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Herpes simiae: A life threatening viral anthropozoonotic disease

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Abstract
Herpes simiae (B virus infection) is a life threatening viral anthopozoonosis that is transmitted from an infected macaque monkey to humans. The infection is reported from several nations including Canada, China, Great Britain, Japan, USA and others. Herpes simiae virus (*Macacine herpesvirus* 1 (*Cercopithecine herpesvirus* 1, CHV-1) is the endemic simplex virus of macaque monkeys. *Cercopithecine herpesvirus* 1 is the new name for it. Monkey B virus, Herpes B virus, B virus, and Herpesvirus simiae are all names for the same virus. The infection with herpes B virus (B virus) is common in macaques. B virus infection in primates is similar to herpes simplex virus 1 infection in humans, but in its natural host, B virus generates only minor localized lesions. Several modes of primates to human transmission of B virus infection have been implicated. In humans, however, B virus can produce a serious disease that can lead to encephalitis and death. The transmission of simian herpesvirus in humans can occur by bites, scratch, contact with monkey saliva, tissues, or tissue fluids; only one case of person-to-person transmission has been described. In two recorded occurrences, airborne transmission is thought to have occurred as a result of clinical conditions, but there is no sufficient evidence to back up this theory. Virus isolation, the presence of particular antibodies, or both, are used to diagnose herpes simiae infection. It is imperative to provide a biosafety level 4 (BSL-4) containment facilities for the isolation of the virus to decrease the risk of exposure for laboratory workers. Herpes simiae infection poses a health risk to the veterinarian, laboratory personnel, and health care professionals who are exposed to macaques or their infected tissues, or secretions. Neurologic sequelae are generally observed in the survivors. Prompt diagnosis and antiviral therapy is highly imperative to decreases the death rate. As herpes simiae infection in human beings is often lethal, it is important to raise awareness of the risk of herpes simiae infection. Post-exposure prophylaxis, personal protective equipment, and monkey handling practices are all strategies of the prevention and control of herpes simiae that poses a serious risk to human health.

Keywords: Herpes b virus, herpes simiae, human, monkey, public health, viral anthropozoonosis

Introduction
Anthropozoonosis is an infectious disease that is transmitted to humans from a variety of animals through various routes, namely direct contact, ingestion, inhalation, animal bite etc. (Pal, 2007) [21]. There are many anthropozoonses, such as anthrax, avian influenza, bovine tuberculosis, brucellosis, cat scratch disease, chlamydiosis, contagious ecthyma, glanders, leptospirosis, listeriosis, Q fever, tularaemia, and others that are reported in both sexes, in all age groups, and from different regions of the world (Pal, 2007; Pal, 2017; Pal, 2018; Berhanu and Pal, 2020; Pal *et al*., 2022) [21, 22, 23, 3, 24]. Monkeys are mammal that belong to the order Apes; and are known to transmit several zonooses of diverse etiologies including rabies, Kyasanur forest disease, tanapox, yellow fever, herpes simiae, simian malaria, Herpes simplex and others to human beings (Pal, 2007) [21]. Herpes simiae also known as B virus infection, Herpes B virus infection, is a deadly viral zoonosis of public health significance (Pal, 2007) [21]. The zoonotic *Macacine Herpesvirus 1* (MHV-1), formerly known as *Cercopithecine Herpesvirus 1* (CHV-1) causes herpes B virus infection in humans (CHV-1). It is most commonly detected in macaque monkeys, who appear to be its natural hosts. Only B virus is known to be harmful for humans among all the simplex Herpesviruses discovered in nonhuman primates (Wisely *et al*., 2018) [28]. The recorded history of herpes simiae goes back to the year 1932 when herpes B virus was identified after the death of a physician who was bitten by a monkey (Sabin and Wright, 1934) [26]. Two laboratory acquired fatal cases of herpes simiae were diagnosed by Hammeler and co-investigators (1959) [11].

Very recently, China recorded *first human death from Monkey B Virus* (Hindustan Times, 2021) [10]. Herpes B virus is an alpha Herpesvirus, which is a subtype of Herpes viruses that travel through the peripheral neurons of their hosts. As a result, there is no evidence of this neurotropic virus in the blood (Weigler, 1992) [27].

