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Topical Review

Pediatric West Nile Virus-Associated Neuroinvasive Disease: A Review of the Literature

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ABSTRACT

Over the past two decades, West Nile virus has become the most common arbovirus in North America, leading to several outbreaks and infecting thousands of people. Mosquitos help transmit the virus in the majority of cases, but transmission occurs via blood transfusions, organ transplantation, and possibly pregnancy and breastfeeding. While most infected patients experience mild to no symptoms, thousands of West Nile virus-associated neuroinvasive cases have been reported in the United States, with over 700 cases occurring in children from 2003 to 2016. Neuroinvasive disease presents as meningitis, encephalitis, or acute flaccid paralysis, and carries a high likelihood of poor outcome, including severe neurological disability or death. To date, no pharmacologic treatment has proven effective. Therapeutic clinical trials have not been successfully completed due to the sporadic nature of viral outbreaks and resultant poor study enrollment. Although older age and chronic disease are risk factors for neuroinvasive West Nile virus disease in adults, the specific factors that influence the risk in pediatric populations have not been fully elucidated. This review summarizes the most recent literature regarding West Nile virus-associated neuroinvasive disease, especially as it pertains to the pediatric population. Moreover, the review describes the epidemiology, clinical, laboratory, and radiographic findings, and outlines the various therapies that have been trialed and potential future research directions.

Introduction

West Nile virus (WNV), a mosquito-borne flavivirus, is the most common arbovirus in North America. The virus was first isolated in 1937 in Uganda and has been well studied since the 1950s when several outbreaks occurred in the Mediterranean basin.[1] The first WNV infection in North America was diagnosed in New York City in 1999 and was followed by rapid spread across the continent. Within four years, patients were reported from 45 states and multiple Canadian provinces.[2,3] Since then, sporadic outbreaks have occurred, the largest of which was in 2012 with over 5000 patients reported in the United States.[4] While most infections result in mild to no symptoms, nervous system involvement can result in severe outcomes, and some cases are fatal.[5] From 1999 to 2016, over 2000 WNV-associated fatalities were reported to the Centers for Disease Control and Prevention (CDC), with an estimated mortality rate of 4% among all reported WNV infections and 9% of neuroinvasive cases.[6] WNV-associated neuroinvasive disease (WNND) primarily affects adults, but children are also susceptible, accounting for 4% of neuroinvasive cases annually.[7] This review summarizes the current literature regarding WNND, especially as it pertains to the pediatric population.

Epidemiology

Incidence and geographic distribution

WNV causes the majority of arboviral-related neuroinvasive disease overall in North America, primarily in adults.[8] Pediatric cases account for 4% of all WNND, with an average annual incidence of 0.68 per million children.[7,8] From 1999 to 2016, 2397 cases in individuals under 19 years of age have been reported to the CDC, 34% of which were neuroinvasive (Fig 1, CDC, personal

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communication, May 3, 2018). It should be noted that this reflects the incidence of neuroinvasive disease of all *reported* cases; the true risk of neuroinvasion following infection remains sparingly low, since 80% of infections are asymptomatic and typically go unreported.[9]

In addition to WNV, children in North America are at risk for other arboviral infections, including Eastern Equine encephalitis virus, La Crosse virus (LACV), Powassan virus, and St. Louis encephalitis virus.[8] Of these, LACV, rarely reported in adults, is the most common cause of neuroinvasive disease in children and adolescents. LACV is found in the Midwest, Appalachian, and Atlantic states, while WNV infections occur throughout the United States, having been reported in every state with the exceptions of Hawaii and Alaska.[6,10] Presumably, much of the difference in geographic distribution is due to habitats of various mosquito species and the activity of the vertebrate host associated with each virus. The wide variety of mosquito and bird species that carry WNV have likely aided in its widespread distribution.[11] While the *Culex* mosquito most often associated with WNV is able to survive relatively cold climates, its population growth is accelerated by warm weather, so as might be expected, the highest frequency of WNV occurs in the highly populated, warm states of Texas and California.[6,11] Consequently, these states are also associated with the highest incidence of WNND, each with over 100 patients in most years since 2002 per CDC data.[6,11] However, sporadic outbreaks have occurred throughout most of the United States and Canada, including regions with typically cooler climates. Many factors are involved in priming a region for an outbreak, including climate of the current season and preceding winter, extent of viral activity the previous transmission season, mosquito control, and human behavior such as dress and outdoor activity.[11] It is therefore quite difficult to predict where outbreaks might occur, although predictive models have recently been developed with some accuracy.[12]

