

Monkey Bites and Herpes B –Virus Infection in Humans

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ABSTRACT: *Herpes B-virus, cercopithecine herpesvirus 1; herpesvirus simian endemic in Asian macaques is related to herpes simplex (HSV) type 1 in humans; infection with herpes B-virus in humans can result in fatal encephalitis and neurologic impairment. Human infections have been by bites, scratches, and percutaneous inoculation. Herpes B-virus infection causes minimal morbidity in macaques. In humans herpes B virus infection presents as rapidly ascending encephalitis with death rate of approximately 70%. Neurologic sequelae are common in survivors. Intravenous antiviral therapy decreases the death rate, prompt diagnosis and treatment is essential to limit CNS damage. New guidelines for prevention and therapy for exposure to herpes B-virus are useful.*

KEYWORDS: *Cercopithecine herpesvirus 1, Herpes B –virus, Macaque, and Therapy*

I. INTRODUCTION

Herpes B virus (cercopithecine herpesvirus 1; herpesvirus simian) causes a disease in macaque monkeys that is similar to that seen with herpes simplex virus (HSV) type 1 in humans; however, infection of immunocompetent humans with herpes B virus can result in a fatal encephalitis [1]. Herpes B virus was first described in 1933 in a researcher who died after being bitten by a macaque [2]. Sabin and Wright isolated the virus and named B virus after patient's last name [13]. About 50 cases of B virus in humans have been reported in the literature with 26 well-documented cases [4]. Human B virus is endemic in old world macaques, and most macaques in captivity should be considered as possibly infected [4]. Humans are inadvertent hosts. Humans have been infected by bites and scratches from macaques. Other exposures that have transmitted the virus are needle stick injury due to contaminated needle, contamination of wounds with macaque saliva, lacerations from bottles containing macaque cell cultures and possible aerosol exposure [4]. A single case of human-to-human transmission of herpes B virus was reported in woman who became infected after applying hydrocortisone cream to her contact dermatitis lesions and her husband's herpes B virus skin lesions [5]. Last identified case of human B virus infection occurred in 2008, with last known fatality occurring in 1997 when Researcher Elizabeth Griffin was splashed in the eye at Yerkes National Primate Research Center [6]. Ten cases of bites from Macaca mulatta monkeys, native to Afghanistan, that can cause serious infections has been reported among US military members in Afghanistan [7]. Cercopithecine herpesvirus 1 (B virus), enzootic among monkeys, causes minimal morbidity in its natural hosts. In contrast, human B virus infection presents as rapidly ascending encephalitis with fatality rate of approximately 70% [8]. Neurologic sequelae are common in survivors. Treatment with antiviral medication may decrease the death rate, but rapid diagnosis and initiation of therapy are essential in controlling the spread of virus in the central nervous system and limiting neurologic sequelae [9]. New guidelines for prevention and therapy for exposure to B virus, by B virus Working Group have recently been published [4]. The paper reviews the current literature, clinical presentation and therapy of human herpes B virus infection.

II. HISTORICAL PERSPECTIVE

Herpes B virus was first identified in 1932 following the death of Dr William Brebner, a young physician who was bitten by a monkey while researching the virus that causes poliomyelitis. Soon after Brebner developed localized erythema, followed by lymphangitis, lymphadenitis and, ultimately transverse myelitis. Neurologic tissue obtained during Dr. Brebner's autopsy revealed the presence of an unfilterable agent that appeared similar to HVS [2]. This isolate was originally termed "W virus". Within a year of Brebner's death, Dr Albert Sabin identified an unfilterable agent from the same tissue [10]. Sabin further described the lethality of B virus by showing that infectivity was independent of the route of inoculation [10]. Additionally, it was observed that B virus induced immunologic responses similar to HSV-1 [11], as well as shared similarities to HVP-2 and Langur herpesvirus, two other nonhuman primate alpha herpesviruses [11]. Another research group: Gay Holden obtained samples from patient B. Both research groups Sabin and Wright and Gay and Holden, demonstrated a similar disease progression in rabbits inoculated with never tissue from patient W.B. and characterized the agent as a herpesvirus. Neither group was able to produce disease in rhesus macaques, presumably because the monkeys were already naturally infected with what Sabin's group named B virus (after patient W.B) [2, 12].

