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PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

West Nile Virus Infections in Children

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Abstract West Nile virus, a flavivirus identified in Africa in the 1930s, appeared in the Western Hemisphere in 1999. Since its appearance, West Nile virus has caused nearly 40,000 cases of human disease in the US and more than 1,500 deaths, mostly among elderly persons with neuroinvasive disease. This review summarizes recent information regarding the clinical manifestations and prevention of West Nile virus infections in children, and emphasizes that although West Nile virus fever and neuroinvasive disease primarily affect adults, infants and children remain at risk of serious complications, including death, from this disorder.

Keywords West Nile virus · West Nile fever · Neuroinvasive disease · Flavivirus

Introduction

Since its appearance in the US in 1999, West Nile virus (WNV), an RNA-containing flavivirus first isolated from humans in Uganda in the 1930s [1], has become the most common arthropod-borne virus infection in North America. Although predominantly affecting adults, WNV can infect children and cause systemic or neurologic disease. This review summarizes current information regarding the epidemiology, clinical manifestations, diagnosis, pathogenesis, treatment and prevention of this potentially serious infection.

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Epidemiology

WNV circulates in a bird–mosquito cycle that involves *Culex* or *Aedes* mosquito species and several bird species living in urban or rural environments. Humans serve as "dead-end" hosts and do not participate in the amplification cycle of WNV. Until the latter part of the 20th century, WNV produced only rare cases of human disease in North Africa and the Middle East [2]. Beginning in the mid-1990s, however, a major shift in human disease occurred, and severe, sometimes fatal cases of WNV infection were reported from Israel, Algeria and Romania [3]. The increased virulence of WNV for humans has been attributed to variations in the viral genome [4].

In 1999 WNV emerged in the US [5], and during the subsequent decade massive outbreaks of avian and human disease spread across the US from New York City, the initial site of WNV human disease in the Western Hemisphere, to the West Coast. Maps and data available on the Centers for Disease Control and Prevention (CDC) WNV website [6] illustrate the dramatic expansion of WNV disease in the US. In 1999 62 cases of human WNV disease producing seven deaths (11 % mortality rate) in New York State only were reported to the CDC, and by the end of 2002 WNV had caused human disease in 39 states with more than 4,000 reported cases and numerous deaths. Because humans and birds in North America lacked previous exposure to WNV, the outbreak continued, peaking in 2003 when nearly 10,000 human cases were reported to the CDC. Only the states of Alaska, Hawaii, Maine, Oregon and Washington did not report human cases during the 2003 outbreak. By the end of the decade (2010), the CDC had received reports of nearly 30,000 cases of human disease from 48 states; human WNV disease has not

been reported, thus far, in Alaska or Hawaii. Approximately 9 % of the reported cases were neuroinvasive, and more than 1,500 deaths due to WNV infection had occurred, primarily among elderly persons with neuroinvasive disease [7]. WNV remains active in the US; during 2012 another major outbreak occurred with nearly 6,000 human cases reported in the 48 contiguous states [8].

Human WNV cases, reported from early May to early November, peak in early August when mosquitoes are most active in the US (Fig. 1). By contrast, cases are rarely observed during the winter months. To date, human cases of WNV in North America have been observed as far north as the southern regions of the Canadian Provinces of Ontario, Quebec, Alberta, Manitoba and Saskatchewan [9]. Whether global climate change will modify the epidemiology of human WNV disease and lead to a northward migration of infected vectors and disease among humans in such regions remains to be seen. Climate can be a major factor in the spread of WNV; recent large outbreaks of WNV disease in the US have appeared after unusually warm winters [10].

Alternative modes of WNV transmission, some unique to pediatrics, have been described. In 2002 reports appeared regarding transmission of WNV via breast milk and transplacentally [11, 12]. The first case of presumed breast-milk transmission occurred in the infant of a 40-year-old woman who became ill with WNV neuroinvasive disease after receiving a post-partum blood transfusion with WNV-infected blood products. Infection was confirmed by detection of WNV-specific IgM in maternal cerebrospinal fluid (CSF). The child had breast-fed for approximately 2 weeks postpartum, including 6 days after maternal symptoms had developed. The child and mother had limited environmental exposures and no known mosquito bites. The breast milk tested positive for WNV IgG, IgM, and RNA 16 days postpartum, and serologic testing in the infant returned positive for WNV IgM at 25 days of life. Fortunately, the infant remained asymptomatic and healthy.

