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HERPES B MONKEY VIRUS

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Herpes B Monkey virus is now known as *Cercopithecine herpes* virus 1. It has also been known as monkey B virus, herpes B virus, B virus or *Herpesvirus simiae*.

Virology

B virus is an alpha herpes virus that infects members of the genus Macaca. Members of this genus include "Old World" monkeys such as rhesus, cynomolgus, pigtail, stumptail and others. “Old world” monkeys are those from Eaurasia and Africa by opposition to the “New world” or the Americas.

Epidemiology

The infection is endemic among macaque monkeys (including rhesus macaques, pig-tailed macaques, cynomolgus monkeys and other macaques). Animals become infected with the virus primarily through exposure of the mucosa or skin to oral or genital secretions from other monkeys. Vertical transmission of the virus to neonates is rare. The prevalence of shedding of the B virus is increased among primates that are stressed, breeding, immunosuppressed, or ill. In one survey, nearly 100% of captive macaques older than 2.5 years of age were seropositive for the virus, whereas about 20% of animals younger than 2.5 years of age were seropositive.

Infected monkeys often have no or very mild symptoms, although oral and genital lesions may develop. The virus persists in the sensory ganglia for the lifetime of the animal and can reactivate, resulting in the shedding of infectious virus from the oral, conjunctival, or genital mucosa of animals with or without visible lesions.

Transmission of B virus to humans occurs through monkey bites, scratches, or contact with infected monkey tissues, cells, or fluids. Although the highest risk is through a bite of an infected monkey with active lesions, exposure of mucous membranes or broken skin to infected fluids or tissues may cause infection. Monkeys who have no active lesions may be shedding virus. Exposure to peripheral blood from monkeys has not been reported to cause infection in humans.

Although hundreds of monkey bites and scratches occur among primate workers in the United States each year, B virus infection in humans is rare.

The virus may be stable on cages and other surfaces, so contact with unclean cages must be considered hazardous. It is not known if the virus is transmitted by aerosol.

At-risk personnel

Any employee who has direct contact with macaque monkeys is at risk of exposure to the B virus. Workers who handle fluids, tissues, or primary cultures from macaques are also at risk. Commercially prepared rhesus monkey kidney cells may be contaminated with B virus; therefore, those who work with these cells are also at risk.

Employees who work around macaques but not directly with them are also at risk. Although rare, B virus infection has been reported from contact with objects that had been in contact with macaques and from exposure to macaque fluids/tissues that were thrown or splashed from a distance. Although about 50 cases of B virus infection in humans have been identified to date, only 26 cases have been well-documented. Of importance, many cases of B virus infection in humans have been associated with exposures that were considered trivial.

Fatal cases of B virus disease in humans have rarely occurred in primate workers who do not recall an obvious exposure or who have had what would be considered a low-risk exposure.

Incubation period

The incubation period for infection in humans after an identified exposure is reported to range from two days to five weeks; most well-documented cases present five to twenty-one days after exposure.

Certain types of exposures may pose greater risks. These exposures include deep puncture wounds that are difficult to clean, inadequately cleansed wounds and wounds sustained on the face (especially wounds to the eye), neck, or thorax. Because the virus replicates at the site of infection and then ascends to the CNS along the axon, inoculation of the head or thorax with the virus allows little time for the development of symptoms that do not involve the CNS; it may be difficult to recognize and treat the disease before the CNS is infected.

Clinical Description

In monkeys, infection with B virus results in lesions on the mouth, face, lips and or genitals. The lesions heal spontaneously but may appear again sporadically in the same way that cold sores do in humans.

In humans, the B virus causes an **acute encephalitis** that is usually fatal. Any macaque handler who has an exposure event and then notices skin lesions or symptoms such as itching, pain, or numbness near the wound or exposure site should notify the supervisor and seek medical attention immediately. Some patients present with a progression of symptoms that first appear near the site of exposure; others present with symptoms limited to the peripheral nervous system or CNS. A third presentation involves flulike illness with fever, chills, myalgias and other nonspecific symptoms, with no focal findings; it may later be followed by the abrupt onset of CNS symptoms.

After infecting humans, the B virus replicates at the site of exposure and may cause development of a vesicular rash at this site. Many patients have no symptoms at the site of infection. Some patients develop lymphadenopathy proximal to the site of inoculation. Within the first three weeks after exposure, paresthesias may develop. The virus spreads along the nerves of the peripheral nervous system to the spinal cord and then to the brain.

