittent reactivation of the latent EB virus leads to clonal proliferation of infected B cells. In immunocompetent subjects, this is kept in check by activated T cells. In the immunodeficient, B cell clones may replicate unchecked, resulting in lymphomas. Hyperendemic malaria prevalent in Africa is believed to be responsible for the immune impairment in children with Burkitt's lymphoma. The frequency of lymphomas seen in many types of immunodeficiencies, most typically in AIDS, may have a similar pathogenesis. Nearly half the lymphomas seen in immunodeficient subjects contain EB virus DNA sequences.

Modes of Transmission

EBV infection usually occurs in individuals of a young age, with low socioeconomic status or development, from a larger than average family, and with poor hygienic standards. By their third decade of life, 80 - 100% of these individuals become carriers of the infection [17]. The oral route is the primary route of transmission of the virus; however, transmission by transfusion has been documented. In developing countries, infection is acquired in the first few years of life. Crowding and/or the practice of pre-chewing food for infants may be contributing factors. In the developed world, infection is often delayed to adolescence, when transmission is more likely because of intimate oral exposure. About 50% of primary EBV infections during young adulthood result in clinical infectious mononucleosis [18]. Infectious mononucleosis is usually acquired from a transfer of saliva, and in young adults, this is more likely to occur after the onset of sexual activity. However, only limited data are available to support this hypothesis [19]. In a cohort study of sexually active young women, the development of detectable antibodies against EBV after primary infection increased with increasing number of sexual partners, and was greatest when a new sexual partner was encountered in the 2 years before seroconversion. In addition, transient EBV DNA loads were detected in cervical cytology samples in some of the women [20]. Delayed primary infection occurs as a result of the high living standards of modern western countries, young adults encounter the virus for the first time at an age when the mode of infection and size of infecting dose are different from those in children: children come into contact with saliva from a shedder as airborne droplets or contamination on some sucked object, and thus receive a much smaller amount of virus than a young person taking in large quantities of virus containing saliva from such a carrier during mouth-to mouth kissing.

Infectious mononucleosis

Infectious mononucleosis is a clinical syndrome caused by Epstein Barr virus (EBV), an acute self-limited illness usually seen in nonimmune young adults following primary infection with the EB virus. The incubation period is 4 - 8 weeks. Typical features of infectious mononucleosis include fever, pharyngitis, adenopathy, malaise, and an atypical lymphocytosis. Splenomegaly, hepatomegaly, jaundice, and splenic rupture can occur in patients with infectious mononucleosis, but these complications are rare [21]. Some patients treated with ampicillin may develop a maculopapular rash due to immune complex reaction to the drug. There is often associated hepatitis which is usually subclinical and demonstrable only by liver function tests. A number of other complications have been recorded, including haematological, neurological, cardiac and pulmonary conditions and splenic rupture. In most cases, spontaneous resolution of the disease occurs in 2 - 4 weeks. In some it may be more prolonged and lead to a state of mental and physical fatigue in convalescence. The incidence in persons younger than 10 years and older than 30 years is less than one case per 1,000 persons per year, but mild infections in younger children often may be undiagnosed [22]. Most patients with infectious mononucleosis have leukocytosis with an absolute increase in the number of peripheral mononuclear cells, heterophile antibodies, elevated serum aminotransferase levels, and atypical lymphocytes. The atypical lymphocytes are primary T cells, many of which are responding to the EBV-infected B cells.

Acute and late sequelae of Infectious Mononucleosis Syndrome (Adapted from references 23-25)

- Cranial nerve palsies and Mono-neuropathies
- Encephalitis/Meningitis
- Retro-bulbar neuritis
- Acute interstitial nephritis
- Haemolytic anaemia
- Myocarditis and cardiac conduction abnormalities
- Thrombocytopenia
- Upper airway obstruction