Although transmission of WNV to offspring through breast-feeding has been demonstrated in a murine model [13], there are no reported cases of clinical illness in a breastfeeding human infant. Thus, the CDC continues to support breastfeeding in mothers with suspected or confirmed West Nile viremia [11, 14]. Transmission of WNV via blood products, first recognized during the 2002 WNV epidemic, led to screening of blood products, beginning in 2003. Screening for WNV in the US via nucleic acid amplification methods continues in an effort to reduce the likelihood of transfusion-related WNV infections [15, 16].

WNV can also be transmitted vertically from the infected mother to the infant via transplacental or perinatal transmission of the virus. At least one infant with severe manifestations of congenital infection, including chorioretinitis and lissencephaly after maternal WNV infection in the second trimester, has been reported [12]. Infants have also experienced WNV disease when born within 1 month of maternal infection [17]. Whether the latter infections were transmitted in utero or via WNV-contaminated fluids or blood during delivery is uncertain. Fortunately, the vast majority of maternal infections do not result in fetal or neonatal disease. In a study of 72 infants born to mothers with confirmed WNV infections during pregnancy, no additional cases of clinical or laboratory-confirmed WNV disease at birth were identified [18]. At this time the CDC encourages pregnant women, along with the general population, to engage in routine prevention, diagnostic, and management measures against WNV disease.

Clinical Manifestations

The majority of human WNV infections do not cause recognizable illnesses; asymptomatic WNV infections outnumber disease cases by approximately 5 to 1. The incubation period among persons with symptomatic WNV infections ranges from 2 to 14 days. When illness does occur, it consists

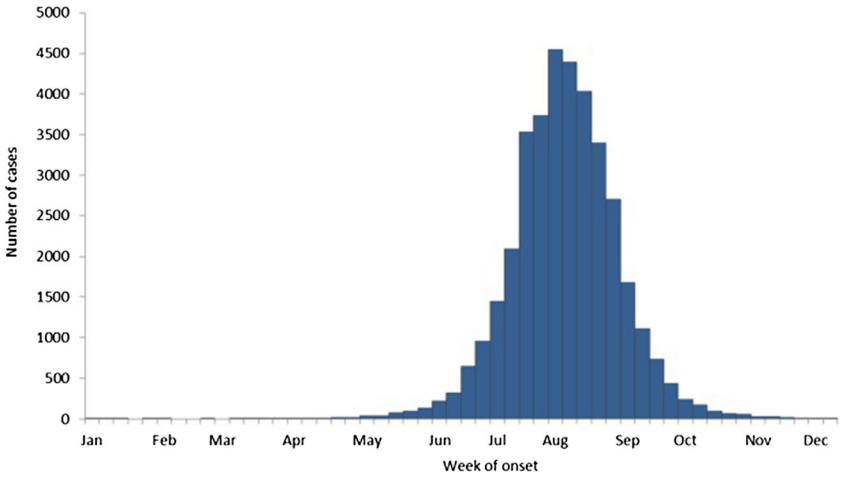

Fig. 1 West Nile virus activity in the US according to the week of symptom onset (source: ArboNET, Arboviral Disease Branch, Centers for Disease Control and Prevention)

primarily of nonspecific systemic manifestations with fever, headache, malaise, myalgias, nausea, vomiting, lymphadenopathy, and an erythematous maculopapular rash in approximately 20 % to 50 % of persons with WNV disease [10, 19]. The rash associated with WNV fever begins on the trunk, head or neck at a median of 5 days after the onset of symptoms and lasts an average of 14 days [19]. Pruritus or dysesthesias occur in 25 % to 33 % of persons with WNV-associated rash.

WNV neuroinvasive disease, occurring in approximately 1 in every 150 to 250 WNV-infected persons [20–22], primarily affects adults over the age of 25 years, especially men and the elderly. Among cases observed in Israel between 2005 and 2010, the median age of persons with neuroinvasive disease was 74 years (range 15 to 95 years) [21]. In this regard WNV resembles disease due to St. Louis encephalitis virus, a closely related flavivirus [23]. WNV encephalitis, the most common syndrome associated with WNV neuroinvasiveness, can begin with a nonspecific systemic prodrome, as above, or abruptly with high fever and neurologic symptoms and signs. Somnolence, meningeal signs, tremor, myoclonus, seizures, paralysis and coma are potential manifestations of WNV neuroinvasive disease in both adults and children [21, 22].

