Global Perspectives

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ARBOVIRUS INFECTIONS OF THE NERVOUS SYSTEM: CURRENT TRENDS AND FUTURE THREATS

Systemic viral infections are common. Symptomatic involvement of the nervous system in viral infections is uncommon.[1] Encephalitis is the most worrying manifestation of nervous system involvement by viruses. Arthropod-borne viruses (arboviruses) are among the most serious international infectious threats to the human nervous system.[2] The neurologic diseases that may be transmitted by arthropods to humans include meningitis, encephalitis, myelitis, encephalomyelitis, neuritis (including anterior horn cells and dorsal root ganglia), and myositis.[2]

Arboviruses are distributed worldwide. Different species, however, have a predilection for different geographical areas. Arboviruses are transmitted to vertebral hosts by blood-feeding arthropod vectors including mosquitoes, biting flies, mites, nits, and ticks.[2,3] The table reviews some of the common arboviruses, their vectors, and their geographical distribution. Transmission pattern of arboviruses is climate-dependent and is broadly divided into 2 groups. In tropical areas, viruses circulate throughout the year, often with a broad seasonal peak. Pattern is different in temperate climates, where virus is transmitted between the vector and vertebrate host species only during the warmer months with no arboviral disease in colder months.[4]

Arboviruses that affect the nervous system are RNA viruses of several genera of the *Togaviridae*, *Flaviviridae*, *Bunyaviridae*, *Reoviridae*, and *Orthomyxoviridae* families.[2,3,5] These arboviruses replicate in peripheral tissues, produce viremia, enter the CNS, replicate in neurons, and spread outward to other neuron populations, a process that may lead to encephalitis.[6] Some of the well-known encephalitides include West Nile encephalitis (WNE), Dengue fever encephalitis (DFE), St. Louis encephalitis, Japanese encephalitis (JE), Toscana encephalitis, Crimean-Congo hemorrhagic fever, Chikungunya virus encephalitis (CHIKV), Eastern equine encephalitis (EEE), and Western equine encephalitis (WEE).

The clinical features of most encephalitogenic arboviruses include varying degrees of meningoencephalomyelitis. Fever, headache, malaise, body aches, vomiting, and nausea usually precede the neurologic manifestation and occur within days after arthropod bite.[2] Disease severity varies among individuals. A virus causing severe neurologic abnormalities or death in one individual may cause little or no disease in another.

A variety of neurologic symptoms and signs can occur due to arbovirus infection. Whereas seizures are common to almost all arbovirus encephalitides, JE, La Cross virus encephalitis (LCE), and tick-borne encephalitis (TBE) may result in chronic epilepsy.[2] Stroke can occur in JE and EEE.[2] Parkinsonism is common in DFE, JE, WNE, EEE, and WEE.[7] The cerebellum and brainstem can be affected by a number of arboviruses.[2] Peripheral neuropathy is more common with DFE, JE, WNE, and TBE.[2]

A high index of clinical suspicion remains important for the diagnosis of an arbovirus infection as laboratory and imaging findings can be nonspecific or normal, particularly in the early stages of disease. Characteristic arboviral CSF findings include lymphocytic pleocytosis with mild protein elevation. CSF glucose is usually normal, but low or high glucose levels can be seen with certain infections. Rapid serum or CSF antibody assays are available for most of the arboviruses.

Imaging findings may be nonspecific or normal in early or mild cases. Certain viruses have a predilection for certain areas of the brain. JE virus (JEV) can affect basal ganglia, brainstem, or spinal cord. The basal ganglia may also be involved in St. Louis encephalitis, LCE, and Murray Valley encephalitis. Edema of the substantia nigra has been reported in patients with St. Louis encephalitis.[8] Temporal lobe and other focal cortical involvement can be seen with JE, LCE, and EEE.[2] Spinal cord involvement (myelitis) may be present in DFE.[9]

A variety of EEG abnormalities can be seen in arbovirus encephalitides, including periodic lateralized

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Table Common arboviruses with their geographical distribution and vectors