Symptoms of infection can include meningismus, nausea, vomiting, persistent headache, confusion, diplopia, dysphagia, dizziness, dysarthria, cranial nerve palsies and ataxia. Seizures, hemiplegia, hemiparesis, ascending paralysis, respiratory failure and coma more commonly occur later in the course of infection. The overall presentation of late-stage disease is that of brain stem encephalomyelitis that may evolve into diffuse encephalomyelitis during its terminal stages. This presentation is in contrast to the more focal neurologic disease observed in association with herpes simplex encephalitis. Among untreated humans, the mortality rate associated with B virus infection is estimated to be 80%. The mortality rate has declined since the advent of antiviral therapy.

Laboratory Testing

Human testing:

Testing of material known or suspected to contain B virus should done at a facility designated as having a Biosafety Level of three or higher. Culture of material from the wound or the site of exposure before cleansing is not recommended because it delays cleansing, may force virus on the surface of the wound. Culture after cleansing is usually negative. Therefore, in short, cultures are not useful.

It may be appropriate to collect and store serum samples at the time of the exposure and again three to six weeks after exposure occurred, and to send them for testing if warranted. In the United States, human serum samples obtained for B virus testing should be sent to the B Virus Research and Reference Laboratory at Georgia State University. The initial serum sample obtained should be frozen at a temperature of –20°C or lower, preferably in a freezer that does not go through freeze-thaw cycles. A second serum sample should be obtained three to six weeks later or, at the onset of clinical symptoms. If sent for testing, these serum samples should be analyzed simultaneously. Seroconversion or a significant (> four-fold) increase in titer is highly suggestive of acute infection.

Animal testing:

The possible benefits of obtaining specimens from the primate must be balanced against the risks incurred by other workers in obtaining these specimens. In less-controlled settings and in the absence of expertise in capturing animals, it may be more advisable to observe the primate and look for obvious lesions, rather than to trap the animal to obtain for blood for testing. However, it is important to note that oral or genital lesions are rarely visible when an animal is shedding B virus and that not all lesions are due to the virus.

Currently, all macaque monkeys should be considered seropositive for B virus. Interpretation of negative serologic test results may be misleading. Monkeys found to be seronegative when tested weeks before an exposure occurred could be seropositive at the time of the exposure.

Surveillance

This is a very rare event. The role of the health department is to provide advice to practitioners or exposed individuals.

Prevention

Exposure Assessment

For each primate exposure, four major variables need to be assessed:

1. The source of the exposure should be determined. **Macaques are the only primates** known to transmit the B virus. Other primates pose no known risk unless they have had the opportunity to acquire infection directly from a macaque. Macaques that have lesions compatible with B virus or that are known to be culture positive for the virus are more likely to be shedding virus. Immunocompromised or otherwise ill animals, stressed animals, breeding animals and recently acquired primates that are still in quarantine, are all more likely to shed the B virus.

2. The timeliness and adequacy of first aid for the wound should be assessed. The wound should be cleansed within five minutes of exposure and the duration of cleansing should be a full fifteen minutes. Mucosal splashes or wounds that are inadequately cleansed are more likely to become infected, because there is an increased duration of exposure to infectious material.

3. The type of wound or exposure, the depth of the wound and the location of the wound should all be determined. Infections that occur as a result of exposure of the head, torso, or neck may result in no signs or symptoms before the CNS is involved and should be classified as high. Because B virus also travels to the CNS by these pathways, we recommend post-exposure prophylaxis for potential exposures to the B virus when the head, neck, or torso is involved. Superficial wounds and scratches are easily cleansed and therefore, usually are considered low risk. Deep punctures - in particular, those caused by bites - are likely to result in inadequately cleansed wounds and pose a higher risk.

4. Exposure to materials that have come in contact with macaques, in addition to direct exposure to the animals, must be evaluated. B virus is latent in the CNS of macaques and is shed intermittently from the mucosa of infected animals. Therefore, punctures with needles that contain material from the CNS, eyelids, or mucosa of macaques are considered high-risk exposures.

Recommendations for postexposure prophylaxis for persons exposed to B virus.