Risk factors

Literature examining WNND risk factors specific to children is lacking, presumably because of its rare occurrence in this population. The few published pediatric epidemiologic studies have found a slight predilection for males and adolescents for both West Nile fever and WNND.[7,13,14] Several studies have evaluated potential host risk factors in adults; from these, there is consensus that advanced age correlates with risk of WNND and death.[15,16] The literature is conflicting regarding other potential risk factors in adults, but may include other demographic factors (male sex and minority race), cancer, diabetes, hypertension, alcohol abuse, renal disease, immunosuppression, and chronic obstructive pulmonary disease.[15-18] Some of the predilection for older adults is likely due to the lack of these comorbidities in most young patients. The high prevalence of chronic disease in older patients is thought to play a role in altering the cerebral endothelium, facilitating viral entry into the central nervous system (CNS).[8] Interestingly, this pattern is similar to that of St. Louis encephalitis but contrasts with LACV, possibly due to an immature adaptive immune response as demonstrated in mouse models.[19,20]

Transmission

Mosquitos

Nearly all cases of WNV are transmitted via a mosquito bite.[21] The virus is maintained in a mosquito-bird transmission cycle, with members of the *Culex* mosquito genus serving as the most common vectors. Several bird species act as viral hosts, transmitting the virus back to the mosquito after infection.[22] After the virus is injected intradermally by the mosquito, it infects targets such as the Langerhans cells that spread via the lymphatic system to the bloodstream, resulting in viremia.[23,24] The virus then further replicates, causing a secondary viremia, and can potentially gain access to the CNS, presumably through hematogenous and transneuronal mechanisms.[25]

Blood transfusion

Transmission of WNV through blood transfusion was first reported in 2002. Four of the 23 confirmed cases occurred in children.[26] In 2003, routine measures were put in place to screen all blood donations in the United States for WNV RNA. Since then, 14

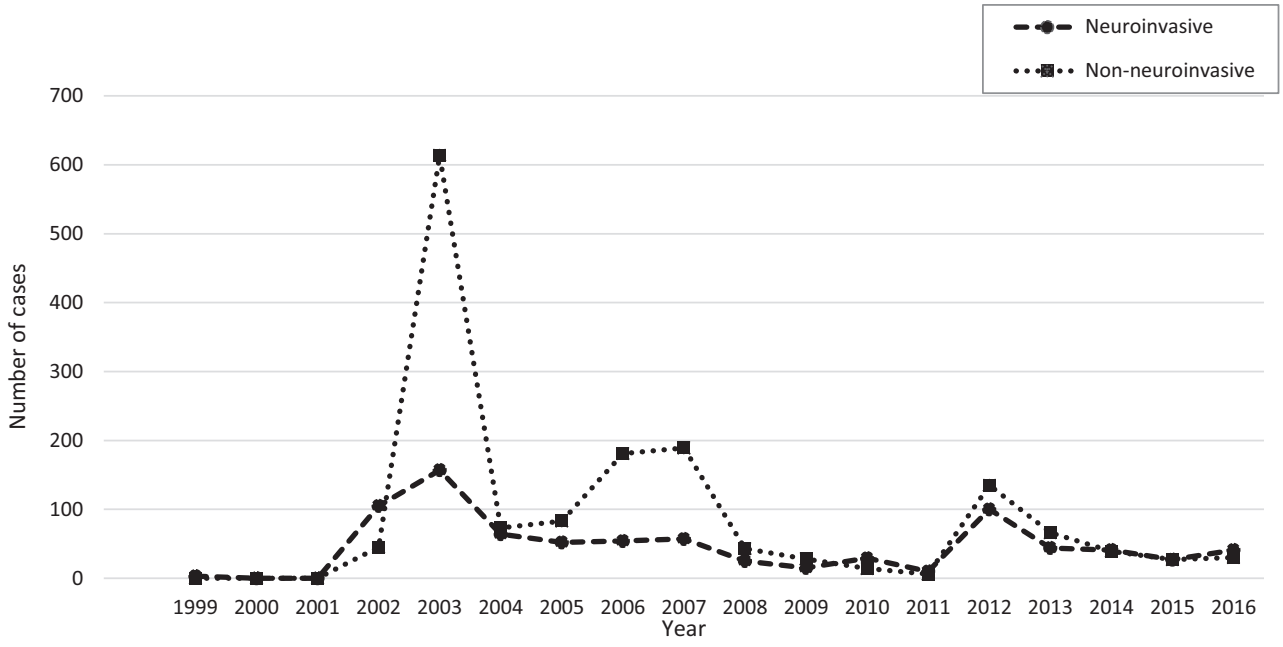

FIGURE 1. Annual number of WNV infections reported in individuals less than 19 years old in the United States. WNV, West Nile virus.