By 1959, B virus was identified as the causative agent in 17 human cases, 12 of which resulted in death [13]. Approximately 50 cases had been identified by 2002, although only two were well documented. The latest identified case of B virus occurred in 2008, per the National B virus Resource Centre in Atlanta, GA. Improvements in handling in human cases have been made in the past several decades. Between 1987 to 2004 the rate of mortality has decreased, largely due to the addition of new forms of treatment and improved diagnosis. There have been a total of 5 fatalities related to Herpes B virus in this time frame [14]. Travelling to an area where macaques are known carriers of the virus and interacting in close contact in such areas such as temples poses a risk of exposure. However even in endemic areas, human cases are rare. There have been no known cases of Herpes B virus in travelers [14].

III. B- VIRUS GENOME

Herpes B virus is an alphaherpesvirus, in the same subfamily as HSV. The complete sequence of herpes B virus shows that it is closely related to HSV with a conserved genomic structure, and the viral glycoproteins show about 50% amino acid identity between the two viruses [15]. The B virus genome was fully sequenced in 2003 from an isolate found in a rhesus macaque. Like all herpes viruses, the B virus genome contains double stranded DNA and is approximately 157 kbp in length. Two unique regions (UL and US) are flanked by a pair of inverted repeats, two of which are found at the termini, with the other two internally located. This arrangement, which is identical in nature to HSV, results in four sequence-oriented isomers. Cytosine and guanine nucleotides represent 75% of the sequence [15]. Sequence analysis suggests that B virus and HSV types 1 and type 2 most likely diverged from a common ancestor during the evolution of these pathogens. Each gene-encoded glycoprotein, including gB, gC, gD, gE and gG, has approximately 50% homology with HSV with a slightly higher predilection towards HSV-2 over HSV-1. Additional glycoprotein sequences have demonstrated that all cysteine residues are conserved, as are most glycosylation sites [15].

IV. B- VIRUS INFECTION IN NATURAL HOST

Limited information is available about B virus infection in the natural host-macaques. Infection is usually acquired at sexual maturity (2-4 years age for rhesus macaques). As seen in humans with HSV, B-virus seropositivity increases with population age; seropositivity rates of 80% to 100% occur among adult captive macaque populations [16]. Oral herpetic lesions such as gingivostomatitis, oral and lingual ulcers, and conjunctivitis have been described, but are usually associated with immunosuppression or stress attributable to recent importation or crowded housing conditions [17]. Genital lesions have not been observed in macaques, although genital infection has been demonstrated by polymerase chain reaction (PCR) [18], virus isolation from the genital mucosa [19], and culture of the sacral ganglia [18]. In general, macaques remain asymptomatic, and identification of oral herpetic lesions is sufficient grounds for euthanasia of affected animal. The infrequent cases of disseminated B-virus disease in macaques are most often associated with immunosuppression, caused by either chemotherapy or concurrent infection with simian type D virus [20]. Although severe HSV disease is commonly observed in humans co-infected with HIV, no cases of B-virus disease associated with simian immunodeficiency virus infection in macaques have been reported [21]. Most cases of human B-virus infection have been associated with apparently healthy macaques (i.e., no obvious herpetic lesions), which indicates asymptomatic shedding of the virus. Lack of clinical signs of recurrent infection makes identification of shedding of animals difficult. People working with these animals should consider every animal a potential source of B-virus and use proper protective equipment and care when handling animals [8].

IV. PATHOPHYSIOLOGY

Animals are infected through the mucosa or skin from oral or genital secretions of other animals. Herpes B-virus rarely causes disease in macaques; although local lesions can occur. The virus is latent in the sensory ganglia of the animals and reactivates with shedding. Sites of shedding include the genital tract and oral and conjunctival mucosa. On a given day, about 2% of herpes B-virus-seropositive healthy adult monkeys shed virus [22]. Shedding is more common in animals that are ill, immunocompromised, stressed or breeding. Like herpes simplex virus in humans, latently infected macaques shed virus intermittently and often in the absence of lesions. Peripheral blood of macaques has been reported to contain herpes B-virus in animals that are ill, and viremia rarely, if ever, occurs in healthy macaques [23, 24]. Humans are infected from monkey oral, genital, or ocular secretions or monkey nervous system tissues, with a usual incubation period of 5 to 3 weeks (range, 2 days to 5 weeks). The virus replicates at the site of infection and then ascends the peripheral nervous system in retrograde fashion before advancing to the central nervous system (CNS). Antibody to HSV does not protect humans from B-virus infection [1].

