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ELEPHANT ENDOTHELIOTROPIC HERPES VIRUS HEMORRHAGIC DISEASE: AN EMERGING THREAT

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ABSTRACT

Elephant endotheliotropic herpesvirus haemorrhagic disease (EEHV HD) is the major cause of death in young Asian and African elephants with the mortality rate of about 85%. It is a moderately understood emerging disease which causes highly fatal acute hemorrhagic infection caused by distinct strains of two different variants of herpes virus which has been a constant threat to the conservation and management of elephants worldwide. EEHVs are the endemic viruses in elephants having co-evolved with elephants with a million of years. Since EEHV is a non-cultivable virus, there is a scarcity of specific diagnosis, therapeutics and vaccines. The review explores and aims in summarizing the current status and idea of EEHV, its etiology, emergence, diagnosis, clinical presentation, prevention of the deadly disease.

Keywords: Elephant, endotheliotropic, herpesvirus, mortality, emergence

INTRODUCTION

EEHV HD is a highly lethal disease of free living and captive juvenile elephants causing severe vascular and endothelial damage resulting in wide spread hemorrhages. Sudden onset of action, non-specific symptoms & multiple strains of the virus make it challenging to treat. EEHV outbreaks have led to a decrease in population of Asian elephants which is a great loss to the ecosystem.

ETIOLOGY

Elephant endotheliotropic herpes virus (EEHV) belongs to the Genus Proboscivirus, family Herpesviridae. It is a double stranded DNA beta-herpesvirus. It was discovered by Ossent in 1990 (Min *et al.,* 2020). The virus is mostly ubiquitous is nature and possess the property of latency in which the entire viral genome is retained in the host cell but the gene expression is restricted. Multiple strains of this virus exist that affects both Asian and African elephants. Six to eight subspecies of Proboscivirus are identified among which strains affecting Asian elephants (*Elephas maximus*) EEHV1a, EEHV1b, EEHV4, EEHV5 and the African elephants (*Loxodonta africana*) are affected by the strains EEHV2, EEHV3, EEHV6, EEHV7. Amongst these, most pathogenic strain is considered to be EEHV type 1. The incidence of gamma-herpesvirus has also been found, shedding in the oral and nasal secretions as well as in oral mucosal papillomas but these do not cause any lethal symptoms

MODE OF TRANSMISSION

The virus only spreads amongst elephants and does not spread to other animals or humans. Major mode of transmission is trunk to trunk contact, through nasal secretions, ocular secretion, saliva or blood transfusion and also by aerosol inhalation.

Studies have found that EEHV type 1a and 1b are usually shed in trunk secretions. Artificial insemination is not believed to be a mode of transmission. A large amount of virus is also shed from the infected animal's faeces. Role of indirect transmission via fomites has not been determined. Trans-placental infection is also observed by positive results of PCR from pregnant animal samples. Stress is often associated with the disease. Oral and genital touching can also serve as a mode of transmission.

INCIDENCE AND OCCURRENCE

The virus causes infection to both captive and free living wild Asian elephants, preferentially targets the calves or juveniles mostly from the age of one year to twelve years. Adult elephants that carry the virus do not show any sign or symptoms. Pregnant animal if around the age 1-10 yrs, do not show any symptoms but may act as carriers. The infection was first identified by detecting inclusions bodies of the virus in lung nodules in an African elephant in 1970s. Incidence of the disease has been mostly reported in North America, Europe, Asia, Africa. In Asia, most cases have been detected in India, Sri Lanka, Thailand, Myanmar, Malaysia and Cambodia. In Europe, its mainly observed in Germany, France, Netherlands. In India, the first case of EEHV was detected in 1997 in South India. Now its most commonly observed in Assam, Tamil Nadu, Kerela and Odisha. Recently in Odisha, a number of elephants in Nandankanan & Chandaka zoo forest were found dead and diagnosed with EEHV through molecular confirmation by PCR.