Prophylaxis recommended:

- Skin exposure (with loss of skin integrity) or mucosal exposure (with or without injury) to a high-risk source (e.g., a macaque that is ill, immunocompromised, or known to be shedding virus or that has lesions compatible with B virus disease)
- Inadequately cleaned skin exposure (with loss of skin integrity) or mucosal exposure (with or without injury)
- Laceration of the head, neck, or torso
- Deep puncture bite
- Needlestick associated with tissue or fluid from the nervous system, lesions suspicious for B virus, eyelids, or mucosa
- Puncture or laceration after exposure to objects (a) contaminated either with fluid from monkey oral or genital lesions or with nervous system tissues, or (b) known to contain Bvirus
- A post-cleansing culture is positive for B virus

Prophylaxis considered:

- Mucosal splash that has been adequately cleaned
- Laceration (with loss of skin integrity) that has been adequately cleaned
- Needlestick involving blood from an ill or immunocompromised macaque
- Puncture or laceration occurring after exposure to (a) objects contaminated with body fluid (other than that from a lesion), or (b) potentially infected cell culture

Prophylaxis not recommended:

- Skin exposure in which the skin remains intact
- Exposure associated with non-macaque species of nonhuman primates

Exposures include macaque bites, macaque scratches, or contact with ocular, oral, or genital secretions, nervous system tissue, or material contaminated by macaques (e.g., cages or equipment).

Exposure Events

The protocol to follow after an exposure event is published on the Internet at http://www.cdc.gov/ncidod/diseases/bvirus.pdf

Briefly, in the event of a mucous membrane exposure, irrigate the area with free-flowing water for fifteen minutes. In the event of a bite or scratch, wash the wound with soap and water for fifteen to twenty minutes. Length of washing time is more important than the use of soap. Post exposure prophylaxis will be carried out according to the Centers for Disease Control and Prevention (CDC) guidelines under the care of a physician who is an infectious disease specialist.

Post-exposure prophylaxis is defined as administration of antiviral medication to a person potentially exposed to B virus but not known to be infected. The use of post-exposure

prophylaxis to prevent B virus infection in humans has not been proven to be effective. However, post-exposure prophylaxis prevents disease in rabbits experimentally inoculated with B virus. Treatment that begins within twenty-four hours after exposure to B virus and that lasts for two weeks resulted in complete protection from death, whereas treatment initiated up to five days after exposure yields a significant decrease in mortality. To be effective, treatment is required every eight hours for fourteen days. A shorter duration of treatment results in delayed onset of ultimately fatal infection.

Antiviral Agents for Post-exposure Prophylaxis

Three orally administered agents - acyclovir, valacyclovir and famciclovir - are currently available for post-exposure prophylaxis of B virus infection. These drugs have not been approved by the U.S. Food and Drug Administration for treatment of B virus infection.

Prophylaxis for exposure to B virus
Valacyclovir, 1 g po q8h for 14 days
Acyclovir, 800 mg po 5 times per day for 14 days

Treatment of B virus disease
CNS symptoms are absent
Acyclovir, 12.5–15 mg/kg iv q8ha
Ganciclovir, 5 mg/kg iv q12ha
CNS symptoms are present
Ganciclovir, 5 mg/kg iv q12ha

To be given until symptoms resolve and the results of two cultures are negative for B virus; see the Discontinuation of Treatment of B Virus Infection section of the text for additional therapy used after intravenously administered therapy has been completed.

Personal Protective Equipment

Animal Resources and Environmental Health and Safety require the use of personal protective equipment. Those who work in direct contact with non-human primates must wear the following personal protective equipment:

1. Disposable head cover
2. Face shield (like a welder's mask) OR eye goggles with surgical mask
3. Surgical scrubs or uniforms with an outer garment of a fluid-resistant cloth or disposable surgical gown
4. Gloves
5. Disposable shoe covers

Those who work around non-human primates but who do not have direct contact must wear the same personal protective equipment, but may substitute a lab coat or surgical gown over street clothes.

Use of personal protective equipment is not optional.

Monkey Handling Practices

Check CDC's "Guidelines for Prevention of *Herpesvirus simiae* (B virus) Infection in Monkey Handlers" published in 1987. This document can be viewed on the Internet at http://www.cdc.gov/mmwr/preview/mmwrhtml/00015936.htm. These handling practices are required by Animal Resources and Environmental Health & Safety.

- Isolation of the Hospitalized Patient: Standard precautions are recommended.

Jeffrey I. Cohen, David S. Davenport, John A. Stewart, Scott Deitchman, Julia K. Hilliard Louisa E. Chapman, and the B Virus Working Group. Recommendations for Prevention of and Therapy for Exposure to B Virus (Cercopithecine Herpesvirus 1). Clinical Infectious Diseases 2002;35:1191–203.