Although primarily a disorder of adults, WNV disease has been reported in newborns after intrauterine or perinatal infections [24, 25•] and in children as young as 2 years after acquired infections [17]. Overall, children account for approximately 5 % of all WNV cases in the US and approximately 4 % of WNV neuroinvasive disease [17]. The 2009 report by Lindsey and colleagues remains the most comprehensive review of WNV disease among children [17]. These authors described 1,478 cases of pediatric WNV disease in the US, beginning with the major WNV outbreak in 1999 and continuing through 2007. Of these cases, slightly more than 1,000 were described as West Nile fever (WNF), and approximately 30 % represented neuroinvasive disease, affecting children at a median age of 14 years for WNF (range 1 day to 17 years) and 12 years for WNV neuroinvasive disease (range 4 days to 17 years). The type of WNV disease was unspecified in a small number of WNV infections (N=26). During this interval more than 400 children experienced neuroinvasive disease, consisting of meningitis in 47 %, encephalitis or meningoencephalitis in 37 %, and acute flaccid paralysis in 1 %; the type of neuroinvasive disease was not specified in the remaining 15 % of cases [17]. Three deaths were reported by Lindsey and colleagues, all in children with WNV neuroinvasive disease.

Since the 2009 report of Lindsey and colleagues, an additional dozen or so publications have included cases of WNV disease among children <18 years of age [10, 20–22, 25•, 26–32, 33•]. Features common to all of these pediatric reports include: (1) cases of WNF greatly outnumber cases of WNV neuroinvasive disease; (2) manifestations of WNV neuroinvasive disease continue to consist of meningitis, encephalitis and acute flaccid paralysis due to a poliomyelitis-like disorder or myelitis; and (3) the rare pediatric deaths due to WNV infections typically occur among children with WNV neuroinvasive disease.

Diagnosis

Pediatric infections with WNV are diagnosed best by detecting WNV-specific IgM in serum or CSF using enzyme immunoassay (EIA) methods [6, 17]. WNV-specific IgM can be detected in the majority of infected persons 3 to 8 days after the onset of symptoms and can persist for as long as 90 days after disease onset [34]. Detection of WNV-specific IgG alone indicates prior infection with WNV. Because of the cross-reactivity of serologic responses to flaviviruses, the seropositivity for WNV of samples should be confirmed by secondary testing at the CDC or a state health department laboratory [34]. WNV RNA can be detected in clinical samples using nucleic acid amplification tests.

The CSF in children with neuroinvasive WNV infections shows a “viral” pattern with a lymphocytic pleocytosis (neutrophils can be present, however, during the acute phase of WNV infection), elevated protein content and normal glucose content. Magnetic resonance imaging, although often normal, can show signal abnormalities of the basal ganglia, thalami, brainstem or white matter in patients with WNV meningitis or encephalitis and abnormalities of the spinal cord in those with WNV-induced acute flaccid paralysis [35].

Pathogenesis

WNV typically infects humans through inoculation of virus-rich saliva from *Culex* mosquitoes. Viral replication then ensues within the Langerhans cells of the dermis and continues in the lymph nodes before the virus spreads hematogenously. The virus can also be transmitted via blood transfusions such that the virus gains direct access to the bloodstream which fosters continued replication. Once children or adults become viremic, symptoms of WNV disease may develop [7, 36•].

The most life-threatening aspect of WNV infection occurs once the virus has invaded the central nervous system (CNS); however, the pathogenesis of West Nile neuroinvasive disease is not fully defined. The most accepted mechanism of WNV neuroinvasion is hematogenous dissemination to the CNS during the viremic phase and invasion of the CNS through passage across the blood–brain barrier during times of increased vascular permeability or directly through the endothelium. Alternative access theories, derived from animal models, include direct retrograde transport along axons of infected peripheral neurons and penetration of virus-infected

macrophages directly through the blood–brain barrier. Once within the CNS, the WNV replicates and induces a cascade of host immune and inflammatory responses that result in varying degrees of symptom severity.

Immunocompromised children appear to be at higher risk of severe disease, but numerous previously healthy children have developed serious symptoms as well [17]. Pediatric patients are less likely to experience WNV neuroinvasive disease, but there is no clear explanation for why children are less vulnerable to neuroinvasion than adults. This phenomenon, albeit unexplained, resembles disease due to St. Louis encephalitis virus, a flavivirus that most commonly causes disease among elderly adults living in the Midwestern US [15]. CDC data indicate that nearly 90 % of the elderly infected with St. Louis virus experience encephalitis and that the case-fatality ratio approaches 15 % in this population [23].

