ISSN No:-2456-2165

Monkey B Virus: from an Exception to Precedence

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Abstract:- Herpes viruses are found in the order primates which are classified into three subfamilies: alpha, beta, and gamma. Herpes Simiae (B virus) is found in rhesus long-tailed monkeys employed in scientific research. The most prevalent mode of transmission of the Monkey B virus is by contact with monkey saliva, tissues, or tissue fluids. A breach of primary skin or mucosal defences leads to human infection, followed by contamination of the site with virus from this animal. The infection affects 75% of macaques and is transferred to people having horizontal contact with macaques, showing 70% mortality. After transmission, minor flu symptoms appear, which subsequently impact various body areas with varying signs and symptoms. This infection is difficult to cure once it has progressed and entered the human host cycle since there are no or few therapeutic options available, one of which is the use of acyclovir. Without treatment, a 4:9 mortality rate has been documented in several studies. The current study updates prior guidelines for the prevention, assessment, and treatment of human B virus infection and addresses the significance of newer antiviral medicines in post-exposure prophylaxis, as well as the necessity to prioritize preventative measures when conducting scientific research.

Keywords:- *Monkey B virus; MBV; herpesvirus simiae; encephalomyelitis; biomedical research; antiviral therapy.*

I. INTRODUCTION

Herpes viruses belong to the Herpes viridae family, which has three subfamilies (Alpha, Beta and Gamma herpesviridae) and are found in the order Primates. Alpha herpesviruses are present in the host as part of their natural lifecycle[1]. Among them, Herpesvirus Simiae (Macacine alpha virus 1, McHV-1, Macaine herpesvirus1, Monkey B virus (MBV), H. Simiae encephalomyelitis, Cercopithecine herpes virus 1) is particularly present among macaque specifically those that include rhesus and long-tailed (Cynomolgus monkey) that are usually used in biomedical research. The virus has traits similar to that of human HSV - 1 and HSV -2 [2] and is highly pathogenic in humans among the 35 identified non-human herpes viruses [3]. MBV infection among humans is rare and occurs as a result of exposure to either macaque or their secretions or tissues [4]. Infections with MBV are usually asymptomatic in macaques, but can present as lesions on the face, mouth, or genital region. They heal spontaneously but may appear sporadically in the same way oral and genital herpes simplex do in humans. However, when transmitted to humans, MBV causes acute ascending encephalitis that is usually fatal if not treated immediately [5].

II. CAUSES

MBV occurs due to the exposure to macaque monkeys of the genus Macaca Mulatta (Rhesus monkeys) and Macaca fascicularis (Cynomolgus monkeys). The incidence of infection in Macaca Fascicularis is minimal and only present in some cases[1]. The common cause of the infection with MBV in the macaque is related to the increasing age of the macaque from infant to adult. Among them, in captive colonies, monkeys less than 2 years of age acquire MBV as infection due to oral contact, while in mature monkeys, the infection occurs due to genital contact. The prevalence of this infection amongst the genus Macaca ranges from 70 to 100%. This infection rarely causes a lethal infection in healthy macaques [1,4].

III. FREQUENCY

A. Animals:

Antibodies of B virus seropositivity have been found in many adult macaques and a few younger animals in the wild. The low frequency of MBV infection antibodies in infants and juveniles has been reported to indicate a very low incidence of infection. According to research, over 75% of adult animals in any given population are affected, and animals acquire disease at a greater rate once they hit puberty [6]. Sexual transmission within the colony appears to be linked with the increasing prevalence. Although antibodies have been found in most macaque species, there has been suspicion that virus obtained from a certain species is less neurovirulent or neurotropic than virus shed by rhesus macaques.According to the available data, macaques shed virus stay for longer durations of time during initial infection and for short durations after reactivation, even hours. In the laboratory, shed virus levels obtained from mucosal swabs range from 10^2 - 10^3 pfu/ml [3].