Family	Virus	Vector	Geographical distribution
Togaviridae	Eastern equine encephalitis virus	Mosquito (*Culiseta*, *Aedes*)	Eastern and Gulf coasts of United States, Caribbean islands, Central America, and northeast coast of South America
	Western equine encephalitis virus	Mosquito (*Culiseta*, *Culex*)	Midwest and western United States, Canada
	Venezuelan equine encephalitis virus	Mosquito (*Aedes*, *Culex*)	South and Central America, southeast and southwest of United States
	Chikungunya virus	Mosquito (*Aedes*)	Africa, India, Southeast Asia
Flaviviridae	St. Louis encephalitis virus	Mosquito (*Culex*)	North America, Central and South America
	Japanese encephalitis virus	Mosquito (*Culex*)	Japan, Northeast Asia, Southeast Asia, Central Asia, and Indian Subcontinent
	West Nile virus	Mosquito (*Culex*)	Africa, Mediterranean region, central Asia, India, Europe, North America, Central and South America
	Dengue fever virus	Mosquito (*Aedes*)	Asia, tropical and subtropical regions of the world
	Murray valley encephalitis virus	Mosquito (*Culex*, *Aedes*)	Australia, New Zealand, New Guinea
Bunyaviridae	California encephalitis virus	Mosquito (*Aedes*)	Western United States
	La Crosse encephalitis virus	Mosquito (*Aedes*)	Midwest and eastern United States
	Toscana encephalitis virus	Sand fly (*Phlebotomus*)	Europe, North Africa
	Rift valley fever virus	Mosquito (*Culex*, *Aedes*, and others)	East Africa, South Africa Nile valley, Saudi Arabian peninsula
	Crimean-Congo hemorrhagic fever virus (*Nairovirus*)	Ticks (*Hyalloma*, *Ixodid*)	Africa, Europe, Asia
Reoviridae	Colorado tick fever virus	Ticks (*Dermacentor*)	Rocky Mountains of the United States

epileptiform discharges, status epilepticus, epilepsia partialis continua, and burst suppression. Nerve conduction and EMG abnormalities may be seen in DFE, WNE, JE, and TBE. Clinical, laboratory, radiologic, and neurophysiologic findings seen in arbovirus encephalitides are summarized in a recent review by Rust.[2]

There is no specific treatment of arbovirus infections. Neither steroids nor antivirals have been proven effective.[2] Supportive treatment remains the mainstay.[2] Treatment of seizures and raised intracranial pressure, along with maintenance of ventilatory and cardiac status, is important. Effective vaccines for prevention of viral encephalitides are available for only a few viral pathogens, including JEV. Vector control and avoiding bites remain the best available strategy for prevention.[1]

The keys to prevention of arboviral encephalitis include reducing prevalence of vectors, reducing host susceptibility, avoidance of the vector, and reduction of human susceptibility through the use of insect repellants or immunization.[2] Effective human vaccines are available for prophylaxis of yellow fever, JE, and tick-borne encephalitis.[10] Some of the widespread and dangerous encephalitides like Dengue and West Nile still lack a vaccine, although vaccines are in the development stage for Dengue virus, West Nile virus (WNV), and CHIKV.[10,11] With the general resistance to chemical control of vectors, novel methods like genetic modification of vector populations are becoming increasingly important for research and development.[12]

Morbidity and mortality from nervous system infections due to arboviruses are substantial.[13] Fatality rate ranges from <1% for LCE to as high as 70% in EEE.[4] Permanent neurologic disability may result in as many as 90% of affected individuals depending on the virulence and type of the virus.[1,2,4] These disabilities are myriad and include epilepsy, cognitive deficits, flaccid paralysis of limbs, focal neurologic deficits, blindness, and permanent vegetative state.[1,2,4]

Emergence and re-emergence of arboviral diseases are largely attributed to human behavior.[4] Antropogenic changes, especially involving viral genetics, composition and dynamics of host and vector population, and envoirnmental factors, may substantially affect natural systems, leading to amplification of these arboviruses to epidemic levels.[3] Modern travel and trade has facilitated the spread of arboviruses and highly efficient, anthropophilic mosquitoes throughout the globe.[4]

Poor living and sanitary conditions (highly prevalent in the developing world) may provide an ideal breeding ground for mosquitoes and environmental factors such as urbanization and crowded living conditions lead to increased human contact with arboviruses and their vectors.[4]

The geographical habitat of arboviruses has expanded in recent decades.[14] WNV underwent a

dramatic geographic expansion into the Americas beginning in 1999, whereas JEV from its origin in Indonesia and Malaysia has spread throughout most of Asia, as far south as Australia.[3] With spread of JEV to most of the Indian subcontinent and the heavy commercial and passenger air travel from this region, Europe and Africa may be potential destinations for this life-threatening virus.[3] Dengue, one of the most prevalent human arboviral pathogens with an estimated 50 to 100 million annual cases worldwide, has become one of the leading causes of hospitalization and death in children in Southeast Asia.[15] Many regions in South Asia, including Pakistan, are now endemic for DFE.[16] CHIKV, thought to have originated in Africa, has become endemic in many Southeast Asian countries as well as India.[3,15] Toscana virus, first isolated from sand flies in the 1970s in Italy, has now become a significant pathogen, causing meningitis in the summer months in large parts of the Mediterranean region, including several European and North African countries.[17]

With the increasing threat from arboviruses, it is imperative that a multidisciplinary approach is used to prevent future catastrophes from these virulent pathogens. Disease surveillance is the cornerstone of response to emerging disease threats. Risk assessment and outbreak preparedness are imperative.[15] Collaborative and integrated efforts are required to control vector populations through biological and nonbiological methods, avoid vector exposure, develop new vaccines, improve and implement mass vaccination programs, find effective therapies, increase surveillance, increase public awareness, and build capacity, particularly in endemic areas.[14]

AUTHOR CONTRIBUTIONS

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