Tick-borne viral encephalitis: are they far from the Americas?

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Within the various pathologies of the Central Nervous System (CNS), the two most important clinical entities due to their frequency of appearance in the world are meningitis and encephalitis. CNS infections constitute a diagnostic challenge because the clinical manifestations are not normally pathognomonic and there are various etiological agents involved. It is only possible to determine between 40-70% the etiological agent of encephalitis cases and in less than 0.1% it is possible to isolate a virus other than enteroviruses or herpesviruses (1).

Emerging and re-emerging viral infections represent a risk due to their ease of geographic expansion, transmission between species, adaptation to new hosts, and new pathogenic properties. In the 1930s, an acute disease of the central nervous system with a high mortality rate was described in the city of Khabarovsk in the Russian Far East bordering China. Initially it was thought to be Japanese encephalitis or polio due to having similar symptoms. In those times of war, many soldiers died from this disease (2). To clarify the etiology, a group of scientists was formed who traveled to the area, analyzed the cases, studied transmission, ecoepidemiology, and isolated the etiological agent; later the disease was called tick-borne encephalitis (TBEV) (2).

Tick-borne encephalitis virus (TBEV) is a member of the Flavivirus genus of the Flaviviridae family. It is a positive-sense, single-stranded RNA enveloped virus. The RNA genome is approximately 11 kb in length and encodes a single polyprotein flanked by 5’ and 3’ untranslated regions that is cleaved after translation by viral and cellular proteases into three structural proteins and seven non-structural proteins (3). Considering the potential to cause severe disease in humans, TBEV along with other flaviviruses are classified as Biosafety Level 3 (BSL-3) pathogens (4).

The virus is transmitted to humans by tick bites mainly of the genus Ixodes (Ixodes ricinus in Europe and Ixodes persulcatus in Russia), although it can also be transmitted by consumption of contaminated unpasteurized dairy products (5). In nature, the virus can persist in ticks for their entire lives, allowing for transmission of the virus for years after initial infection and to be maintained through a transmission cycle involving an ixodid and a vertebrate host. Many animal species can be reservoirs of TBEV (6,7).
TBEV is endemic in much of Europe and central Asia; about 10,000 cases are reported annually, the majority in Russia. In many European countries TBEV have a well-established surveillance system. Despite the availability of an efficient vaccine for prevention, the incidence of TBEV is increasing since vaccination coverage is insufficient for many risk groups (5,7).

TBEV is a complex of phylogenetically closely related viruses. However, despite these genetic similarities, these viruses present a wide range of clinical syndromes that are shown in Table 1 (7,8).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Associated Pathology</th>
<th>Vector</th>
<th>Geographical location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkhurma haemorrhagic fever virus</td>
<td>Hemorrhagic fever</td>
<td>Ornithodoros savignyi y Hyalomma dromedari</td>
<td>Saudi Arabia, Egypt, Djbouti</td>
</tr>
<tr>
<td>(AHFV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gadgets Gully virus (GGYV)</td>
<td>Unknown</td>
<td>Ixodes uriae</td>
<td>Australia</td>
</tr>
<tr>
<td>Karshi virus (KSIV)</td>
<td>Encephalitis</td>
<td>Ornithodoros tholozani</td>
<td>Uzbekistan, Russia, Kazajistan</td>
</tr>
<tr>
<td>KF DV</td>
<td></td>
<td>Ornithodoros papillipes H. asiaticum</td>
<td></td>
</tr>
<tr>
<td>Langat virus (LGTV)</td>
<td>Encephalitis</td>
<td>Haemaphysalis spinigera</td>
<td>India, China</td>
</tr>
<tr>
<td>Louping ill virus (LIV)</td>
<td>Encephalitis</td>
<td>Ixodes ricinus</td>
<td>United Kingdom, Ireland, Norway, Spain</td>
</tr>
<tr>
<td>Omsk haemorrhagic fever virus</td>
<td>Hemorrhagic fever</td>
<td>Derma centor reticu laris</td>
<td>Russia (Siberia)</td>
</tr>
<tr>
<td>(OHFV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powassan virus (POWV)</td>
<td>Encephalitis</td>
<td>Ixodes cookei, I. marxi, I. scapularis, I. spinipalpus D. andersoni</td>
<td>USA, Canada, Siberia</td>
</tr>
<tr>
<td>Royal Farm virus (RFV)</td>
<td>Unknown</td>
<td>Argas hermanni</td>
<td>Afghanistan</td>
</tr>
</tbody>
</table>

Source: The table was prepared based on references 8, 9 and 10.

The mortality and morbidity of TBEV varies according to the viral subtype and five subtypes are known. However, severe cases of TBEV have been reported with all subtypes. Mortality from TBEV in Russia is 2% (7.11), but it may vary with geographic location and with the type of virus.

- TBEV-Eu - European [neurological sequelae > 10%; mortality 2%].
- TBEV-Sib - Siberian [prolonged infections; mortality 2-3%].
- TBEV-FE - Far East [high rates of neurological sequelae; mortality >40%]
- TBEV-Him – Himalayas [reported in the rodent Marmota Himalayana - China].
- TBEV-Bkl–Baikalano [Similar to the Siberian subtype].

