National Center for Infectious Diseases

Epstein-Barr Virus and Infectious Mononucleosis

DISEASE INFORMATION

Epstein-Barr virus, frequently referred to as EBV, is a member of the herpesvirus family and one of the most common human viruses. The virus occurs worldwide, and most people become infected with EBV sometime during their lives. In the United States, as many as 95% of adults between 35 and 40 years of age have been infected. Infants become susceptible to EBV as soon as maternal antibody protection (present at birth) disappears. Many children become infected with EBV, and these infections usually cause no symptoms or are indistinguishable from the other mild, brief illnesses of childhood. In the United States and in other developed countries, many persons are not infected with EBV in their childhood years. When infection with EBV occurs during adolescence or young adulthood, it causes infectious mononucleosis 35% to 50% of the time.

Symptoms of infectious mononucleosis are fever, sore throat, and swollen lymph glands. Sometimes, a swollen spleen or liver involvement may develop. Heart problems or involvement of the central nervous system occurs only rarely, and infectious mononucleosis is almost never fatal. There are no known associations between active EBV infection and problems during pregnancy, such as miscarriages or birth defects. Although the symptoms of infectious mononucleosis usually resolve in 1 or 2 months, EBV remains dormant or latent in a few cells in the throat and blood for the rest of the person's life. Periodically, the virus can reactivate and is commonly found in the saliva of infected persons. This reactivation usually occurs without symptoms of illness.

EBV also establishes a lifelong dormant infection in some cells of the body's immune system. A late event in a very few carriers of this virus is the emergence of Burkitt's lymphoma and nasopharyngeal carcinoma, two rare cancers that are not normally found in the United States. EBV appears to play an important role in these malignancies, but is probably not the sole cause of disease.

Most individuals exposed to people with infectious mononucleosis have previously been infected with EBV and are not at risk for infectious mononucleosis. In addition, transmission of EBV requires intimate contact with the saliva (found in the mouth) of an infected person. Transmission of this virus through the air or blood does not normally occur. The incubation period, or the time from infection to appearance of symptoms, ranges from 4 to 6 weeks. Persons with infectious mononucleosis may be able to spread the infection to others for a period of weeks. However, no special precautions or isolation procedures are recommended, since the virus is also found frequently in the saliva of healthy people. In fact, many healthy people can carry and spread the virus intermittently for life. These people are usually the primary reservoir for person-to-person transmission. For this reason, transmission of the virus is almost impossible to prevent.

The clinical diagnosis of infectious mononucleosis is suggested on the basis of the symptoms of fever, sore throat, swollen lymph glands, and the age of the patient. Usually, laboratory tests are needed for confirmation. Serologic results for persons with infectious mononucleosis include an elevated white blood cell count, an increased percentage of certain atypical white blood cells, and a positive reaction to a "mono spot" test.

There is no specific treatment for infectious mononucleosis, other than treating the symptoms. No

antiviral drugs or vaccines are available. Some physicians have prescribed a 5-day course of steroids to control the swelling of the throat and tonsils. The use of steroids has also been reported to decrease the overall length and severity of illness, but these reports have not been published.

It is important to note that symptoms related to infectious mononucleosis caused by EBV infection seldom last for more than 4 months. When such an illness lasts more than 6 months, it is frequently called chronic EBV infection. However, valid laboratory evidence for continued active EBV infection is seldom found in these patients. The illness should be investigated further to determine if it meets the criteria for chronic fatigue syndrome, or CFS. This process includes ruling out other causes of chronic illness or fatigue. For additional information about chronic fatigue syndrome, please call CDC's toll-free line at 888-232-3228; after the call goes through, press 22136 to get the CFS menu.

DIAGNOSIS OF EBV INFECTIONS

In most cases of infectious mononucleosis, the clinical diagnosis can be made from the characteristic triad of fever, pharyngitis, and lymphadenopathy lasting for 1 to 4 weeks. Serologic test results include a normal to moderately elevated white blood cell count, an increased total number of lymphocytes, greater than 10% atypical lymphocytes, and a positive reaction to a "mono spot" test. In patients with symptoms compatible with infectious mononucleosis, a positive Paul-Bunnell heterophile antibody test result is diagnostic, and no further testing is necessary. Moderate-to-high levels of heterophile antibodies are seen during the first month of illness and decrease rapidly after week 4. False-positive results may be found in a small number of patients, and false-negative results may be obtained in 10% to 15% of patients, primarily in children younger than 10 years of age. True outbreaks of infectious mononucleosis are extremely rare. A substantial number of pseudo-outbreaks have been linked to laboratory error, as reported in CDC's *Morbidity and Mortality Weekly Report*, vol. 40, no. 32, on August 16, 1991.