Diagnosis

The Infectious mononucleosis syndrome is characterized by an absolute and relative lymphocytosis and an increased proportion of atypical lymphocytes. When a higher cut-off point is used to define an abnormal number of atypical lymphocytes, the sensitivity decreases (i.e. more false-negative diagnoses) and the specificity increases (i.e. fewer false-positive diagnoses). The original serologic test for infectious mononucleosis, the Paul-Bunnell test, detected heterophile antibodies by agglutination of sheep or horse red blood cells [26]. Later, guinea pig kidney absorption of serum was added to increase the specificity of the test [27]. These tests are now available in convenient latex agglutination or solid phase immunoassay form. Although they are relatively specific, heterophile antibody tests are somewhat insensitive, particularly in the first weeks of illness. The false-negative rate is as high as 25 percent in the first week, approximately 5 to 10 percent in the second week, and 5 percent in the third week of illness. Heterophile antibody tests are less sensitive in patients younger than 12 years, detecting only 25 to 50 percent of infections in this group,

compared with 71 to 91 percent in older patients [28]. During infectious mononucleosis, heterophile antibodies agglutinate sheep erythrocytes. However, such antibodies may also occur after injections of sera and sometimes even in normal individuals. Infectious mononucleosis antibodies may be differentiated by absorption tests. Inactivated serum (56°C for 30 minutes) in doubling dilutions is mixed with equal volumes of a 1% suspension of sheep erythrocytes. After incubation at 37°C for four hours the tubes are examined for agglutination. An agglutination titre of 100 or above is suggestive of infectious mononucleosis. For confirmation, differential absorption of agglutinins with guinea pig kidney and ox red cells is necessary. The Forssman antibody induced by injection of horse serum is removed by treatment with guinea pig kidney and ox red cells. Normally occurring agglutinins are removed by guinea pig kidney, but not by ox red cells. Infectious mononucleosis antibody is removed by ox red cells but not guinea pig kidney. This differential agglutination test has largely been replaced by a simple slide agglutination test employing sensitised horse erythrocytes, with the same sensitivity and specificity. The Paul Bunnel antibody develops early during the course of infectious mononucleosis, and disappears within about two months. Tests are also available for the demonstration of specific EB virus antibodies. Immunofluorescence and ELISA are commonly employed. More sensitive tests have been developed that detect viral capsid antigen (VCA-IgG and VCA-IgM). VCA-IgG and VCA-IgM tests are useful in diagnosing patients who have highly suggestive clinical features but negative heterophile antibody test results. Antibody to Epstein-Barr nuclear antigen (EBNA), while typically not detectable until six to eight weeks after the onset of symptoms, can help distinguish between acute and previous infections. If EBNA is positive in a patient with acute symptoms and suspected infectious mononucleosis, previous infection is suggested. Elevated hepatic transaminase levels are relatively common in patients with infectious mononucleosis, occurring in approximately one half of patients [29]. If the patient has more than 20 percent atypical lymphocytes or more than 50 percent lymphocytes with at least 10 percent atypical lymphocytes, infectious mononucleosis is quite likely, and further confirmation of the diagnosis is not needed. A positive result of a heterophile antibody test also is strong evidence in favor of a diagnosis of infectious mononucleosis. A negative result of an antibody test, particularly during the first week of illness, may indicate that the patient does not have infectious mononucleosis. However, it also could be a false negative result or could indicate that the patient has an infectious mononucleosis like syndrome caused by CMV or toxoplasmosis. The patient should be treated symptomatically, and if the patient does not clinically improve within five to seven days, a second heterophile antibody test should be performed. If an accurate diagnosis is urgently required, a VCA-IgM test may be selected. A negative result is strong evidence against the diagnosis of infectious mononucleosis. The IgM antibody to VCA (virus capsid antigen) appears soon after primary infection and disappears in 1 - 2 weeks. It is a reliable indication of primary infection. The IgG anti-VCA antibody persists throughout life and indicates past or recent infection. The new appearance of antibody to the EB nuclear antigen (EBNA) is also a useful marker for primary infection. Antibodies to early antigens (EA) are present in high titres in EBV associated lymphomas. However, these specific tests are of limited availability. The infectious mononucleosis syndrome can follow infection by other agents such as cytomegalovirus and toxoplasmosis or as a reaction to non-infectious stimuli. However, the heterophile Paul Bunnel test is positive only in disease caused by the EB virus.