B. Humans:

Employees who have been bitten or scratched by infected monkeys or exposed to virus-infected simian tissue cultures are most likely to get the Simian B Virus. In 1932, the illness was first discovered in a monkey handler. Approximately 17 more instances were documented in the medical literature between 1973 and 1974. In 1987 there were four positive cases reported for it, including the first-ever known case of human-to-human transmission of Monkey B Virus. [7] So far, only 40 cases of Simian B Virus infection in humans have been recorded. Recently in 2021, China reported its first case of Human B virus infection in a veterinary surgeon after he dissected two dead monkeys. Some people have been exposed to pet macaque's saliva in non-occupational situations, according to experts at the Centers for Disease Control and Prevention (CDC). Scientists investigated seven non-occupational exposures

involving 24 humans and eight animals. According to a CDC report another person showed signs of infection at the wound site after exposure to the virus [3, 7].

IV. TRANSMISSION

The infection is normally transmitted from one macaque to another horizontally via direct contact through oral, scratches from an infected monkey and lesions contact, or it may occur due to the exchange of bodily secretions through genitals. The chances of vertical transmission are very rare. This infected macaque commonly has the virus in their body that can cause infection to the human host if triggered [1]. This infection can be found in the macaque's saliva, feces, urine, brain and spinal cord tissue, and cells from an infected monkey in the lab. This B virus can survive on moist surfaces for hours affecting the individuals who are exposed to it. Exposure in human hosts is quite rare as most people do not come in contact with the monkeys, so the risk of acquiring the infection is very low. On the same side, the risk is higher in the case of the population working in the laboratories, veterinary doctors and others exposed to the monkeys or their specimens [1, 8].

This transmission to the human host can occur through: [8]

- Being bitten or scratched by an infected monkey.
- Get an infected monkey's tissue or fluid on your broken skin or in your eyes, nose, and mouth.
- This can also be spread via a needle scratch by a contaminated syringe.
- Scratch or cut from a contaminated cage or sharp-edged surface. Technicians are exposed to an infected monkey's brain, spinal cord or skull.
- Infected human hosts to healthy individuals (human-to-human)-This transmission is only once reported in which the infected person transmits the MVB infection to another person [8].

Human B-virus illness usually develops within a month after exposure, with an incubation period ranging from a few days to a week [9]. The place of exposure determines the rate at which the disease develops and progresses and the amount of virus injected. The flu-like symptoms of fever, muscular pains, tiredness, and headache are common during the outset of the illness. Lymphangitis and lymphadenitis, nausea and vomiting, stomach discomfort, and hiccups are some of the other symptoms [10, 11]. The involvement of the patient's CNS as a target of infection, especially the upper spinal cord and lower brain, is the most remarkable feature of human B virus infection [12]. After the virus moved to the brain, symptoms such as hyperesthesias, ataxia, diplopia, agitation, and ascending flaccid paralysis have been reported. Viruses can be recovered for long periods at injection sites on the skin, and viral DNA can be found in CSF fluid when neurological symptoms appear. Antibodies can be found in the CSF as well. The spread of the virus to the central nervous system is a warning sign; even with antiviral medication and supportive care, most patients die, and those who live have significant neurologic consequences. Respiratory insufficiency linked with ascending paralysis is frequently blamed for deaths [10, 11, 13].

V. PATHOPHYSIOLOGY

This virus spreads through two phases; in phase I (animal phase), this virus affects the mucosal epithelium of the macaque and develops latent infection of the sensory ganglion. This remains in the macaque's latent phase or replicates further spreading the infection throughout the body. Activation from this latent phase sheds virus, which enters phase II (human phase) through direct or body fluid contact harbouring flu-like symptoms followed by blistering and lymphadenopathy at the site of infection.Later, stages progress with symptoms of GI discomfort, respiratory illness that further affects the PNS and causes palsies, ataxia and in extreme conditions affects the brain stem leading to death [1, 8]. **(Fig. 1: Pathophysiology of monkey B** virus**)**