transfusion-related transmissions have been reported to the CDC.[27,28] In 13 of these patients, the donor samples were screened with false-negative results.[28] This typically occurs because blood is often initially screened through minipool-nucleic acid testing (NAT) consisting of six or 16 individual donors, which is less sensitive than individual-nucleic acid testing (ID-NAT).[28] The Food and Drug Administration therefore recommends using ID-NAT instead of minipool-NAT for initial screening during periods of high WNV activity.[29] Selective use of ID-NAT as of 2004 has resulted in greater detection of WNV by blood banks; however, whether this has translated into fewer clinical infections is unclear due the brief interval since this change, and that not all transfusions of infected samples result in clinical infection.[30]

Organ transplant

WNV transmission via solid organ transplant has been documented in 20 adults, whereas cases of community-acquired WNND in the setting of immunosuppression *after* transplant have been reported among both pediatric and adult recipients.[16,31-35] Among the published reports of donor-derived infection, 70% of recipients developed WNND (as compared with the estimated 1% of the general population who contract infection via mosquito bite), and 30% resulted in persistent coma or death.[36] Some patients remain asymptomatic, and those who do not develop coma tend to recover to variable degrees.[36-41] The proper management of immunosuppressants in these cases is uncertain.[42] Of the six published cases documenting an immunosuppressant reduction following WNV infections, two of the patients recovered, one remained asymptomatic, and three died.[36,37,39,40] It should be noted that these patients received other therapies as well, as listed in Table 3.

Pregnancy and breastfeeding

While cases of transmission related to pregnancy and breastfeeding have been reported, such cases are rare and often unconfirmed. There are no confirmed cases of clinical illness secondary to breast milk ingestion. There has been a single clearly documented case of seropositivity in an infant following ingestion of infected breast milk, but the infant remained healthy.[43] Two other breastfed infants whose mothers contracted WNV before delivery tested positive for WNV IgM antibodies; therefore, it is unclear whether this was transmitted through breastmilk, placenta, or through mosquito exposure. One of these infants developed a rash, and the other was asymptomatic.[44]

Transplacental transmission has been reported, but the risk appears to be quite low. A 2004 study determined that of 72 infants born to mothers who contracted WNV during pregnancy, only three became infected, and two developed clinical neuroinvasive disease. However, transplacental transmission could not be verified due to the unavailability of appropriate specimens (umbilical cord, cord blood, or placenta) for confirmatory testing.[45] There does not appear to be a significant risk of congenital malformations, developmental delay, or pregnancy complications among pregnancies of WNV-infected mothers, but larger studies are needed to confirm these findings.[46]

Clinical features

West Nile fever is the most common symptomatic presentation of WNV infection, characterized by fever, headache, fatigue, and myalgia. Vomiting, diarrhea, rash, and lymphadenopathy can also be present. These nonspecific symptoms typically resolve within a week.[47] The three most common presentations of WNND are meningitis, encephalitis, and acute flaccid paralysis (AFP). In adults, involvement of the spinal nerve root, brachial plexus, and peripheral nerve has also been described.[48,49] Other uncommon presentations of WNV infection in children have included cerebellitis, cranial nerve palsies, and hepatic and cardiac involvement.[50-53]