VI. CLINICAL PRESENTATIONS

Asymptomatic infection (i.e., seropositivity without disease) of human primate workers with herpes B-virus, including most of those who had histories of bites, scratches, has been detected [25,26]. Most human infections have been reported from animals without any symptoms. Infection of humans with herpes B-virus can be initially manifest in three different forms. First, patients may present with nonspecific flu-like symptoms including fever, chills, myalgia, and malaise before presenting CNS symptoms. Second, patients may present with symptoms at the site of herpes B-virus inoculation, which can include itching, tingling, numbness, or pain. Some patients have vesicular rash at inoculation site and may have lymphadenopathy in the draining lymph nodes. Third, patients may present directly with peripheral or CNS symptoms [25,26]. Patients with first two presentations may develop weakness or paresthesias involving the nerve at the site of infection before developing CNS symptoms. These symptoms include headache, nuchal rigidity, vomiting, confusion, dysphagia, dysarthria, ataxia, urinary retention, and cranial nerve palsies. The disease progresses from the upper spinal cord to the brainstem and then results in a global encephalitis manifested in seizures, ascending paralysis, hemiplegia, coma, and respiratory failure. Additional symptoms can include sinusitis, conjunctivitis, hiccups, and abdominal pain. The mortality rate in untreated humans is estimated at 70% and is considerably lower in persons treated at an early stage of disease [25, 26].

VII. DIAGNOSTIC WORKUP

After exposure. Some authorities recommend obtaining baseline serum at the time of exposure in order to simultaneously test it with serum obtained about 3 to 6 weeks later to document seroconversion or a four-fold rise in titer. Persons receiving acyclovir may have delayed seroconversion; serum might be obtained from patients receiving post exposure prophylaxis 3 to 6 weeks after the exposure and at 12 weeks. Since asymptomatic infection never been reported other authorities do not recommend testing serum, except to confirm a diagnosis in persons with symptoms compatible with B-virus disease. Positive serologies are confirmed using competition ELISA or Western Blotting [25]. Cultures of the wound or exposed mucosa should be obtained only after cleansing is performed, so as not to delay first aid or removal of virus from the site. Some authorities feel that cultures are not especially helpful, since decision must be made regarding post exposure prophylaxis before results return. While a negative culture is not helpful (since sampling error may have occurred), a positive culture indicates a true exposure, although not necessarily an infection. Any patient who has a positive culture for herpes B-virus needs subsequent follow-up cultures to be certain that they are not shedding virus [25]. Polymerase chain reaction (PCR) for herpes B-virus DNA can be performed on lesions swabs, spinal fluids, and other sites; a positive PCR in setting of symptoms consistent with herpes B-virus is considered diagnostic infection [27,28].

Post exposure. First aid, with prompt thorough irrigation of wounds and exposed mucosal tissues is essential to reduce likelihood of infection. Mucosal membranes should be flushed with saline, and wounds irrigated with detergent (e.g. Chlorhexidine or povidone-iodine) for 15 minutes [4]. A health care professional should evaluate the inoculation site and thoroughness of cleansing, document the type of exposure (including whether it involved a macaque), consider obtaining baseline serum samples, consider culturing the wound, educate the patient regarding signs and symptoms of herpes B-virus, identify a local medical doctor if the need arises, and consider post exposure prophylaxis. The medical history of monkey should be evaluated, including whether it is ill or immunocompromised or has lesions compatible with herpes B-virus infection. All these factors increase the risk that animal is actively shedding herpes B-Virus. [1].

Post exposure prophylaxis with oral acyclovir or ganciclovir has been shown to be effective in a rabbit model of herpes B-virus infection [29, 30], but has not formally been shown to be effective in humans. Nonetheless, although post exposure prophylaxis with antiviral therapy has been recommended only since 1995, no cases of herpes B-virus have been reported to date in persons receiving post exposure prophylaxis within 3 days of exposure [8,4]. A working group convened by the Centers for Disease Control and Prevention (CDC) prepared a series of recommendations for post exposure prophylaxis of herpes B-virus in 2002 [4]. Certain types of exposure to macaques were considered to impart a much higher risk of herpes B-virus infection in humans. These include inadequately cleansed wounds, deep puncture wounds (which are difficult to clean), bites to head and face (in which virus can quickly travel to the CNS, exposures involving materials known or highly likely to be infected with herpes B-virus or exposures involving ill or immunocompromised macaques or those with lesions consistent with herpes B-virus disease [1]. Post exposure prophylaxis is given as early as possible and within 5 days of the exposure, since animals given antiviral medication have benefited as late as 5 days after inoculation [29,30]. Post exposure prophylaxis is not a substitute for prompt and thorough cleansing of the infected site. Most authorities recommend either valacyclovir 1 g three times daily or acyclovir 800 mg five times daily for 14 days, although these medications are not approved for use by the U.S. Food Drug

Administration. High doses of the oral drugs are used, since the dose needed to inhibit virus replication by 50% (IC₅₀) for herpes B-virus is 18µg/ml, which is about 10 times higher than those for herpes simplex virus[30].

