Mini-Review

Wetland Virus and the Increasing Threat of Tick-Borne Arboviruses

Balamurugan Shanmugaraj[1,2]*, Harish Mani Chandra[3]

1. Department of Biotechnology, Karpagam Academy of Higher Education, Coimbatore, 641021, Tamil Nadu, India.
2. Centre for Natural Products and Functional Foods, Karpagam Academy of Higher Education, Coimbatore, 641021, Tamil Nadu, India.
3. Department of Biotechnology, Thiruvalluvar University, Serkkadu, Vellore- 632115, Tamil Nadu, India.

***Correspondence**

Dr. Balamurugan Shanmugaraj

Department of Biotechnology
Karpagam Academy of Higher Education
Coimbatore, 641021, Tamil Nadu, India
Email: balasbm17@gmail.com

Abstract

Arboviruses are responsible for many emerging and reemerging diseases that represent a significant public health threat globally, affecting millions of people annually and put over half of the global population at risk. These viruses primarily depend on mosquito or tick vectors for transmission to vertebrate host. Ticks are one of the major vectors transmitting wide range of arboviruses that are known to cause serious infectious diseases in both animals and humans. The geographic expansion and increasing prevalence of tick-borne viruses pose significant prevention and control challenges. Amid the global health challenges resulting from the Coronavirus disease pandemic and the recent resurgence of monkeypox which has been designated a public health emergency of international concern, another febrile illness has been reported in northeastern

China that has drawn attention. Recently a new tick-borne virus, wetland virus associated with human febrile illness which is closely related to Crimean–Congo hemorrhagic fever virus has been identified in a patient admitted in a hospital in Jinzhou, Liaoning province after a tick bite in China. The affected individuals showed variable degrees of clinical symptoms. It is essential to remain vigilant about this new viral outbreak. As it is a new virus, there are no reports available demonstrating effective vaccines or drugs for the treatment of wetland virus. In this review, an outline of the wetland virus and insights into the tick-borne arbovirus infections were provided. Further, the need for the development of effective treatments, surveillance measures and prevention strategies to mitigate the future outbreaks is also highlighted.

Keywords: viral diseases; arbovirus; tick borne viruses; transmission.

1. Context

Arboviruses comprise a diverse family of viruses infecting both animals and humans. Most of these viruses pose public health challenges, as it causes severe diseases with substantial mortality and morbidity during epidemics. These viruses circulate among wild animals and are transmitted to susceptible host through an insect vector such as infected mosquitoes, flies and ticks (1, 2). Ticks are one of the major arthropod vectors for the transmission of human pathogens including bacteria, viruses, and parasites. The prevalence and distribution of tick populations and tick-borne diseases has gradually expanded due to climate change and human activities and present a threat to global health (3, 4). The tick-borne viruses are the group of viruses categorized in two orders, nine families, and twelve genera, along with other unclassified members (5) which are carried and transmitted by ticks, some of which are known to cause severe diseases with high morbidity and mortality rates and associated with major epidemics. Several tick-borne viruses have been identified so far and have long been a significant concern for veterinary and human health worldwide (6, 7). Some of the medically important tick-borne viruses are tick-borne encephalitis virus, crimean–congo hemorrhagic fever virus, bourbon virus, dhori virus, powassan virus, omsk hemorrhagic fever virus, colorado tick fever virus, heartland virus and kyasanur forest disease virus (8-10). These viruses are common in many regions and cause millions of infections worldwide. Notably, the high incidence of tick-borne diseases has been reported in China (11). However, the current knowledge about the association of tick-borne viruses and tick species are limited and the disease burden is considerably underestimated.

2. Acquisition of Data

We conducted a review of relevant articles from Scopus, PubMed, and Google Scholar databases to collect and analyze existing literature on the wetland virus and threat of tick borne viruses. The search terms included “wetland virus”, “tick borne virus”, “arboviruses”, “public health impact of tick borne viruses” “ticks control and prevention measures” and the relevant articles were identified. Research papers, review articles, perspectives and commentaries providing appropriate information that fits with the aim of the study were included. The data from the collected articles were used to highlight the current state of knowledge on the growing public health threat posed by tick-borne viruses.

