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Tick-Borne Encephalitis - A Threat to Life

AUTHORS DETAIL

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INTRODUCTION

Tick borne encephalitis is a serious arbo-viral zoonotic infection in human affecting their Central Nervous System (CNS) and commonly found in Asia and Europe (Ruzek et al. 2019). The virus is transmitted by Ixodes ticks spp. and taxonomically belongs to the family Flaviviridae and genus Flavivirus (Simmonds et al. 2017). Transmission of virus typically occurs during the infestation of tick hence, the incidence of TBE is linked with expansion of these ecto-parasites (Salat and Ruzek 2020). Additionally, it is also transmitted through ingestion of TBEV-infected milk and milk products. Sheep, goat, horses, dogs, rodents and other animals is its reservoir host and human are dead end host (Buczek et al. 2022). The most serious form of TBE virus is inflammation of brain and spinal cord known as encephalomyelitis (Gritsun et al. 2003).

It was earliest narrated in Austria and detached in Russia, in the years 1931 and 1937 respectively (Valarcher et al. 2015). TEBV is an enveloped, spherical, positive sense, RNA (single stranded) virus and roughly 50 nm in width. It is appeared in three distinct forms viz. mild, moderate and severe. This viral genome is encoding one polypropylene that split into 3 structural (C, M, E) and seven non-systemic proteins. Its nucleo-capsid is comprised of viral nucleic acid and capsid protein C, which is enveloped by a lipid protein consisting of protein M and E (Füzik et al. 2018). The principal part of viral exterior surface is Protein E and take part as virus-neutralising antibodies while post infection (Heinz and Stiasny 2012).

TBE is transmitted both transtadially and transovarially between their developmental stages. Ticks have long life cycle and TEBV have ability to survive throughout their developmental stage yet, its cycle is affected by certain factors as microclimate, host factor and environmental changes. In the winter season, some tick's activity become limited. Furthermore, ticks mostly active in plantation weathers with sufficient amount of moisture and increased temperature. During moulting, it's size contract with discharge of water and toughness of skin and until the upcoming spring, ticks develop itself for cold season (Wondim et al. 2022).

Etiology

Tick-borne encephalitis (TBE) is a serious infectious disease that affects the central nervous system (CNS) of animals and humans (Ruzek et al. 2019). About 10,000 to 15,000 cases are reported in Europe and Asia annually (Bogovic and Strle 2015). TBE virus (TBEV) is the causative agent of the disease, that represents arboviruses, including viruses, which are transmitted by blood-sucking arthropods. Phylogenetical character of the virus relates it to the Flaviviridae family and genus Flavivirus (Simmonds et al. 2017). TBEV includes 3 sub-types namely:

1) The European subtype that is transmitted by *Ixodes* (*I.*) *ricinus* ticks
2) The Far eastern subtype that is transmitted significantly by *I. persulcatus* and
3) The Siberian subtype that is transmitted by *I. persulcatus.*

The viral genome is a single-stranded RNA genome that encodes one polyprotein and split into three structural viz. C, M and E and seven non-structural proteins. The nucleocapsid of the virus consists of the viral nucleic acid and capsid protein C. The nucleocapsid is enveloped by a lipid membrane containing two proteins i.e., M and E (Füzik et al. 2018). Protein E is the main surface antigen, which allows the host cells to mediate infection by binding with the surface receptors (Heinz 1986).

Epidemiology

This virus is endemic in Russia, Mongolia, central, eastern and northern Europe, northern part of the China and Japan. According to a survey, about 170,000 cases of humans have been appeared in Europe and Russia since 1990 to 2009 (Suss 2011). This virus has three subtypes that is prevalent across the Eurasian continent i.e. the Western European subtype previously known as central European encephalitis virus, commonly found in the regions of central, eastern and northern Europe (pastoral and woodland), where *I. ricinus* is the main vector; the Siberian subtype earlier called as West

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Siberian encephalitis virus, typically present in Ural region, far-eastern Russia and north-eastern Europe, where *I. persulcatus* is the main vector responsible for disease transmission; and the far-Eastern subtype previously named as Russian spring-summer encephalitis, indigenous in the far-eastern Russia and some woodland of Japan and China. It is also transmitted by *I. persulcatus* (Valarcher et al. 2015).
According to survey of 2000-2019, 51,519 confirmed cases have been reported in Europe, though the number of cases get declined during the years 2014 and 205 but after 2015, instances of cases have climbed again. The main reasons for the prevalence of TBEV are host community, movement of host, environmental conditions and traveling of people around foci area. Overall, mean incidence rate was 3.27 in this entire period (2000-2009) (Wondim et al. 2022).
It is reported in 28 different countries around the globe and recent presence of TBEV virus in north Europe indicates the disclosure of new foci of TBE (Wondim et al. 2022). Its distribution is not constant and the data is still insufficient in some countries i.e., Germany and Austria, where information regarding TBEV virus is inadequate and their reporting habits differ from geographical and historical reasons (Dobler et al. 2012). Therefore, a lot of research needs to be done on this virusotherwise it will get prevalent across the globe and become threat for the human health.