Meningitis and encephalitis

Similar to adults, WNND represents 30% of all reported pediatric WNV infections. In contrast to older adults, however, children with WNND are more likely to present with meningitis rather than encephalitis.[7] This differentiation is of important prognostic significance as patients with encephalitis have more severe outcomes.[7] The initial presenting symptoms of both meningitis and encephalitis may be quite vague, most often consisting of fever (which can be low-grade), headache, and vomiting or abdominal pain. Rash may occur in WNND but is more frequently reported in children with WNV fever; it has been postulated as a positive prognostic sign.[14,54] Meningismus may or may not occur in children with WNV meningitis, and it can develop later in the course if not initially present.[55] Children with WNV encephalitis (WNE) may first present with the above nonspecific symptoms with progression to altered mental status or obtundation within one to seven days, while others initially present to the emergency room with unresponsiveness or seizures.[16,34,56] In addition to altered mental status, WNE can manifest as movement disorders such as myoclonus, tremor, and parkinsonism, which may be secondary to the frequent involvement of the basal ganglia.[57] Patients with suspected meningoencephalitis should undergo fundoscopy, given the high incidence of associated chorioretinitis, papilledema, and optic neuritis.[34,55,58] In one child the characteristic pattern of WNV chorioretinitis, described as scattered or linear lesions, guided the treating team toward the diagnosis of WNV.[56]

Acute flaccid paralysis

AFP has been reported in around 1% of children with WNND, and can occur with or without encephalitis, with the former being more common.[59] Similar to poliomyelitis, the syndrome is caused by WNV invasion of the anterior horn cells. This results in a rapidly progressive, asymmetric paralysis, however, a slow progression may also be observed in children.[52,59] Paralysis may be preceded by pain of the affected extremity.[52,59] The neurological examination in these patients reveals asymmetric flaccid paralysis with loss of deep tendon reflexes in the affected limbs.[52,59,60] Nerve conduction studies and cerebrospinal fluid (CSF) characteristics can be helpful in differentiating viral AFP from other treatable causes of paralysis, such as Guillain-Barré syndrome (Table 1).

Neuroimaging

Brain

Although brain magnetic resonance imaging (MRI) and computed tomography are often normal in patients with WNV meningoencephalitis, MRI should be performed in the initial evaluation of patients with suspected CNS disease given its usefulness in including or excluding differential entities. Computed tomography is often insensitive to manifestations of WNV, but offers an important supportive screening role during primary evaluation of the patient with a neurological deficit who will undergo lumbar puncture when MRI is unavailable.[61] A significant number of patients with WNV meningoencephalitis may have normal brain imaging findings even with significant symptoms such as alteration in mental status and dysphasia.[62] Several reports, including one pediatric, have documented that imaging may be initially normal

TABLE 1.
Ancillary Studies in Viral AFP and Guillain-Barré Syndrome[48]

	Viral AFP, Including WNV	Guillain-Barré Syndrome
CSF	Elevated protein with pleocytosis	Elevated protein with no pleocytosis
NCS	Decreased motor action potentials	Slow conduction velocities
	Normal sensory action potentials	Decreased sensory action potentials

Abbreviation:
NCS = nerve conduction studies

with follow-up imaging proving abnormal; therefore, an initial normal imaging pattern may be a function of time bias.[56,63,64]

On conventional sequences, T2 signal (with corresponding low T1 signal) abnormality with or without diffusion signal abnormality may be seen in the lobar gray and white matter, basal ganglia, thalami, brainstem, and even cerebellum. MRI findings among pediatric patients are similar to those of adults, with abnormalities of the thalami and basal ganglia most often described, and midbrain and brainstem involvement also reported.[55,56,65] While such findings may be focal, patchy, and asymmetric, strikingly symmetric signal abnormality may also occur especially at the level of the central gray matter (Fig 2).[62,66-68] In fact, certain flaviviruses, such as WNV, eastern equine encephalitis virus, Japanese encephalitis virus, and Murray Valley encephalitis virus, have a predilection for bilateral symmetric central gray matter. In contrast, such a pattern is less common with postnatal Zika.[62,66-68] Ultimately, imaging findings are nonspecific to WNV and overlap with a wide variety of viral infections including many arboviruses, as well as nonarboviral infections, such as Epstein–Barr virus and *Mycoplasma pneumoniae*.[69-79] Hemorrhagic necrosis within the central gray matter may be seen with Japanese encephalitis, dengue fever, and *M. pneumoniae*.[70,74,79] WNV meningoencephalitis imaging findings may also be mimicked by many parainfectious and noninfectious processes, such as acute disseminated encephalomyelitis, acute necrotizing encephalitis, toxic-metabolic or mitochondrial disorders, and vasculitides, emphasizing the importance of clinicoradiologic interpretation (Fig. 3 and 4). Focal diffusion restriction with T2 prolongation may mimic lacunar or thromboembolic stroke.