When "mono spot" or heterophile test results are negative, additional laboratory testing may be needed to differentiate EBV infections from a mononucleosis-like illness induced by cytomegalovirus, adenovirus, or *Toxoplasma gondii*. Direct detection of EBV in blood or lymphoid tissues is a research tool and is not available for routine diagnosis. Instead, serologic testing is the method of choice for diagnosing primary infection.

EBV-Specific Laboratory Tests

Laboratory tests are not always foolproof. For various reasons, false-positive and false-negative results can occur for any test. However, the laboratory tests for EBV are for the most part accurate and specific. Because the antibody response in primary EBV infection appears to be quite rapid, in most cases testing paired acute- and convalescent-phase serum samples will not demonstrate a significant change in antibody level. Effective laboratory diagnosis can be made on a single acute-phase serum sample by testing for antibodies to several EBV-associated antigens simultaneously. In most cases, a distinction can be made as to whether a person is susceptible to EBV, has had a recent infection, has had infection in the past, or has a reactivated EBV infection.

Antibodies to several antigen complexes may be measured. These antigens are the viral capsid antigen, the early antigen, and the EBV nuclear antigen (EBNA). In addition, differentiation of immunoglobulin G and M subclasses to the viral capsid antigen can often be helpful for confirmation. When the "mono spot" test is negative, the optimal combination of EBV serologic testing consists of the antibody titration of four markers: IgM and IgG to the viral capsid antigen, IgM to the early antigen, and antibody to EBNA.

IgM to the viral capsid antigen appears early in infection and disappears within 4 to 6 weeks. IgG to the viral capsid antigen appears in the acute phase, peaks at 2 to 4 weeks after onset, declines

slightly, and then persists for life. IgG to the early antigen appears in the acute phase and generally falls to undetectable levels after 3 to 6 months. In many people, detection of antibody to the early antigen is a sign of active infection, but 20% of healthy people may have this antibody for years.

Antibody to EBNA determined by the standard immunofluorescent test is not seen in the acute phase, but slowly appears 2 to 4 months after onset, and persists for life. This is not true for some EBNA enzyme immunoassays, which detect antibody within a few weeks of onset.

Finally, even when EBV antibody tests, such as the early antigen test, suggest that reactivated infection is present, this result does not necessarily indicate that a patient's current medical condition is caused by EBV infection. A number of healthy people with no symptoms have antibodies to the EBV early antigen for years after their initial EBV infection.

Therefore, interpretation of laboratory results is somewhat complex and should be left to physicians who are familiar with EBV testing and who have access to the entire clinical picture of a person. To determine if EBV infection is associated with a current illness, consult with an experienced physician.

Additional Information about EBV Antibody Tests and Interpretation
Antibody tests for EBV can measure the presence and/or the concentration of at least six specific EBV antibodies. By evaluating the results of these different tests, the stage of EBV infection can be determined. However, these tests are expensive and not usually needed for the diagnosis of infectious mononucleosis.

It is not appropriate for CDC to interpret test results or to handle counseling for the public. We suggest that questions be directed to a local physician who is familiar with the patient's history and laboratory test results. In addition, CDC cannot recommend specific physicians for referral. Our general recommendation is for patients to consult with an infectious disease specialist or their local or state public health department.

SUMMARY OF INTERPRETATION

The diagnosis of EBV infection is summarized as follows:

Susceptibility
If antibodies to the viral capsid antigen are not detected, the patient is susceptible to EBV infection.

Primary Infection
Primary EBV infection is indicated if IgM antibody to the viral capsid antigen is present and antibody to EBV nuclear antigen, or EBNA, is absent. A rising or high IgG antibody to the viral capsid antigen and negative antibody to EBNA after at least 4 weeks of illness is also strongly suggestive of primary infection. In addition, 80% of patients with active EBV infection produce antibody to early antigen.

Past Infection
If antibodies to both the viral capsid antigen and EBNA are present, then past infection (from 4 to 6 months to years earlier) is indicated. Since 95% of adults have been infected with EBV, most adults will show antibodies to EBV from infection years earlier. High or elevated antibody levels may be present for years and are not diagnostic of recent infection.

Reactivation
In the presence of antibodies to EBNA, an elevation of antibodies to early antigen suggests reactivation. However, when EBV antibody to the early antigen test is present, this result does not

automatically indicate that a patient's current medical condition is caused by EBV. A number of healthy people with no symptoms have antibodies to the EBV early antigen for years after their initial EBV infection. Many times reactivation occurs subclinically.

Chronic EBV Infection

Reliable laboratory evidence for continued active EBV infection is very seldom found in patients who have been ill for more than 4 months. When the illness lasts more than 6 months, it should be investigated to see if other causes of chronic illness or CFS are present.

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