PATHOGENESIS OF THE DISEASE

The virus has very short duration of onset of action approximately 24- 35 hr. The incidence of viremia is detected within 12-72hr with an incubation period of about 7-14 days. It causes a disruption in the blood coagulative system resulting in massive endothelial destruction and inflammation of various organs (Gutwang *et al.,* 2021). It circulates throughout the body and affects the blood cells mainly monocyte. These viruses infected monocyte then tend to attach to the endothelium which serve as the replication site for the virus. The affected endothelium leads to the exposure of the sub-endothelial tissue to various coagulation factors eventually leading to aggregation of platelets and formation of platelet plugs. These result in hemorrhages, inflammation and edema of the affected cells which leads to the up regulation of inflammatory cytokines such as IL-1, IL-2, IL-4 and TNF-alfa. As it impairs the coagulation system, there is decreased synthesis of anticoagulants and suppression of fibrinolysis. Sometimes, there are thrombo emboli observed in the blood vessels which leads to disseminate intravascular coagulopathy (DIC). DIC leads to significant decrease in platelets, fibrinogen, coagulation factors thus play a major role in hemorrhage and edema. The bleeding tendency and incidence of capillary rupture increases leading to hypovolemic shock. Thrombocytopenia, DIC are considered as the main reason for the death of infected elephants. Virus causes a mortality up to 85%.

CLINICAL SIGNS AND SYMPTOMS

The calves affected by the virus experience non-specific signs and symptoms. The two most observed clinical presentations are Per-acute and Acute. In Per-acute cases, there is death within a few hours without any premonitory clinical signs. In acute conditions, typical clinical signs include high fever, dullness, anorexia, bloody diarrhea, mild colic, lacrimation, facial edema, tachycardia. With the progression of the disease, there is reduced trunk movement, weak thready pulse, unresponsiveness to commands, dribbling saliva due to swollen tongue, nervous symptoms like ataxia, staggering drowsiness due to intracranial bleeding, recumbent and eventually death after about 1-7 days.

Hemorrhagic diathesis is the hallmark of EEHV infection. Cyanosis of the tongue tip that gradually progresses caudally, ulcers in oral cavity are sometimes detected. There is oedema of the limbs, head (mostly ventral part), neck etc. Nodules on the skin, pericardial effusion are also observed grossly.

POST MORTEM LESIONS

Post mortem lesions include widespread petechial and ecchymotic hemorrhages throughout the tissues and internal organs, cyanosis of tongue, ulcers in the oral cavity specifically hard palate, larynx, large intestine and small intestine, oedema of the submucosa and subserosa of internal organs, follicular lymphoid nodules, hepatomegaly and spleenomegaly, expansion of hepatic sinusoidal expansion, ulcerative dermatitis on skin. Some African elephants were detected with pulmonary nodules which caused asphyxia, multi-focal, proliferative cutaneous nodular lesions on the trunk mainly and sometimes on the limbs and lateral sides of the body, and also lymphocytic vulvitis in females (inflammation mucous membrane of vulva with lymphoid cell infitrations).

DIAGNOSIS OF THE DISEASE

Diagnosis of the virus is usually based on history and clinical signs, hematological alterations, biochemical alterations, molecular tests, post mortem lesions, histopathology, immuno- histochemistry (Kochagul *et al.,* 2018). However, the detection of infectious DNA in the body samples by PCR is considered to be the gold standard for confirmatory diagnosis of EEHV. TaqMan realtime PCR is the most effective to screen EEHV1 in clinical samples such as saliva, nasal, ocular secretions, blood, whole/anticoagulated in EDTA containing tube or heparin. Among serological tests, ELISA is found helpful as it can also be used in conjunction with PCR for evaluation of active infection upon exposure of animals to EEHV (Hoornweg *et al.,* 2021). Isolation of the agent is also done by tissue sections from frozen heart, lung, skin nodules, liver, kidney and tongue.