Bilateral or unilateral mesial temporal involvement T2 hyperintensity is an additional imaging pattern that has been reported with WNV meningoencephalitis. When diffusion restriction coexists with such mesial temporal involvement, findings may mimic herpes simplex meningoencephalitis although the aggressive necrotizing appearance of this entity is usually absent.[66] Many other viral agents may produce a limbic encephalitis including most classically HHV-6.[78] Histopathologically, imaging findings correlate with perivascular lymphocytic infiltration, microglial nodules, and neuronal loss.[80]

In some patients, diffusion-weighted imaging may independently show signal abnormality (i.e., restricted diffusion) without corresponding findings on conventional T1 and T2 sequences. This is likely a time bias effect in that diffusion imaging may be positive in the earliest phases with a more mature inflammatory cascade resulting later in signal abnormality on conventional sequences. Diffusion restriction is presumed a function of inflammatory infiltration rather than true ischemia, although this remains incompletely discovered in the literature.[66] Vasculitis has not been reported as a primary feature in WNV meningoencephalitis.[80]

Postcontrast imaging is often normal, distinctly different from typical bacterial, atypical bacterial, and fungal entities. However, leptomeningeal and pachymeningeal enhancement have been reported.[62] T2 fluid-attenuated inversion recovery precontrast imaging may show lack of suppression of T2 signal within the sulci due to alterations in protein and cellular content of the CSF.[62] Subarachnoid imaging findings may be secondary to reactive lymphocytic and plasma cell infiltration.[81]

Spine

Progressive extremity weakness with sensory sparing has been well reported in the literature. As with brain imaging, spinal MRI may be normal enforcing the known understanding that negative imaging does not exclude myeloradiculitis. When positive, imaging will identify myelitis, polyradiculitis or combination thereof.

Postcontrast imaging may demonstrate diffuse or ventral enhancement of the cauda equina and lumbosacral nerve roots supporting the presence of polyradiculitis.[62,82] While Guillain-Barré syndrome was initially cited as the causative process, clinical, laboratory, and electrodiagnostic features typically do not support such a diagnosis despite imaging similarity.

Primary myeloradiculitis with anterior horn cell involvement and extension into the spinal nerve roots consistent with poliomyelitis has been accepted as the primary manner in which paralysis occurs.[83,84] Many authors have described imaging predilection for the anterior horns of the central gray matter which may demonstrate long segments of contiguous T2 signal

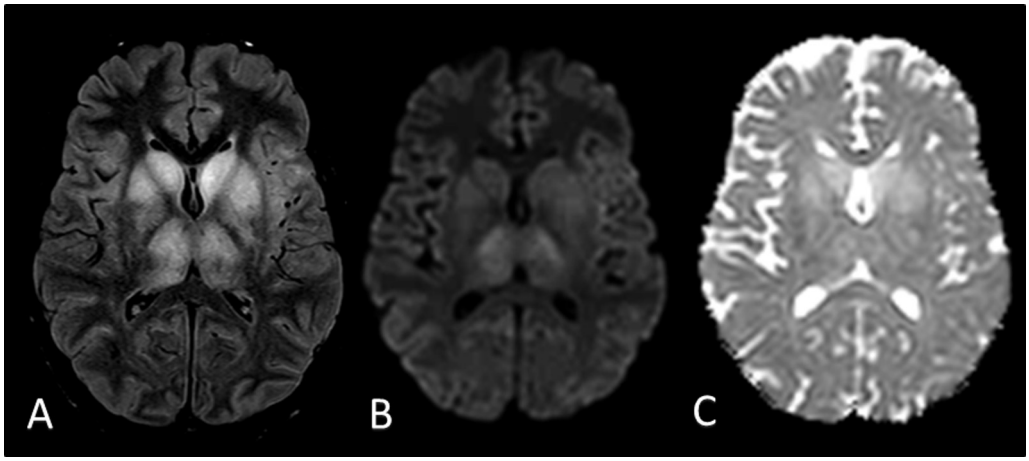

FIGURE 2. West Nile encephalitis. (A) T2/FLAIR demonstrating isolated symmetric signal abnormality throughout the basal ganglia and thalami. (B) DWI and ADC sequences demonstrate a lack of corresponding diffusion restriction. Enhancement is not present (not shown). Such findings are typical but not specific for West Nile encephalitis. A wide variety of viral encephalitides may present with similar imaging findings. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; T2/FLAIR, T2 fluid-attenuated inversion recovery.