Herpesvirus simiae infects macaque monkeys. The virus is enzootic in all macaque subspecies (*Macaca* spp.). In early epidemiological studies, 72 percent to 92 percent of wild-caught adult monkeys were found to have antibodies to the B virus (Engel, 2005) [8]. In macaques, B virus infection is typically asymptomatic, comparable to HSV infection in humans (Keeble, 1958) [14]. The infection with the zoonotic B virus, if not treated promptly, can cause encephalitis, encephalomyelitis, and mortality is very high in the infected people (Palmer, 1987, Weigler, 1992) [25, 27]. It is pertinent to state that infected monkeys remain latent carriers throughout the life (Pal, 2007) [21]. In this context, Ostrowski and others (1998) [19] mentioned that B-virus from pet monkeys posed an emerging threat in the United States.

Cercopithecine Herpesvirus 1 (CHV-1) infection in humans is rarely observed (Huff and Barry, 2003). The virus has a pathogenesis in the natural host that is comparable to that of the human herpes simplex virus (HSV). Patients who are zoonotically infected with the B virus, on the other hand, can develop severe central nervous system disease, which can lead to irreversible neurological impairment or death. The severity of the disease worsens in untreated individuals, as the fatality rate reaches very high. The importance of early detection and treatment in surviving an infection cannot be overstated. The purpose of this mini review is to provide an overview of herpes simiae, a life-threatening viral disease that spreads by monkeys to human beings.

Etiology

Herpes B virus is a member of the family *Herpesviridae*, subfamily *Alpha herpesvirinae*, and genus *Simplexvirus*. *Macacine herpesvirus 1* (McHV-1) is the correct taxonomy name for this virus (ICTV, 2019) [5]. The virus has a molecular weight of about 110 megadaltons and contains double-stranded linear DNA (approximately 162 kilobase pairs). It has roughly 50% of its genes in common with human herpes simplex viruses and expresses the same glycoprotein D (HSV-1 gD) binding proteins (Fan *et al*., 2012; Ohsawa *et al*., 2014) [9, 18]. The herpes B virus envelope contains at least nine glycoproteins that are immune response targets and serve to determine cellular tropism. Glycoproteins B and D contain 80% and 56% sequence similarity to the HHV1 glycoproteins, respectively, but glycoproteins G and C have considerable sequence variance (Perelygina *et al*., 2002; Ohsawa *et al*., 2014) [18].

Transmission

Several modes of primates to human transmission of B virus infection have been implicated (Pal, 2007) [21]. Macaques spread the B virus by contacting mucous membranes or lesioned skin in the mouth, eye, or genitally (Cohen *et al*., 2002) [7]. Humans are most commonly infected by monkey bites, but transmission has also happened after direct inoculation of the eye or respiratory tract with infected monkey body fluids (NIOSH, 1987; Acha and Szyfres, 2003; Pal, 2007) [17, 1, 21]. A less prevalent form of transmission is direct infection of a pre-existing wound with CHV-1 infected monkey saliva (Weigler, 1992) [27]. Human infection has also occurred as a result of indirect contact, such as injury from a contaminated fomite (e.g. needle stick injury, cuts from broken tissue culture bottles containing infected monkey cells, or cage scratch) (Weigler, 1992) [27]. The infection with B virus in a 26-year-old veterinary technician following a needle stick injury was described by Artenstein and others (1991) [2].

Clinical Spectrum

In Humans

The incubation period of herpes simiae is 1 to 5 weeks (Pal, 2007) [21]. Acute ascending encephalomyelitis (AAE) caused by B virus can result in death or severe neurologic disability (CDC, 2010) [4]. Pain or pruritus at the exposure site, vesicles or ulcers at or near the exposure site, and local lymphadenopathy or lymphadenitis is all possible early symptoms. Fever, malaise, diffuse myalgias, headache, numbness or paraesthesias at or around the exposure site, nausea and/or abdominal pain, and persistent hiccups are examples of intermediate symptoms. Persistent headaches, mental changes, and focal neurological symptoms are examples of late manifestations (CDC, 2019) [5]. The respiratory involvement and mortality can occur anywhere from one day to three weeks after the onset of symptoms (CDC, 2010) [4]. The mortality rate in humans may reach to about 70% (Pal, 2005; Mustafa *et al*., 2015) [20, 16].

In Non-human primates

The animal may remain asymptomatic without showing any clinical symptom (Pal, 2007) [21]. Mild cold sore-like lesions of the mucous membranes, dorsum of the tongue, lips, or face may be caused by the virus, which are similar to those caused by herpes simplex in humans. In most cases, these will heal on their own in 7 to 14 days. Mild conjunctivitis and nasal discharge may also be present. The condition can be severe in certain animals, causing significant discomfort as well as neurologic signs and symptoms. The virus remains dormant and may reactivate spontaneously or in response to stress, cause virus shedding. An animal should be considered infected for the rest of its life (CDC, 2010) [4].