Leucopenia, thrombocytopenia and a decrease in erythrocytic count are the usual findings. Anemia persists for about a week or two (Yun *et al.,* 2021). The hematological count shows an enhanced platelet count to around 2-2.5 lakhs cu/mm. TLC is reduced to almost half within 5 days. Fragments of monocytes are detected in some cases. Certain staining methods like hematoxylin and eosin staining showing the viral inclusion bodies in endothelial cells. Blood mononuclear cells isolation for detection of the causative agent is done by staining with an immunofluoroscent solution. Loop mediated isothermal amplification (LAMP) is a rapid and simple detection method for the virus in blood by amplifying and detecting the nucleic acid under isothermal conditions. Histopathological findings confirming the diagnosis include- Extensive micro-hemorrhages throughout the heart, tongue, multifocal sinusoidal expansion of hepatic cells, basophilic inclusion bodies observed in the trophoblastic layer of the placenta, capillary endothelial cells in myocardium, tongue, muscle contain basophilic intra nuclear inclusion bodies.

Treatment

There is no true cure for the EEHV infection till now. Elephants may however recover if diagnosed and treated early. Based on the research ongoing in the elephant care institutions and health organizations, the treatment protocols are seen to improve the health by lessening the extend of infection. General regimen includes blood plasma transfusion, interferon therapy, administration of immunomodulators, antipyretics, fluid therapy to support the hypovolemic shock. First line of treatment is rectal fluids. Plain water administered through a rubber tube pump can be life saving for elephants. If the

animal's condition is more deteriorated intravenous fluids can be administered (@1litre per 450 kg body wt). Plasma transfusions are very helpful for instant increase in platelets. Plasma or blood stored from another elephant which is healthy @2-4litres per elephant have been found beneficial. Among antiviral drugs Famciclovir is most commonly used orally or rectally @ 16mg/kg for one day then 12mg/kg, Acyclovir with a dose rate @5.0 mg/kg body weight about 12 hourly orally and Ganciclovir can also be given orally but shows side effects like bone marrow suppression or Fanconi's syndrome. Opiods like Butorphanol can be given @0.01-0.03mg/kg i/m or iv. Antibiotics like Ceftiofur 21,1mg/kg i/m can be administered for any secondary bacterial infection. Vitamin supplements like Vitamin E @2.2IU/kg orally and Vitamin C @30-40mg/kg orally, methylprednisolone @1mg/kg body weight i/v daily once or dexamethasone @0.05-0.5 mg/kg i/m is seen to show slow improvement. The other supportive additional medication include infusion with Dextrose and Ringer's Lactate, diuretics like Furesamide, anti-inflammatory drugs like Meloxicam, Vitamin B complex and H2 blockers. Oxygen therapy at a flow rate of 5litres a minute is considered useful for depressed cardiovascular system. Pericardiocentesis can be performed in case there is cardiac tamponade secondary to pericardial effusion diagnosed through pericardial tapping.

PREVENTION, CONTROL AND MANAGEMENT

Vaccines- Presently in India, there are no vaccines that can control the disease but recently an mRNA vaccine for the strain EEHV1a was developed as a result of collaborative efforts of Bayor College of medicine and Hauston zoo by Dr. Paul Hauling which was tested on a 40yr old Asian elephant, Tess. But as the vaccine is in its early stages, a lot more research is needed to improve the efficacy.

Its seemingly difficult due to the short course of the diseases i.e the time between attack of the virus and visibility of the clinical signs as its mostly an acute condition. Prevention of the disease can be brought about by keeping the elephant in a healthy environment, timely deworming, vaccination and exercise, keep a ready stock of medicine so that the medication can immediately start on observing the clinical signs, daily checks carried out on every elephant, oral examination of ulcer, tongue lesions, fecal ball temperature, routine blood tests should be done and matched with the EEHV blood parameters.

CONCLUSION

A healthy juvenile elephant should be monitored every week. Regular close visual inspection of different parts of the body, blood sample and trunk wash should be screened in weekly interval. Screening protocol for carriers should be carried out. Animal brought in exchange / rescue programme should be quarantined for about 6 months with routine checkups. Besides, proper awareness and training on EEHV should be given to the zoo personnels including Zoo Vet, Mahunta or elephant care takers at regular interval for refreshing the update knowledge on EEHV.

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