Diagnosis of herpes B-virus disease.A physical examination of the lesion site (looking for vesicles) and a complete neurologic examination should be performed in persons with herpes B-virus disease. Cultures of conjunctiva, oropharynx, and the exposure site are recommended, along with obtaining serum for herpes B-virus serologic testing. An MRI of the brain should be performed, and CSF should be sent for PCR [31]. Electroencephalography may help differentiate herpes B-virus, which initiates with upper spinal cord and brainstem involvement and results in diffuse encephalitis, from HSV encephalitis, which usually involves one of the temporal lobes. Somatosensory evoked potentials can help identify early lesions in the brain or spinal cord[36].PCR for herpes B-virus has been reported using primers for glycoprotein G(gG),which differs from gG in HSV-2.Real time PCR was as specific, but twice as sensitive, as culture to detect herpes B-virus in human and monkey specimens[31].

VIII. THERAPY AND PREVENTION

Therapy.Immediate intravenous treatment rather than oral prophylaxis should be initiated in any patient with signs or symptoms of herpes B-virus, or a positive culture or PCR(not including a post –cleansing culture or PCR from wound) if the patient has had a documented exposure to a macaque. In the absence of CNS symptoms, either acyclovir 12.5mg/kg intravenously every 8 hours or ganciclovir 5 mg/kg intravenously every 12 hours is recommended until symptoms resolve and two cultures over two week period are negative for herpes B-virus[4].Since animal model show that herpes B virus is more sensitive to ganciclovir than acyclovir most experts recommend ganciclovir for patients with CNS symptoms[30].

If herpes B-virus can establish latency and reactivate in humans, then discontinuation of antiviral therapy could allow reactivation to occur. Therefore, many authorities recommend that persons who survive herpes B-virus infection be maintained on oral acyclovir, initially at doses used for post exposure prophylaxis and later at suppressive doses, for a prolonged time after intravenous therapy is stopped [4,8].Repeated cultures for herpes B-virus are often recommended after intravenous therapy has been changed to oral therapy to confirm that herpes B-virus shedding is not occurring or when antiviral therapy is discontinued[1].Prior to antiviral therapy, about 80% of persons with herpes B-virus died; with antiviral therapy, it is estimated that 80% of patients survive[32].Although, there had been relatively few cases of documented herpes B-virus infection treated in the era of antiviral therapy, five patients with laboratory – confirmed infection with herpes B-virus(some of whom had CNS symptoms) who were treated with intravenous acyclovir or ganciclovir had their symptoms resolve within 2-to 3 weeks of therapy[5].Like HSV encephalitis, therapy for herpes B-virus encephalitis is likely to be more effective when given earlier[5].

Prevention.A vaccine for herpes B-virus does not exist yet exist. Prevention of herpes B-virus requires strict precautions when working with nonhuman primates In view of herpes B-virus occurring in a woman who received a splash to her eyes, primate workers exposed to macaques should wear goggles or glasses with side shields, and a mask or chin length face shield and a mask to prevent infection of the eyes and oral mucosa[4].While only a single of person-to- person transmission of herpes B-virus has been reported, persons infected with the virus can shed infectious virus over 1 week, even while receiving intravenous acyclovir, therefore body fluids should be considered potentially infectious[5,4].Oral and genital secretions from persons who have been exposed to herpes B-virus, when it is not yet known whether they are infected, should be considered potentially infectious to others. If the incubation period for herpes B-virus(generally 5 weeks in untreated person) has passed and person is asymptomatic and/or serologist are persistently negative(at least 12 weeks after exposure in patients given antiviral prophylaxis),then the likelihood of infection and virus transmission is exceedingly low[4].It is essential that persons exposed to macaques be educated regarding the importance of first aid and the need for rapid cleansing of wounds or mucosal exposure, the need to see health care personnel regarding evaluation for post exposure prophylaxis, and the signs and symptoms of herpes B virus disease so that early therapy can be initiated[1].

XI. CONCLUSION

Paramount to educate persons exposed to macaques, initiate post exposure prophylaxis, and prompt antiviral therapy to prevent neurologic damage.

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