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West Nile virus: Should pediatricians care?

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Summary Given the recurrent serious outbreaks of West Nile Virus (WNV) in the United States over the past decade, the spread to Canada and South America, the recurrent outbreaks in Europe, and the potential for serious neurological disease even in children under 18 years, paediatricians in affected areas must consider WNV in the differential diagnosis of all children presenting with aseptic meningitis, encephalitis and acute flaccid paralysis. Additionally, given that WNV encephalitis can occur after WNV infection, suspicion for neurological WNV disease must remain high even after otherwise benign febrile illnesses if the child lives in or has traveled to an affected region. Under-diagnosis in the pediatric population is likely a serious problem, necessitating further educational efforts. More follow-up studies of WNV neurological disease in children and youth are needed to better understand the potential long-term sequelae during vulnerable times of neurodevelopment and neural remodeling. Similarly, more research is need on short and long-term fetal outcomes of maternal WNV infection.

Introduction

West Nile Virus (WNV) has gained increased attention in North America and parts of Europe over the past 15 years because of large outbreaks, predominately affecting adults, and for the virus' propensity to cause neurological complications among symptomatic individuals. The question arises: should paediatricians care? This overview provides evidence for why pediatricians should, indeed, care.

Virus details

WNV is an enveloped, single-stranded, positive-sense RNA virus that belongs to the genus *Flavivirus* and the family

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Flaviviridae. Classified as an arbovirus (arthropod-borne virus), WNV is transmitted by infected mosquitoes, and possibly by ticks, to vertebrates causing disease in both humans and animals. WNV is related to the Japanese encephalitis virus complex that includes the infectious agents responsible for Japanese encephalitis, Murray Valley encephalitis, and St. Louis encephalitis.[1] The WNV genome measures approximately 11 kB in length and encodes a single polyprotein, that is post-translationally cleaved by host and virus proteases into three structural (capsid (C), premembrane (prM)/membrane (M), and envelope (E)) and seven nonstructural (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) proteins.[2] The use of phylogenetic analysis, based on nucleotide sequence data, has identified the existence of at least two and potentially five distinct WNV genetic lineages[3] (Fig. 1).

Epidemiology/history

WNV likely evolved in Africa during the past millennium, separating from other members of the Japanese encephalitis virus complex and subsequently diverging into individual WNV lineages.[4] WNV was first isolated from a woman with an undiagnosed febrile illness in the West Nile region of Uganda in 1937. During the 1950s—1980s, WNV caused several outbreaks of relatively mild febrile illness in regions of Africa, the Middle East, India, and Australia. However, starting in the mid-1990s more frequent outbreaks, with increased severity of associated neuroinvasive disease, were observed in the Middle East and Eastern Europe.[5]

WNV first appeared in the United States in 1999, as an outbreak of 62 cases in New York City.[6] Genomic sequencing of the virus demonstrated genetic similarity to a WNV strain isolated from Israel in 1998.[7] Subsequent to the original outbreak in 1999, human WNV cases were reported across the United States, with a peak of 9862 cases reported in 2003.[8] In 2012, 5674 WNV cases were reported, the highest number since 2003.[9] Since 2001, WNV has also spread northward to Canada as well as southward into Latin America and the Caribbean.[10,11] In contrast to other locales with WNV, bird mortality has only been reported for WNV transmission in North America[12] and Israel.[13]

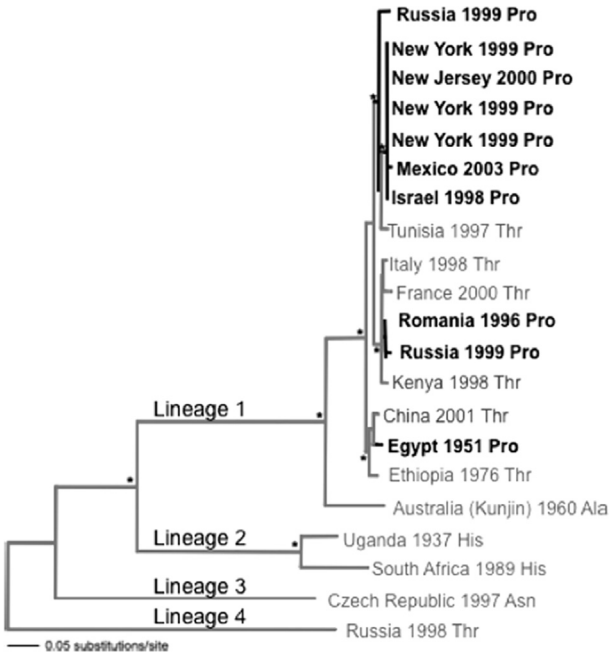

Figure 1 West Nile Virus phylogenetic tree.[3] (Figure 3 from Brault AC. Changing patterns of West Nile virus transmission: altered vector competence and host susceptibility. Vet Res. 2009; 40: 43).

The ability to alternate replication between vertebrate and invertebrate hosts, termed the "trade-off hypothesis", may help explain the adaptation success of WNV upon arrival in the United States. This hypothesis proposes that WNV exchanges superior fitness in a single host for the ability to replicate in two disparate hosts.[14] Although WNV, like other RNA viruses, is more prone to replication errors and higher mutation rates than DNA viruses,[4] the use of a two-host system counters the rapid genetic evolution of WNV.[14]

Epidemiologic triangle

The traditional model of infectious disease causation, known as the epidemiologic triangle, can be useful in understanding the epidemiology of WNV disease (Fig. 2). WNV is generally transmitted in a bird-mosquito cycle with mosquitoes serving as the vector and birds, through developing prolonged high-level viremia, as the amplifying host.[15] While some female mosquitoes are ornithophilic (i.e. they only feed on birds), other mosquitoes feed on birds and other species transmitting WNV to humans, horses, and other mammals. The resultant viremia tends to be mild (e.g. short-duration, low titer) and insufficient to infect mosquitoes. Therefore, mammals, including humans are incidental rather than true WNV hosts.[16]

While mosquito-to-human transmission is the primary route of human infection, transmission has also occurred through blood transfusion,[17] organ transplantation,[18] transplacental transmission[19] and possibly, breastfeeding.[20] Transmission may also occur through dialysis[21] and occupational exposure to WNV.[22] Screening of blood products in many countries has served to substantially decrease the risk of WNV transmission[23] while the screening of transplant organs for WNV remains controversial.[24]

Multiple factors, rather than a single mechanism, likely supported the recent spread of WNV in North and South America including: the availability of competent mosquito vectors and susceptible avian hosts, viral adaptation, and climatic conditions (e.g. warmer summers attributable to climate change).[3,25,26] Given this degree of complexity, it is difficult to predict future changes in WNV epidemiology.[26] Hence, surveillance efforts and public health measures (e.g. education of the public, timing of blood product screening) must remain highly sensitive to changes in patterns of WNV epidemiology.

Pathogenesis

While the pathogenesis of WNV infections is not completely understood, a 2013 review by Suthar and colleagues