Treatment

In most children with WNV, the disease is mild and self-limited, and thus supportive care only is required. However, WNV neuroinvasive disease can be associated with death, and WNV-induced acute flaccid paralysis in children can cause permanent disability [37, 38]. Two recent case reports, involving a 2-year-old child and a 10-year-old child with flaccid paralysis, indicate that both children experienced considerable improvement after treatment with intravenous immune γ-globulin (IVIG) [25•, 33•]. The 2-year-old made a slow but complete recovery after IVIG, whereas the 10-year-old had near-complete recovery with only a residual left foot drop after treatment. Several reports in adults with WNV-induced flaccid paralysis support the use of IVIG as a treatment for severe WNV neuroinvasive disease [39, 40•]. IVIG, although used in other childhood neurologic disorders, requires further study before being considered a safe and effective treatment option for pediatric WNV neuroinvasive disease. Occasional case reports of WNV infections in adults describe the use of immune-modulating agents such as neutralizing monoclonal antibodies, steroids, and interferon α-2b or antivirals such as ribavirin in the management of WNV disease. Due to the lack of controlled studies and the inherently variable clinical course of WNV disease, the efficacy of these strategies in adults and children is unproven at this time [7, 39, 40•].

Prevention

Because mosquitoes serve as the principal vector of WNV disease, mosquito abatement, use of insect repellants, and avoidance of behaviors that increase mosquito exposure remain the best strategies for preventing WNV disease in humans. Adults and children can reduce exposure to mosquitoes by remaining indoors at night when mosquitoes are most active and wearing protective clothing, head nets, and mosquito repellants when outside, especially from dusk until dawn. Insect repellants, including those with no more than 30 %*N*,*N*-diethyl-*m*-toluamide (DEET) may be used in children over 2 months of age to decrease the risk of exposure to WNV-infected mosquitoes [41, 42].

No effective vaccines are currently licensed for human use. Several veterinary vaccines are available, but investigations of human vaccines have consisted, to date, of only phase I and phase II clinical trials [40•, 43•]. While WNV is of considerable public health concern, commercial interest in human WNV vaccines remains limited given the high production costs, uncertain clinical benefits, and initial reports suggesting that a vaccine may not be cost-effective, especially in the pediatric population [44].

Two phase I trials have evaluated a DNA vaccine which utilizes a premembrane (prM) protein and an envelope glycoprotein (E) of the WNV strain NY99. During the first trial in 2007, the vaccine passed safety requirements and initiated both T cell and antibody responses in recipients. Modification of this vaccine's promoter region to enhance transcription and immunogenicity was tested in a 2011 phase I trial. This modified vaccine passed safety measures and showed a greater T cell response in participants and immunity in recipients over 50 years of age compared with the 2007 tested vaccine [45, 46]. A recombinant subunit vaccine, WN-80E, using a soluble WNV E protein without the transmembrane section induced WNV antibodies in human subjects within 2 weeks of vaccine administration [47•].

After successful phase I trials, a recombinant, chimeric WNV vaccine WN/DEN4-3'delta30 that combines WNV and dengue virus is reportedly undergoing phase II trials [48, 49]. The ChimeriVax-WN02 combines WNV antigens with the Yellow Fever 17D vaccine and shows strong potential as a safe, well-tolerated, and immunogenic vaccine against WNV. Most current vaccines under trial require two to three doses to induce adequate host immune responses [48]. Given the relatively infrequent occurrence of WNV infections in children, however, current vaccine development continues to focus on disease in adults, especially the elderly.

Conclusion

WNV infection in children remains a rare, but potentially serious, public health concern. Although only 5 % of known WNV cases have occurred in patients less than 18 years of age, WNV can cause death and permanent disability in pediatric patients. WNV disease should be considered in children with fever or neurologic symptoms, especially during outbreaks of WNV infections in the summer months, and can be diagnosed by detecting WNV IgM via EIA or WNV RNA

in the serum or CSF. Therapy with IVIG may benefit children with WNV-induced acute flaccid paralysis; supportive care remains the standard treatment for infants, children, or adolescents with WNF or other forms of WNV neuroinvasive disease. Human vaccines for WNV are under development, and although some are in phase II clinical trials, a licensed human vaccine for WNV seems years away.

Compliance with Ethics Guidelines

Conflicts of Interest Carey A. Wilson declares that she has no conflict of interest.

James F. Bale, Jr. declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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