ISSN No:-2456-2165

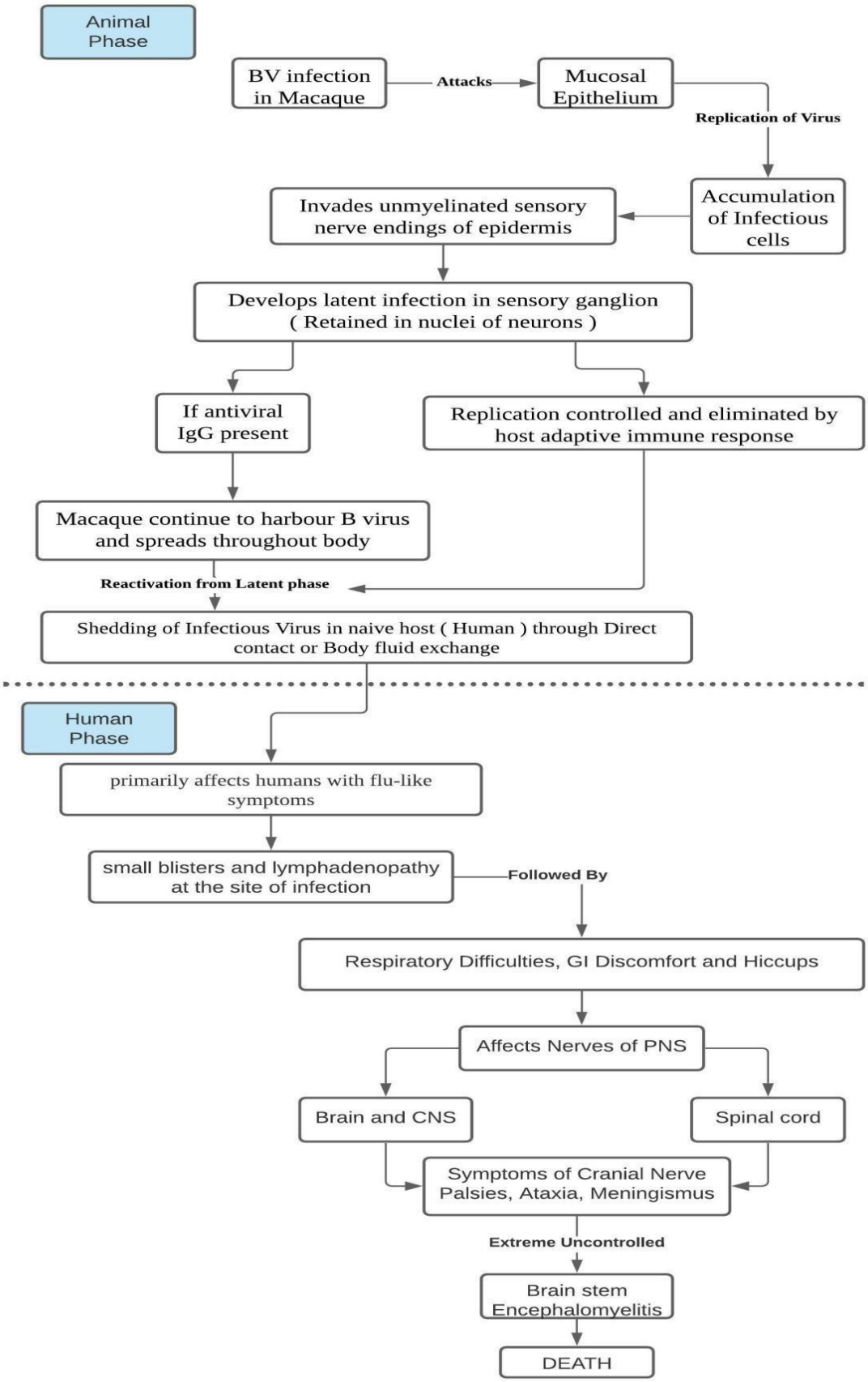

Fig. 1: Pathophysiology of monkey B virus

VI. SYMPTOMS

- The infection due to MBV is usually asymptomatic or is known to have mild symptoms in the case of infected macaque. When it infects the human host, it primarily progresses with flu-like symptoms, including fever with chills, fatigue, myalgia and headache [1].
- This is followed by skin eruption (vesicular rash) similar to eruptions through HSV-1 infection at the wound site. Causing signs of tingling, itching, pain, and numbness. In some cases, lymphadenopathy can occur at the site of infection [14].
- Later in stages, it can cause paresthesias and affect the proximal extremities, showing signs and symptoms of fever, myalgia, weakness of the affected extremity, abdominal pain, sinusitis, and conjunctivitis. Further, it can also affect the individual's lungs and liver, leading to respiratory problems and metabolic disturbances[14].
- As it spreads along the nerves of the peripheral nervous system, it can mimic the symptoms of meningismus, nausea, vomiting, persistent headache, confusion, diplopia, dysphagia, dizziness, dysarthria, cranial nerve palsies, and ataxia [8].
- Seizures, hemiplegia, hemiparesis, ascending paralysis, respiratory failure, and coma can occur in the final stages of illness [8].

VII. DIAGNOSIS

A. Non-human primates:

B virus infection is characterized by the ballooning of cells, necrosis of epithelial cells, and the presence of intranuclear inclusion bodies, as well as moderate inflammation that varies with the degree of secondary infection, according to histological analysis of lesional tissues [14].

In macaques, B virus infection is detected by viral isolation, the presence of particular antibodies, or both. While choosing an assay for antibody detection, the sensitivity and specificity of the test for a certain macaque species should be understood and considered when evaluating the findings. Tests based on monoclonal antibodies or recombinant reagents should have established sensitivity and specificity for each macaque species to be examined. The gold standard for diagnosing infected macaques is virus isolation [4].