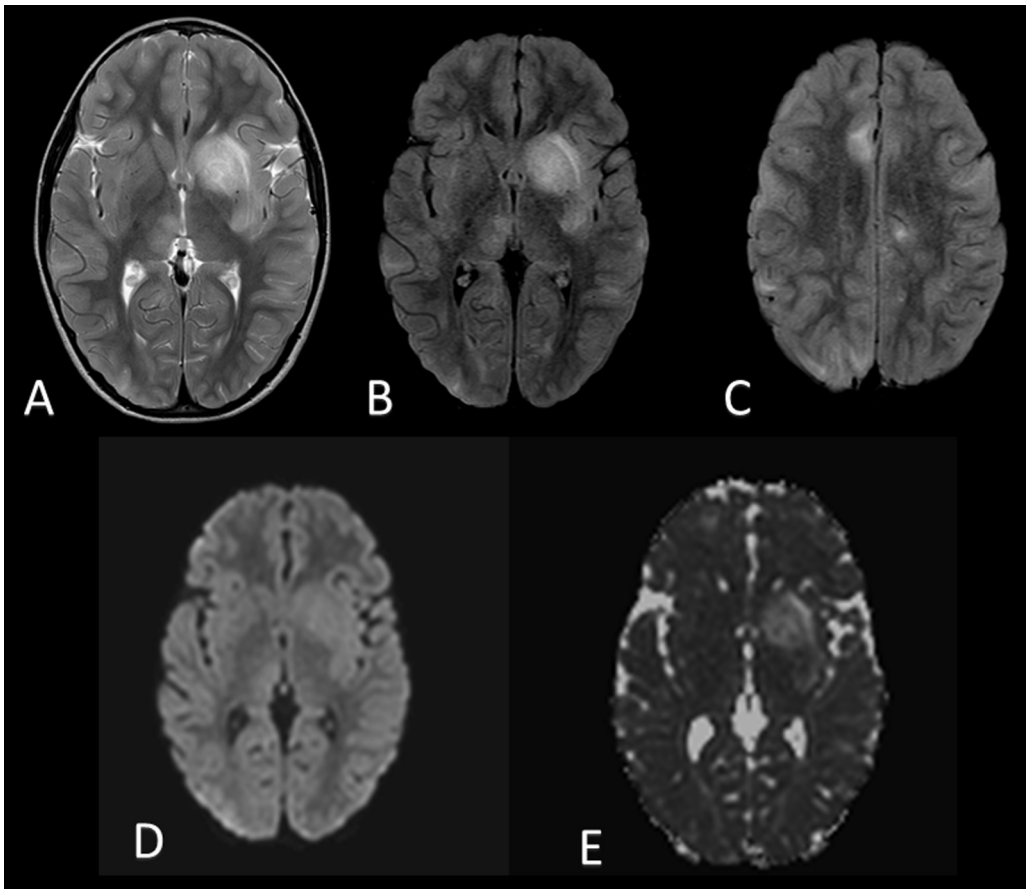

FIGURE 3. ADEM. (A) T2, (B) T2/FLAIR, and (C) T2/FLAIR sequences show patchy regions of signal abnormality asymmetrically involving the left basal ganglia, right thalamus, and cortical-subcortical supratentorium. (D) DWI and (E) ADC sequences demonstrate lack of diffusion restriction. While restricted diffusion and enhancement is not present (not shown) in this case, such findings may occur. Note that viral encephalitides commonly isolate to the cortex without subcortical white matter involvement and are usually less focal than ADEM. Viral encephalitis and ADEM may be impossible to differentiate by imaging alone. ADC, apparent diffusion coefficient; ADEM, acute disseminated encephalomyelitis; DWI, diffusion-weighted imaging; T2/FLAIR, T2 fluid-attenuated inversion recovery.

abnormality with or without enhancement consistent with this pathophysiology.[48,85] In cross-section, this has been sometimes referred to as the "owl-eye sign." Pathologically, these imaging findings correlate with perivascular lymphocytic infiltration, microglial nodules, and neuronal loss.[86] Such a pattern has been described with a variety of viral myelitides presenting with motor weakness to include polio and nonpolio enterovirus (enterovirus D68, enterovirus 71), dengue, St. Louis encephalitis, Powassan, eastern equine encephalitis, Murray Valley encephalitis, and rabies myelitis, among others.[68,87-90] Bilateral signal abnormality of the anterior horns of the spinal cord may be seen in noninfectious causes such as spinal cord ischemia and spinal muscular atrophy.

