West Nile Virus Infections in Children

A Disease Pediatricians Should Think About

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West Nile Virus (WNV)—*Flaviviridae* family, genus *Flavivirus*—causes an emerging vector-borne disease transmitted mainly by mosquitoes (mostly *Culex pipiens* genus). WNV is maintained in nature by a mosquito-bird-mosquito cycle in which humans and other mammals (eg, horses) are accidental hosts. Most human infections are accidental, but other possible, if less common, routes of transmission include blood transfusion and organ transplantation from infected donors. Rarely, congenital infections and transmission through human milk have been reported.1

Since its isolation in 1937 in the West Nile province of Uganda,2 WNV has become one of the most widely distributed arboviruses. In temperate areas, it causes seasonal outbreaks; its activity peaking from midsummer to late fall.

Until 1996, WNV was only known to cause sporadic outbreaks of mild febrile disease in humans with an extensive distribution in the Old World and was therefore considered of minor public health importance. Since then, several WNV outbreaks were described throughout Africa, in parts of Eastern Europe and the Middle East, particularly in Romania, Russia, and Israel.3

In the Americas, WNV was first isolated during the 1999 New York City outbreak, and associated with serious neurologic disease in humans.4 It is unknown how WNV arrived in the United States. The WNV variant responsible for the US outbreak was more virulent then other strains known in the Old World and was closely related to a virus identified in Israel, suggesting a possible importation from the Middle East.5 Since that time, the virus has dramatically spread in the US; it is ubiquitous in almost every Southern state and in Canada.6

In the 2000s, WNV became a major public health problem in Europe as outbreaks occurred in previously unaffected countries and human cases of WNV neuroinvasive disease (WNND) were reported in Western Europe. In Italy, 18 cases with 4 deaths occurred in 2009 (ranging from 62 to 82 years of age), with a westward expansion of WNV activity in the Country.7 In Portugal, one autochthonous probable case was detected in 2010. Several outbreaks were also recently reported in Greece, Russia, Israel, and Romania, with more than 100 confirmed human WNND cases.8 In the last decade, awareness of WNV disease (WNVD) has increased due to heightened epidemiologic surveillance in human and animals, availability of new and simple laboratory confirmation tests, and screening of blood donors and transplant individuals in affected countries.9 However, due to the different clinical presentations of WNND, it is still very difficult to estimate the effective disease burden.

Although WNVD affects mainly healthy children,10,11 cases can occur in children. In the US, between 1999–2007, 1478 WNVD cases occurred in children (<18 years), and 443 presented as WNND (5% of WNVD and 4% of WNND reported in all age-groups).1

**CLINICAL PRESENTATION OF WNV INFECTIONS IN CHILDREN**

Incubation ranges from 2 to 14 days, with longer periods observed in immune-compromised hosts. WNV infections are asymptomatic or subclinical in 70% of cases.10,11

In children, symptomatic disease presents mostly (67% of cases) as West Nile fever (WNF), a mild illness characterized by fever, headache, rash, muscle pain, or gastrointestinal symptoms. Rash appears in approximately 50% of the patients, is typically maculopapular, involving the chest, back, and arms, and generally lasts for less than 1 week. Acute symptoms typically last 3 to 10 days, but may last longer (median time to fully recover was 60 days).1

WNND occurs in approximately 1% of infections, manifesting generally as meningitis, encephalitis, or acute flaccid paralysis (AFP).10,11 Available data show that the proportion of WNND over the total of WNVD is similar in children and young adults (30%), whereas it is higher in individuals older than 50 (50%).10 In addition, encephalitis has been more commonly reported in older age groups whereas meningitis is more frequently described in children.5 Meningitis is usually associated with more favorable clinical outcomes, even though long-term sequelae may occur. Acute flaccid paralysis from WNV is asymmetric and can occur without clinical CNS involvement.7

It should be noted that rash, which is frequent in WNF, can also appear in a lower proportion of patients with WNND. It has been reported as a prognostic indicator for severe disease and death.8

Although immune-compromised children seem to be at higher risk of developing severe disease, many WNND cases described in literature occurred in previously healthy children.10 Once a patient recovers, immunity to West Nile virus is thought to be life-long.

**DIAGNOSIS OF WEST NILE VIRUS INFECTIONS**

WNV infection should be strongly considered in children presenting with unexplained fever, rash, encephalitis, and/or meningitis, or AFP during the mosquito season. The epidemiology of WNV activity, in the regions where the patient resides or has traveled, should be considered for differential diagnosis. Since the disease in temperate climates has a seasonal pattern, outbreaks of WNF in humans should be suspected in areas
where circulation of WNV in animals as been confirmed. 

Results of cerebrospinal fluid exams in pediatric WNND cases are reported as similar to those found in other viral meningitis, presenting mostly with mild-to-moderate leukocytosis (average, 0.321 × 10⁶ WBC/L) and slightly elevated protein (average, 71.6 mg/dL). 

Because laboratory investigations for WNV are not included in the routinely performed tests for diagnosis of viral infections, and routine exams are aspecific, it is important to consider WNV when planning laboratory investigations in patients with compatible symptoms.

Diagnosis can be confirmed either by finding specific IgM antibodies or viral nucleic acid in appropriately timed samples. A comprehensive study of the dynamics of viremia and antibody production in people with WNV infection was performed in 245 viremic blood donors over 6 months or until seroconversion. The median time from RNA detection to IgM seroconversion was 3.9 days and IgGs appeared in 7.7 days. The mean time before RNA levels became undetectable was 13.2 days and the average time to IgM negativity was 156 days. This study was performed among healthy adults and to date no such data is available for children.

PREVENTION AND TREATMENT

The starting point of disease prevention is personal protection to avoid mosquito exposure. This should be complemented by mosquito control programs, employing integrated pest management techniques at community level. Moreover, removal of mosquito breeding sites and application of larvicides, for reducing the production of adult mosquitoes, is recommended in endemic areas. When human or mosquito surveillance indicates human infection risk, vector control strategy targeting adult mosquitoes should be immediately implemented by local health authorities. These measures may considerably reduce human infection risk with negligible pesticide exposure. 

Another crucial aspect of disease prevention in affected areas is screening of blood and organ donors. This has greatly reduced the risk of transfusion and transplant transmission. 

Treatment of WNV infection is mainly supportive. Recent animal models and case reports from literature suggest that the use of specific intravenous immunoglobulin may be beneficial. Plasmapheresis in AFP can be considered to obtain a rapid removal of auto-antibodies generated following infection, inducing their redistribution in circulatory and tissue organs. 

There has been great interest in a WNV vaccine, and studies of different candidates in animals suggest efficacy. Human vaccines are unlikely to be available in the near future, however, there are encouraging preliminary reports of potentially safe and efficacious vaccine candidates. Evidence suggests that universal vaccination would not be cost effective, however, cost benefit models for vaccination of high-risk groups alone have not been conducted. Moreover, methods used for estimating the economic value of WNV vaccines did not take into account indirect cost due to the disease (such as working days lost of patients and caregivers). 

CONCLUSIONS

The establishment of new vector-borne pathogens that cause diseases with nonspecific clinical presentation is a serious concern. In affected and at-risk areas, surveillance for WNV (monitoring population densities and infection rates of principal vectors, serosurveys on vertebrates and exposed human groups, and routine diagnosis of human infections) is a useful tool to contain and mitigate the impact of the disease. Even though WNV is rare in children, pediatricians should suspect this infection if the clinical and epidemiologic picture is compatible. For children living or traveling in temperate countries, diagnosis should be suspected when symptoms develop from midsummer to late fall.

REFERENCES