The differences in virulence from the genetic point of view have not yet been determined in detail, since the variation of the amino acid sequences in the polyprotein does not show much variation (2.2%-5.6%) (5).

The Powassan virus (POWV) is the closest phylogenetic relative of TBEV and is the only one known to date from the Americas. POWV causes encephalitis with long-term neurological sequelae and a mortality of 10%. Between 2006 and 2015 in the United States, POWV was responsible for 6.8 cases per 100,000 cases of encephalitis that occurred. Ixodes cookie is one of the main vectors of POWV and is found in Canada and the United States. There is serological evidence of animals and of the virus in vectors in British Columbia, Cranbrook (Canada), California, Alaska, and New Mexico, demonstrating that the distribution of POWV is more extensive than initially reported (8).
In a retrospective study conducted by the CDC in the USA, sera from travelers with encephalitis from Europe and Asia between 2000 and 2009 were analyzed. Five patients presented IgM antibodies to both TBEV and POWV. TBEV is phylogenetically close to POWV and there is serological cross-reactivity between them. However, the final diagnosis of TBEV was determined by PRNT (12).

Recent seroprevalence studies carried out at the Institute of Biological Research of the Tropics (IIBT) - University of Córdoba where 200 sera were analyzed, it was found that 93% of them were seropositive for TBEV, but they were also positive for Dengue. It is very probable that the endemicity with other flaviviruses could be making the diagnosis of the TBEV complex difficult in tropical countries.

Currently, in South America there is no evidence of tick-borne viruses affecting humans or animals. However, there is evidence of viruses reported in ticks:
- Matucare virus (Reoviridae: Orbivirus) / *Ornithodoros kohlsi* / Bolivia,
- Huacho virus (Reoviridae: Orbivirus) / *Ornithodoros amblus* / Peru.
- Cacipacoré virus (Flaviviridae: Flavivirus) / *Amblyomma sculputum* / Brazil.
- Bunyamwera orthobunyavirus (Family: Peribunyviridae)/Brazil.
- Mogiana virus (Flaviviridae: Jingmenvirus) / *Rhipicephalus microplus*/Brazil.

Recently a *Bunyamwera Orthobunyavirus* (Family: Peribunyviridae) was detected in *Amblyomma sculputum* ticks, Minas Gerais, Brazil. This virus is closely related to the Maguari virus (Family: Peribunyviridae), the etiological agent of mosquito-borne encephalitis, which has been detected in Ecuador, Brazil, Trinidad and Tobago, Colombia, Argentina, and French Guyana (13,14). This shows that viral adaptation is possible in phylogenetically distant arthropods such as mosquitoes and ticks, which implies a further challenge for public health surveillance.

In Colombia, in relation to encephalitis, those transmitted by mosquitoes are considered mandatory notification, such as: Venezuelan, East, West and West Nile. However, agents such as TBEV have not been reported. Regarding viruses that cause tick-borne encephalitis, in Colombia there are no specific studies on this subject. However, some have been carried out in the department of Córdoba where Lihan's Phlebovirus was detected in ticks of the genus *Rhipicephalus* (15).

Massive sequencing (NGS) studies provide more diverse results with respect to the tick virome; Therefore, it is necessary to carry out these studies for the detection of viruses in ticks. Two studies using NGS have been conducted in Colombia; In both, a great diversity of viral orders such as Tymovirales, Mononegavirales and Totiviridae, among others, and viral families such as Phenuiviridae, Flaviviridae and Chiviridae have been detected. No known viruses were found other than those reported for mosquito-borne encephalitis (16,17).

One of the concerns about the increase in tick-borne diseases is climate change, as it increases the abundance and expands the habitats of tick species. It is also important to consider that as travel and immigration have increased, cross-border movements have become common. Colombia, for example, is a transit and displacement territory for thousands of people from different countries who use areas of the Caribbean as corridors to reach Panama and then migrate to the USA.

On the other hand, the population of the Colombian Caribbean is exposed to ticks, and therefore, they could also suffer febrile syndromes or undiagnosed encephalitis. For these reasons, it would be important to establish epidemiological surveillance to search for cases of the TBEV complex. In addition to case surveillance, ecoepidemiological studies in vectors are crucial to close the epidemiological ring on TBEV infections.

Colombia has a great diversity of tick species, 52 species (15 Argasidae species and 37 Ixodidae species) have been described. Many of these species are recognized as vectors of infectious agents. The following genera are important in human and animal public health.
- *Rhipicephalus*: *R. microplus and R. sanguineus*. 

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https://doi.org/10.21897/rmvz.3125
• Dermacentor: *D. nitens*.
• Haemaphysalis: *H. leporispalustris*.
• Ornithodoros: *O. puertoricensis* and *O. rudis*.
• Ixodes: *I. tropicalis* (18,19).

Based on the literature previously exposed, it is possible that given the wide biodiversity of ectoparasites–vectors reported in Colombia, there are many viruses in ticks. In addition, climate change, environmental pollution and unplanned urban growth could trigger a new public health problem. Undiagnosed cases of encephalitis could be the beginning of an interesting study on encephalitis caused by tick-borne viruses. The variables could trigger a new “virus-tick” eco-epidemiological association that would lead to the appearance of new viruses that cause emerging diseases.

**REFERENCES**


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