Treatment and Prevention

The treatment of infectious mononucleosis is mainly supportive. It includes maintenance of adequate hydration of the patient; use of nonsteroidal anti-inflammatory drugs like paracetamol and diclofenac to suppress fever and myalgia. Gargling with a 2 percent lidocaine, povidone-iodine or concentrated salt water solution will help to relieve pharyngeal irritation. Recommendation of bed rest in IM is controversial. Experimental studies found that enforced bed rest slowed recovery. As there is lack of evidence for bed rest in many other conditions, it seems sensible to recommend that patients base their return to usual activities on their energy levels. Systemic steroids have also been indicated for the treatment of patients with infectious mononucleosis [30]. Various clinical studies have shown benefit from use of systemic corticosteroids like Prednisolone in IM which may lead to normalization of body temperature and laboratory findings. But these drugs should be used with great caution in any pyrexia of unknown origin as there high risk of worsening the clinical condition of the patient and of course the added adverse effects of corticosteroids should be taken into consideration [31]. A multicenter, double-blind, placebo-controlled study by Tynell E., *et al.* with use of Acyclovir and Prednisolone for treatment of acute infectious mononucleosis concluded that there was no benefit from combination of these two drugs in IM either in terms of reliving signs and symptoms or in the laboratory findings [32]. In a small, double-blinded, randomized trial of 40 children with suspected infectious mononucleosis, those who were given oral dexamethasone (0.3 mg per kg) had less pain at 12 hours but not at 24, 48, and 72 hours. These findings indicate that repeated doses of corticosteroids are needed at frequent intervals. The most

important clinical indication of using corticosteroids is in patients with significant pharyngeal and laryngeal edema that causes respiratory obstruction based on clinical experience and case reports [33]. A meta-analysis by Torre D., *et al.* of five randomized controlled trials involving 339 patients, found that patients who took acyclovir had less oropharyngeal shedding at the end of therapy, but this treatment provided no significant or consistent clinical benefit and is therefore not recommended [34]. This study shows that use of Acyclovir has great potential in reducing the secondary attack rates in house hold contacts of infectious mononucleosis patients even though no significant benefit found in infected patients. Vendelbo Johansen L., *et al*. studied the role of an antihistamine, Ranitidine versus placebo in the treatment of infectious mononucleosis. Study concluded that no significant benefit elucidated from the use of ranitidine in patients with infectious mononucleosis [35]. Therapy for EBV lymphoproliferative disease should include reduction in the dose of immunosuppressive medication when possible. Reducing the dose may result in complete resolution of some lesions. Surgical removal or irradiation of localized lymphoproliferative lesions, especially in the gastrointestinal tract, has been effective in selected patients. Acyclovir, which inhibits the replication of linear EBV DNA but does not affect EBV episomes in latently infected cells, is generally not effective. Interferon alfa has been effective in some patients. Monoclonal-antibody therapy has also been used in patients with EBV lymphoproliferative disease. Researchers in mid-1970s have found that vaccine prevention of the virus infection might be a way of decreasing the incidence of the associated cancers in high-risk populations for EBV infections [36]. Recombinant vaccinia viruses expressing gp340 have been made, and a small scale vaccination experiment using this in nine Chinese children has given some evidence of protection but a wild-type strain of vaccinia was employed for the construct which would not be acceptable for general application [37].

Conclusion

EBV the most common etiological agent of heterophile positive Infectious mononucleosis (IM), which is an acute self-limited illness usually seen in non-immune young adults following primary infection with the EB virus. As with other herpes viruses, infection with the EB virus leads to latency, periodic reactivation and lifelong persistence. The original serologic test for infectious mononucleosis, the Paul-Bunnell test, detected heterophile antibodies by agglutination of sheep or horse erythrocytes. The Paul-Bunnel antibody develops early during the course of IM and disappears within about two months. Tests are also available for the demonstration of specific EB virus antibodies. The treatment of infectious mononucleosis is mainly supportive with adequate hydration of the patient; use of nonsteroidal anti-inflammatory drugs to suppress fever and myalgia. Small scale vaccination experiments using recombinant Vaccinia virus expressing gp340 have been attempted, which provided some evidence of protection but further clinical trials are needed to introduce the vaccine in general population.

Conflict of Interest

Author declares no conflicts of interest.

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