B. Human Primates:

For various reasons, diagnosing human BV infections is considerably more challenging. Because BV infections in individuals are so serious, getting a diagnosis as soon as possible is critical. Although serologic tests are a mainstay of diagnosis, they rely on antiviral antibody detection and hence cannot identify infections until at least 7 to 10 days after infection. The majority of BV proteins react with HSV proteins that are similar. Anti-HSV antibodies in human sera will react with BV antigen, causing false positive findings because most adult people are infected with HSV1, HSV2, or both [2].

VIII. TREATMENT

To avoid B virus infection in humans and non-human primates, various approaches can be utilized, ranging from attempting to eradicate the virus to developing ways to be used safely in situations where this agent is more likely to be encountered. The Centers for Disease Control and Prevention (CDC) has issued extensive instructions for optimizing protection for those who deal with macaque monkeys [8].

If you come into contact with a macaque monkey, get medical help right once [8].

- First, use soap, detergent, or iodine to wash thoroughly and gently clean the wound or region of your body that came into touch with the monkey for 15 minutes [8].
- Then, for another 15 to 20 minutes, run water over the cut or region. Then go to the doctor right away. Tell your doctor you might have been exposed to a B virus-infected macaque monkey [8].

Attempts were undertaken as early as the 1930s to find an efficient vaccination to prevent anyone who could be exposed to the virus while dealing with macaques, their cells, or tissues. Although short-term antibody was produced in human volunteers in limited vaccination trials, it was seen to fade fast, and the vaccine was not explored further at the time [3].