Pathogenesis

Tick bite is considered as a significant source of TBEV infection rather than the consumption of unpasteurized dairy products. After infected tick bite, virus replicate first at the inoculation site, afterwards drain into lymphatic system. Virus has been found in dermal, Langerhans and dendritic cells that is the primary site of infections before enter into regional lymph nodes. Plasma viremia occurs after replication of virus inside the lymph nodes. From this site, virus reach to different tissue i.e., spleen, liver and bone marrow via heamatogenic route that results inflammation, lysis and cellular dysfunctions (Ruzek et al. 2010).
Significant proportion of virus tires are required to cross the blood brain barrier. Patients having small number of TBEV specific antibodies, rarely neutralizes the titres to avoid CNS infection, consequently, virus replicate at neurons target site and cause inflammation, cellular lysis, necrosis, apoptosis and cellular dysfunction. This infection leads microglia and TBEV-specific T lymphocyte migration toward CNS, particularly to the grey matter and prone to immunopathogensis at the infected sites. In lethal state, it also affects spinal cord, brain stem and cerebellum (Mansfield et al. 2009).

Transmission

In every active developmental stage, ticks can be infected with TBE virus. After entering in ticks, this virus localized in tissues, salivary glands and ovaries. It's presence in ovaries indicates that transovarial transmission are common in ticks. Moreover, the virus present in the entire organism, transstadial transmission is also plausible (Ličková et al. 2020).
Larvae are infected with virus via transovarial transmission. Furthermore, larvae and nymph are also get infection while co-feeding the same rodent host and keep their infection after molting in the subsequent stage through transstadial transmission. Once infected, ticks carry that infection throughout their lives. Mammals are infected by tick's bites or contact with the wounds having eggs of infected virus. Virus attached with saliva enter into mammals and reach their organs. Its incubation period is 7-14 days depends on the host species and their immunological conditions. During this entire period, virus multiplies and spread to entire organisms. This make horizontal transmission possible between co-feeding ticks species. Apart from this, transmission is also spread via milk and milk products obtained from the infected host. Additionally, it is also spread through inhalation with dust and blood transfusions (Karbowiak and Biernat 2016). Fig. 1 shows the cycle of TBEV transmission to the host.

Clinical Manifestations

Canine Tick-borne Encephalitis

The common clinical manifestations of tick-borne encephalitis in canines include an elevated body temperature up to 106.5 F and behavioral changes that include denying of food, shyness, apathy and increased aggressiveness. Musculoskeletal disorders are often found in the affected animals, with forelimb and hindlimb motion disabilities being the most common. Severe neurological and brainstem damage is evident from the neurological symptoms such as paresis of the forelimbs or hind limbs, quadriplegia, seizures, convulsions, ataxia, perceptual disorders, hyperalgesia in the neck, hyperesthesia, loss of head sensitivity, facial nerve paralysis, strabismus, anisocoria, nystagmus, miosis, loss of the corneal reflex, and optical neuritis (Valarcher et al. 2015).

Equine Tick-borne Encephalitis

Studies on the prevalence of TBE-specific antibodies in horses have revealed that this species is also susceptible to TBEV infection, though the disease is asymptomatic in the vast majority of cases. The signs of disease reported in individual cases include poor general condition, loss of appetite, anorexia, shyness, nervousness, ataxia, spasms, epileptic seizures, and hyperalgesia in the neck (Klaus 2013).

Ruminants Tick-borne Encephalitis

In Ruminants, Tick-borne encephalitis is usually asymptomatic and do not typically cause problems in the infected host. However, rare descriptions of symptomatic TBE in ruminants also exist (Böhm et al. 2017).

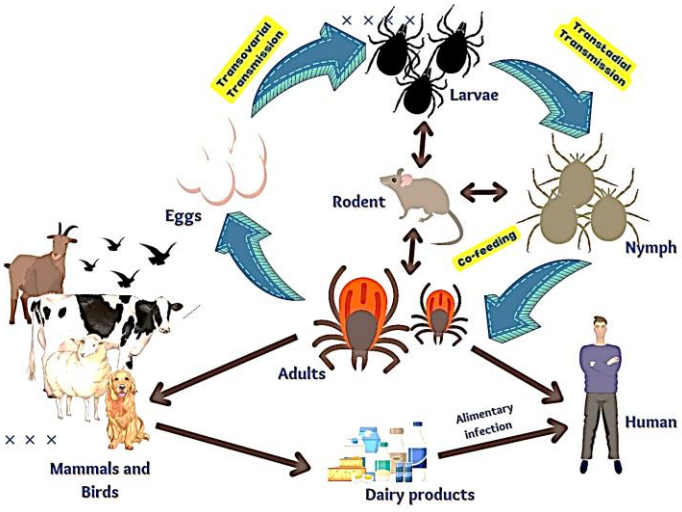

Fig: Tick borne Encephalitis

Fig. 1: Transmission cycle of Tick-Borne Encephalitis Virus

TBE Manifestation in Humans (Tick-borne Encephalitis zoonoses)