Diagnosis

The gold standard for diagnosing B virus infection in an exposed individual is the examination of clinical symptoms associated with an antibody or virus positive case. Humans infected with the B virus can be diagnosed using both serological and virological methods (Pal, 2007) [21]. Virus isolation is still considered the gold standard for diagnosis of disease; nevertheless, even in the best of circumstances, isolation of virus is usually impossible. Only a few facilities that have been licensed and have access to BL-4 containment laboratories for the synthesis of B virus antigen are now performing human diagnostic tests (Davenport *et al*., 1994) [6]. In macaques, herpes B virus infection is detected by the isolation of virus, the presence of particular antibodies in the sera, or both (Blewett, 1999). In both human and primate cases, polymerase chain reaction (PCR) technology may allow for a faster and more precise assessment. Newer research aims to create a PCR test that is not only sensitive but also specific, allowing for HSV distinction (Oya *et al*., 2004). It is emphasized to develop a simple, rapid, sensitive, specific and low cost test to make an unequivocal diagnosis of herpes simiae.

Treatment

The only way to avoid a contaminated wound from becoming infected is to clean the exposed area as soon as possible after the incident. Within 5 minutes, the virus is likely to infiltrate host cells. Scrubbing and/or irrigating the exposed area for at least 15 minutes are advised. For the eye, sterile saline or quickly flowing water is utilized, and decontaminants (such as soap solution, povidone-iodine, or chlorhexidine) can be used elsewhere. B virus cultures should be performed after a high-risk site has been cleaned. In suspected clinical cases of human B virus infection, antiviral medication is obviously indicated. Despite antiviral treatment, advanced encephalitis is generally fatal. The treatment options for early symptoms without central nervous system (CNS) is acyclovir 12.5-15 mg/kg IV every 8 hours. In this context, Artenstein and co-investigators (1991) [2] reported that acyclovir was found effective to treat a case of B virus infection in a veterinary technician. Ganciclovir 5 mg/kg IV every 12 hours is used to treat CNS symptoms. It is pertinent to mention that incisions made to diagnose or treat wounds are usually ineffective, and can increase the risk of subsequent bacterial infection. Therefore, it is not generally advised (Cohen *et al*., 2002) [7].

Prevention and Control

The prevention and control strategies include those who work in direct contact with non-human primates must wear the personal protective equipment such as disposable head cover, face shield (like a welder's mask) or eye goggles etc. (Pal, 2007) [21]. Macaques should only be utilized for study where it is clearly stated, and B virus-free animals should be employed whenever possible and kept in settings that ensure this status is maintained. Direct handling of macaques should be avoided as much as possible, and proper restraint methods should be used (i.e., squeeze cages, chemical restraint, pole and collar etc.). When working with macaques or macaque tissues, protective clothes should be used (long sleeves, gloves, mask, and goggles), Sharp edges that can cause harm should be kept out of cages and equipment. Access to regions containing macaques should be restricted. Animals should not be screened for the B virus on a regular basis. Animals with lesions should be isolated until the lesions have healed, and personnel should be educated and trained (Holmes *et al.*, 1995, CDC, 2019) [11, 5]. It is advised to keep the imported monkeys under quarantine for 6 to 8 weeks (Pal, 2007) [21]. Given the possibility of delayed findings, post-exposure prophylaxis is indicated for up to 5 days after exposure or longer if a post cleansing wound culture is positive for B virus. Valacyclovir 1000 mg PO every 8 hours for 14 days and Acyclovir 800 mg PO 5 times per day for 14 days are two post-exposure prophylaxis regimens (Cohen *et al*., 2002) [7]. Prompt medical attention of all bites or scratches by monkeys must be given to prevent the spread of infection (Pal, 2007) [21].

Conclusion

Herpes simiae is usually a fast-advancing, deadly disease that can be stopped if antiviral medications are used effectively and quickly enough after infection. Treatment and preventative guidelines have been widely disseminated and are now easily accessible. Standard methods must be followed in the workplace due to the risk of human infection. B virus zoonotic infections can be reduced by paying close attention to the details of housing, management, and handling of macaque monkeys, as well as organizing exposure response measures utilizing the health service centers for disease control and prevention guidelines. Early detection of infection is critical for the prompt institution of antiviral medication therapy, which can reduce the risk of additional mortality caused by this fascinating alpha herpesvirus. Further work on the pathophysiology, virulence, reservoirs, and epidemiology of herpes simiae should be conducted.

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Contribution of Authors

Every author contributed equally. All the authors read the final version, and approved it for publication.

Conflict of Interest

There was no conflict of interest.

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