3. Results

3.1. Wetland Virus

Amid the global health challenges resulting from the coronavirus disease (COVID-19) pandemic, the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants (12) and the recent resurgence of mpox (13, 14), which has been designated as a public health emergency of international concern, another febrile illness has been reported in northeastern China that has drawn attention. Recently, Zhang et al., (15) reported a human febrile illness caused by a previously unknown *orthonairovirus* transmitted by ticks. This vector borne human illness was caused by a newly discovered *orthonairovirus* which was designated as Wetland virus. The virus was identified in a patient admitted in a hospital in Jinzhou, Liaoning province after a tick bite at a wetland park in Inner Mongolia, China in 2019. This virus belongs to the family *Nairoviridae* under the genus *orthonairovirus*. The viral genome consists of negative sense single-stranded RNA genome segmented into large (L), medium (M) and small (S). The large segment encodes the L protein consists of 3948 aminoacids, M segment codes for glycoprotein precursor with 1436 amino acids and S segment encoding N protein made up of 485 amino acids. This virus is closely related to the tick-borne *Hazara orthonairovirus* (62.2 to

89.6% similarity), which includes Crimean-Congo hemorrhagic fever virus (16). The *Haemaphysalis concinna* tick was the possible vector that can transmit the wetland virus. The female ticks transmit the virus to its offspring through eggs (transovarial transmission) (15).

Wetland virus RNA was identified in five tick species (*Haemaphysalis concinna*, *Haemaphysalis japonica*, *Ixodes persulcatus*, *Dermacentor silvarum*, *Haemaphysalis longicornis*) as well as in the samples from sheep (2.3%), horses (5%) and pigs (0.9%) collected in northeastern China (15). In a recent study, other five novel wetland virus tick vectors were identified, including species like *Ha. qinghaiensis*, *Ha. tibetensis*, *De. nuttalli*, *Hy. asiaticum*, and *Rh. microplus*. The regional prevalence patterns showed vector specialization, with different species dominating in specific regions. Further, various domestic and wildlife animals were found harboring wetland virus-positive feeding ticks, indicating a wide host range for the virus. Serological evidence in animals suggested their role as amplification reservoirs, contributing to the transmission cycle. Wetland virus demonstrated the ability to infect various multiple animal hosts, with phylogenetic analysis confirming ecological overlap driving spillover risk (17). However, further detailed investigations are still needed to assess the possible circulation of this virus in ticks, animals and humans. The pathogenicity of this virus was studied in Balb/c, C57BL/6J, Kunming, and IFNAR1−/− and C57BL/6J mice by intraperitoneal injection. The virus caused lethal infections with the death occurring between 2-8 days post infection. In contrast, the virus did not cause mortality in hamsters. The high viral loads were observed in the infected mice while lower viral loads were noted in the hamsters (15).

3.2. Symptoms and treatment

The wetland virus infection in 17 patients in China was diagnosed through reverse transcription-polymerase chain reaction (RT-PCR). The affected individuals displayed non-specific symptoms of wetland virus infection including fever (94%), dizziness (65%), headache (53%), malaise (53%), myalgia (29%), arthritis (18%), and back pain (12%). Gastrointestinal symptoms such as nausea, vomiting, and diarrhea were reported in 53% of patients. Neurologic symptoms, petechiae (24%) and localized lymphadenopathy (29%) reported in certain instances. As the symptoms are nonspecific, it is necessary to perform differential diagnosis to distinguish wetland virus from other tick borne viruses (15).

As it is a new virus, there are no reports available demonstrating effective vaccines or drugs for the treatment of wetland virus. Recently, Wang et al., demonstrated the antiviral activity of the ribavirin, remdesivir, molnupiravir, sofosbuvir and 4'-fluorouridine. The results demonstrated that the ribavirin and 4'-fluorouridine inhibited the virus replication *in vitro* and reduced mortality in a lethal immunocompetent mouse model. The study concluded that ribavirin and 4'-fluorouridine are promising therapeutic candidates for the treatment of wetland virus infection (18).