The Centers for Disease Control and Prevention (CDC) published infection control guidelines for preventing MBV spread in 1987. Because large titers of human antiserum to herpes simplex virus may destroy the virus in vitro, the natural human defence against the virus could give cross-immunity to the B virus. In postexposure immunoprophylaxis for B virus infection, large doses of human gamma globulin have been proposed [15]. However, there is evidence that some individuals infected with MBV were all seropositive for herpes simplex virus, suggesting that this naturally acquired antibody may not protect against the virus in vivo.High doses of oral acyclovir are recommended for urgent prevention when people have been exposed to B virus infection. If signs and symptoms are present, intravenous acyclovir should be given at a dosage of 10 to 15 mg/kg every 8 hours, starting no later than 24 hours after exposure, followed by oral acyclovir 800 mg five times daily until the serologic test or culture is negative. The advantages of early diagnosis and ganciclovir therapy are clear in this situation. In our opinion, ganciclovir treatment should be explored for individuals with clear CNS involvement who have a considerable history of B virus exposure or who have a positive B virus culture or serology.Other instances should be treated with intravenous acyclovir until more information is known [15, 16, 17].

The best treatment period for B virus infection is still unclear. Because of a lack of evidence and confusion concerning the incidence of chronic or subclinical infections, there is debate. For individuals with documented MBV infections, long-term oral suppressive treatment with acyclovir (800 mg five times daily) has been advised. When administered in large doses, such as 10–15 mg/kg three

times a day for 14–21 days, acyclovir and the related family of nucleoside analogues have been shown to be efficacious [9]. A recombinant vaccination was recently tested in macaques and proven to produce antibodies, although the lifetime of antibodies and protection remain unknown. When provided adequately early after exposure, antiviral treatment effectively prevents infection development in human and animal studies.Ganciclovir has a higher in vitro effectiveness; it has been successfully used in all confirmed instances since 1989. Surprisingly, people did well in the absence of antiviral treatment in at least five retrospectively reported cases prior to 1987, although the CDC still advises acyclovir and ganciclovir therapy [3].

IX. DISCUSSION

Sabin (1934) demonstrated the mortality of B virus infection in rabbits, demonstrating that infectivity was independent of the inoculation method. Following deadly zoonotic infections, the B virus was first identified from rabbit brain homogenates. According to the first case reported in the medical literature, a laboratory worker was accidentally bitten by a monkey, appeared to recover from the bite, but then developed a febrile illness with progressive ascending myelitis symptoms and died 15 days after the first signs of central nervous system involvement. The genome of the B virus is roughly 162 kbp of double-stranded DNA. The genome has two distinct sections (Ul and Us) flanked by a pair of inverted repeats, two of which are at the termini and two of which are internally placed, allowing for four sequence-orientation isomeric forms. The genome is somewhat bigger than HSV-1 (152 kbp) and HSV-2 (152 kbp) (155 kbp). Between a recorded case in 1973 and the emergence of four cases in 1987 in Pensacola, Florida, there appeared to be a 14-year gap. At least three unreported instances were discovered at this time (J. K. Hilliard, unpublished observation), and only one additional case was recorded after that [3, 7].

Between 1973 and 1987, the overall number of asymptomatic, undiagnosed, or unreported infections is unclear [18, 19]. The real rate of human B virus infection is certainly relevant, given that over 47,000 monkeys are employed in scientific research in the United States. The case-fatality rate for B virus infections has been as high as 78 percent in the past [20]. Since 1987, four (44 percent) of nine well-documented instances of encephalitis have resulted in death, all of which were discovered in the late stages of the disease [21]. The majority of these instances happened before specialized antiviral treatment was available.Various tissues obtained from primates were initially classified as HSV, but they were later shown to have varied features and were dubbed "the B virus." The disease was first reported in a monkey handler in 1932 when a medical researcher was bitten on the finger by a macaque used in poliovirus research. The researcher developed typical herpetic lesions on the finger, which later progressed to involve the central nervous system, and the patient died of acute ascending myeloencephalitis.Over the years, several other human illnesses have emerged irregularly after the initial occurrence. BV infections in humans are notable for their severity, despite their rarity. If left untreated, it has a 70% to 80% mortality rate, with many survivors suffering from significant neurologic impairments and others seeing a gradual decrease in neurologic functioning. Survivors with latent BV raise the possibility of human-to-human transmission, although just one such case has been documented. During the acute illness phase of infection, the infected individual had considerable close and direct contact with a BV patient (her spouse). More than 130 other people, including healthcare workers, who had contact with these two patients were tested, but no new cases of BV were found [2].