TBE virus is one of the principle causes of the central nervous system (CNS) infection in humans. It causes clinical disease in all ages but adults are particularly more vulnerable. TBEV infection is of biphasic nature (Grešíková 1999). The incubation period varies between 2 to 28 days, with an average of 7 days. In the first phase of infection that is the viremic phase which encompasses first two to eight days of infection, flu-like symptoms with an increased temperature, nausea, headache, lethargy and aching back and limbs are most evident. Subsequently, there follows an asymptomatic period and, in 1/3rd of the patients, a second phase of the disease is reported, which is characterized by a sudden onset of fever. This is the phase chiefly affecting CNS and is manifested by clinical symptoms including anorexia, fever, headache, vomiting, photophobia, sensory changes, visual disturbances, paresis, paralysis, or even coma. Other reported symptoms include hyperkinesis of the limbs and face muscles, convulsions, lingual tremor and paresis of the respiratory muscles. This disease might prove fatal a week after the onset of clinical disease (Füzik et al. 2018).

In case of a severe disease observed in 10-20% of the patients, chronic neuropsychiatric or nervous sequelae are observed, such as lack of concentration, depression or paresis of the face or limbs due to chronic myelitis or encephalitis (Chambouris et al. 1989).

Treatment

The TBEV infection has no specific treatment options. When neurological symptoms are present, antiviral therapy is not used as a form of treatment because the virus has already disappeared. The treatment is primarily symptomatic and includes nonsteroidal anti-inflammatory medication. According to the severity of their symptoms, patients typically require hospitalisation and supportive care, which includes giving antipyretics, analgesics, antiemetics, maintaining a healthy balance of water and electrolytes, and giving them anticonvulsive agents if necessary. Intubation and ventilatory support are necessary for patients with neuromuscular paralysis who have respiratory failure. For patients in a coma or experiencing difficulty breathing, reanimation therapies are administered (Böhm et al. 2017). A possible consequence of acute viral encephalitis is cerebral oedema, which worsens the clinical presentation and foretells a poor neurologic outcome. Intravenous mannitol and/or steroids are frequently administered to patients with significantly increased intracranial pressure. Mannitol induces the fluid from an oedematous brain to return to the intravascular space, which strengthens cerebral perfusion pressure, increases circulation volume, and decreases intracranial pressure by cerebral autoregulation. Additionally, it influences the fluidity of the erythrocyte membrane, which enhances blood flow and oxygen delivery by lowering blood viscosity. Five percent of patients with cerebral hypertension experience a rebound phenomenon. When the serum osmolality exceeds 320 mOsm/L, it is often advised to discontinue administering mannitol to avoid complications. No credible (comparative) research supports the use of mannitol in TBE patients, despite the fact that it is a fairly common clinical practise to administer intravenous mannitol to people suffering from extremely increased intracranial pressure (Füzik et al. 2018).

Prevention and Control

The primary methods for controlling TBEV are infection prevention through active immunisation of populations at risk (Christine Klaus et al. 2010) and prevention of transmission from ticks or food products (such as pasteurised milk), wearing light-colored clothing (light colours make ticks easier to spot) having full sleeves and pants tucked into

socks or shoes, using repellents, and carefully checking for ticks over the entire body are the possible options to avoid getting ticks. Avoiding ticks means limiting contact to vegetation, particularly in deciduous and mix forests with a dense understory and a layering of decomposing vegetation on the ground that offers enough humidity for tick formation and survival. However, within a few minutes of attachment, an infected tick's saliva may transfer TBEV since it is present in its salivary glands. The most effective method to prevent the disease in a risk area is active immunization by vaccination. Two TBE vaccines, FSME-IMMUN® and Encepur®, are licensed in Europe. In addition to the European vaccinations, Russia has registered two vaccines (TBE-Moscow and EnceVir) based on the Far-Eastern subtype of Tick born encephalitis virus. The viruses are produced in cells of chick embryo and formalin has been used to inactivate them and aluminum hydroxide is used as adjuvant in both of the vaccines. Another vaccination based on the Far-Eastern subtype of tick born encephalitis virus has been produced and used in China (Riccardi N et al. 2019).

Conclusion

Tick serves as a vector for transmission of tick-borne encephalitis virus and its cycle is affected by certain factors including microclimate, host factor and environmental changes. After infected tick bite to the host, virus replicate first at the inoculation site, and then drain into the lymphatic system. Virus has been found in dermal, Langerhans and dendritic cells that is the primary site of infections before entering into regional lymph nodes. During this entire period, virus multiplies and spread to entire organisms. This makes horizontal transmission possible between co-feeding tick species. The primary methods for controlling TBEV are infection prevention through active immunization of populations at risk leading to prevention of transmission from ticks or food products (such as pasteurised milk), wearing light color clothing (light colours make ticks easier to spot) having full sleeves and pants tucked into socks or shoes, using repellents, and carefully checking for ticks over the entire body.

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