3.3. Control and Prevention Measures

The risks of tick-borne diseases affecting domestic animals and humans are rising globally. Ticks transmit a wide range of infectious agents to both humans and animals. In addition to the challenges related to the accurate diagnosis and clinical management of tick-borne diseases, the prevention and control of these diseases is often difficult. The prevention and managing strategies of tick-borne diseases include minimizing tick exposure or tick bites by avoiding tick habitats, using repellents along with personal protection measures such as wearing protective clothing such as long-sleeved shirt and long pants will reduce the risk of disease transmission (19-21). Further implementation of vector control measures focusing on chemical, biological, physical, and integrated pest management strategies could reduce the tick populations and complement public health-directed educational efforts through social media, campaigns and advertisements could create awareness and promoting preventive measures to minimize tick-borne disease risks. Importantly, development of rapid and specific diagnostic kits/assays, and tick borne virus-targeting antivirals are highly essential to limit the burden of tick-borne diseases on public health-care systems. The development of efficient broad spectrum vaccines that can induce long lasting immune response to wider range of tick-borne viruses could be a valuable contribution for disease prevention globally (11, 22-25).

The recent identification of new viruses including wetland virus, langya virus (26) is a reminder that the viruses are a constant threat to humans with more yet to be identified. There is still limited data available about the wetland virus and much is yet to be learned. The human infection potential of this *orthonairovirus* is still underexplored. As the initial findings about this virus are based on the limited number of patients in China, this restricts the understanding of the virus true prevalence and impact. Further research is necessary to determine the severity of this infection, transmission mechanism and to assess the extent of spread of the viral infection. Although this newly discovered virus did not cause any worrisome concerns to public health so far, it is essential to stay prepared by adopting appropriate preventive measures and implementing proactive control measures that could limit the potential future impact. Additionally, regular screening/testing of vectors and humans is vital for timely identification of the virus to keep the disease under control (27, 28).

Overall, the public health impact and the seriousness of tick-borne diseases are significantly underestimated. These diseases demand immediate attention from public health experts and the research community. Still the host and viral determinants of the pathogenesis of many tick-borne diseases are poorly understood (29). Therefore, it is crucial to strengthen surveillance, vector control, accurate diagnosis and detection efforts, awareness campaigns to better understand and monitor tick-borne pathogens. This also includes identifying the hosts and vector species that transmits these viruses (30, 31). This can be achieved by adopting proactive strategies such as implementing comprehensive methodologies for monitoring tick-borne virus distribution such as real time surveillance, the development of portable diagnostic kits for field testing and early detection, establishing global database for centralized information, and harmonizing the surveillance efforts at national and international level. Additionally, the implementation of one health approach involving various stakeholders from public and private sectors on a global, national and regional level is particularly relevant for a comprehensive understanding and effective management of the human pathogens. This approach requires improved coordination, collaboration and communication across human, environmental, and animal health sectors by sharing knowledge, resources and identifying gaps in order to effectively addressing the health threats and improving overall public health outcomes (32-34).

4. Conclusion

The geographic expansion of vectors increases the risk of emerging and reemerging viral infections in previously unreported regions thereby complicating the disease prevention and control efforts. Many viruses that are earlier reported to be existing mainly in rural tropical settings are now distributed worldwide and emerged as global pathogens now. This trend shows the growing concern about the spread of diseases carried by vectors, such as ticks, mosquitoes, and other arthropods, which have facilitated the movement of pathogens worldwide. Tick-borne viruses are the major threat to human and animal health worldwide. In recent times, the number of tick borne infections is increasing and it is expected to increase further in the coming years. Timely identification of ticks and the associated pathogens is essential for preventing tick-borne viral diseases. Any disease outbreak should be informed to the health department which helps to prevent further spread and protect public health. Although first tick-borne pathogenic virus was identified over ten decades ago (5), our knowledge about the relationship of tick borne viruses with their vectors and the disease pathogenesis are still limited. There are still remains the gap in understanding the complexity and variability of human disease. Intensive laboratory studies along with the development of suitable *in vitro* and *in vivo* models, application of multiomic system biology approaches is essential in understanding the disease pathogenesis, progression in human infections and diagnosis which help with disease prevention and control measures (35, 36). A deep understanding of mechanisms driving the factors responsible for disease transmission will help us to prevent and control the disease outbreaks. The outbreak of diseases in new regions reinforces the call for action against tick-borne infections and the need for improved healthcare infrastructure, trained personnel, and development of new diagnostic assays, effective vaccines, therapies, vector control, surveillance measures and prevention programs for effective disease management.

Declarations

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Conflict of Interest

None. The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

I hereby provide consent for the publication of this manuscript.

Availability of data and material

The data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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