Approximately 17 more instances were documented in the medical literature between 1973 and 1974. In addition, four more people were infected with the disease in 1987, including the first documented case of human-to-human disease transmission, in which survivors with latent BV raised the spectre of infection if the infected person had extensive close and direct contact with a BV patient during the acute disease phase. More than 130 other people, including healthcare workers, who had contact with these two patients were tested, but no new cases of MBV were found. Only 40 cases of Simian B Virus infection in humans have been recorded.Importing primates as pets have been forbidden in the United States since 1975 due to public health concerns. However, according to experts at the Centers for Disease Control and Prevention (CDC), many cases have been exposed to pet macaque saliva in non-work contexts (e.g., due to bites or scratches). According to a CDC report, investigators looked at seven non-occupational exposures involving 24 people and eight monkeys. One member of the exposed household had flu-like symptoms, while another developed symptom at the wound site, indicating infection [22].

After years of exposure, in 2021, China reported the first MBV infection in a 53-year-old veterinary surgeon who was exposed while dissecting two deceased monkeys and had virus-like symptoms of nausea and vomiting, followed by neurological symptoms and fever a month later. After visiting many hospitals in pursuit of treatment, the doctor was declared dead. Samples were taken from the patient's corpse to determine the cause of death, which was subsequently determined to be a probable alpha herpesvirus infection, and a series of RT-PCR testing showed B virus infection [23].

X. CONCLUSION

B Virus is a natural disease that infects 75 percent of adult macaque monkeys. Direct contact with a macaque actively shedding infected cells is the major mechanism of viral transmission. In newborn and juvenile macaques, oral infections predominate, but sexual transmission appears to be the major mechanism of transmission in adult animals. Although B Virus infection is not lethal in macaques, it can cause fatal infections involving the CNS in other primate species, including humans, where the virus is known to spread in two stages and presents with symptoms ranging from mild flu-like to severe encephalomyelitis. At the molecular level, MBV is linked to other -herpes viruses of nonhuman primates, most notably HVP2 of baboons and

SA8 of vervets. However, it is unclear why the extremely similar viruses of baboons and vervets have never been documented, and further research is required to find solutions.

Looking closely for treatment options after being infected by the macaque has not yielded much evidence, and thus more preventive measures are to be implemented while working with and around the macaque monkeys, as the neurovirulence of B Virus infections in a small number of humans who have been infected has elevated MBV to the top zoonotic concern. Evidence suggests that untreated B virus infections in humans result in an exceptionally high death rate (80%), posing unique and potentially deadly problems for those handling macaque monkeys or macaque cells and tissues, posing a serious occupational health risk to those exposed. Following the investigations and reported instances, the topic of the virus's latency time emerges, as no cases of the virus infecting a healthcare professional handling the macaque have been documented between 1987 till 2021. This recurrence of B virus infection necessitates attentive intervention on the virus's neurovirulent and molecular structure, as well as prompt antiviral intervention (like acyclovir and ganciclovir), to successfully minimize the ways of B virus-associated morbidity and therefore avert a catastrophic consequence.

DECLARATIONS

- **Ethical Approval:** Not Applicable
- **Competing interests:** All the authors confirm no conflict of interest.
- **Authors' contributions:** Ria Patel and Jaydev Patel has contributed in the writing and designing of the manuscript, Manthan Prajapati, Kenil Choksi, PriyanshuThaker,Dhruvil Gajera and Madhav Oza has contributed in the review and formatting of manuscript, Dr. Mrudangsinh Rathod has reviewed and approved the manuscript for the submission.
- **Funding:** No funding received.
- **Availability of data and materials:** Not applicable

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