Laboratory testing

Laboratory diagnosis should be initiated by testing the CSF and serum with WNV-specific IgM immunoassays. IgM antibodies can first be identified as early as three to eight days after disease onset; thus the absence of WNV-specific IgM does not rule out infection if the sample is tested early in the clinical course. Additionally, the presence of IgM antibodies is not sufficient for confirmation of disease. Table 2 lists the criteria for probable and confirmed diagnoses of arboviruses. While these assays serve as readily available screening tools, additional steps must be taken to rule out past WNV infection or infection with another flavivirus. IgM antibodies can persist for up to 90 days after infection, and longer in rare cases. Previous infection can therefore be ruled out by examining acute and convalescent phase serum antibody titers, with a fourfold increase in titers indicating acute infection. Because antibody immunoassays can cross-react with other flaviviruses, a sample with a positive IgM result should be sent to the CDC or state health department for confirmatory testing. The plaque reduction neutralizing test, performed at the CDC and some state health departments, can differentiate among flavivirus infections. Nucleic acid detection methods and virus isolation techniques may be useful in certain cases, such as in immunocompromised patients in whom antibody production may be delayed or absent.[91]

Management

Prevention

Because there is currently no effective treatment for WNV infection, prevention by limiting mosquito exposure is paramount. Breeding can be reduced by eliminating bodies of free-standing water or treating with larvicide.[92] Adult mosquito abatement occurs at the community level through the distribution of insecticide via ground or aerial spraying. These measures can be quite effective in reducing the mosquito population; aerial spraying, for instance, leads to a 90% reduction in the number of mosquitoes, and was associated with a significant drop in the number of WNND cases in the Dallas-area outbreak of 2012.[93,94] At the personal level, prevention measures include reducing skin exposure and applying insect repellant when in areas of high mosquito activity.[91] The

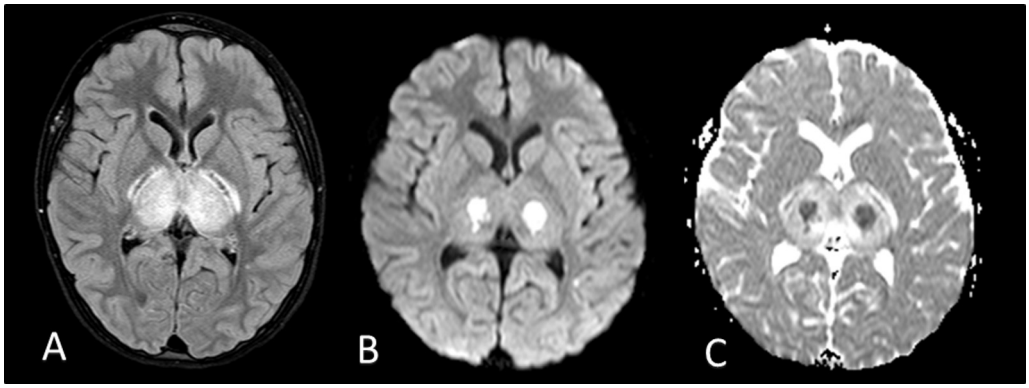

FIGURE 4. Acute Necrotizing encephalitis (ANE). (A) T2/FLAIR demonstrating signal abnormality within both thalami extending into the diencephalon (not shown) with regions of hemorrhagic necrosis. (B) DWI and (C) ADC show diffusion restriction in both thalami. Findings are characteristic of infectious/ parainfectious ANE in this influenza A positive patient. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; T2/FLAIR, T2 fluid-attenuated inversion recovery.

efficacy and duration of repellant depends on several factors, including the type and concentration of the repellant, as well as the type of mosquito. In general, *N,N*-diethyl-meta-toluamide provides 95% to 100% protection against all mosquito species. Of note, *Culex* mosquitoes tend to be sensitive to all commonly used repellants. Per the CDC, insect repellants can be used in infants as young as two months; however, the natural repellant oil of lemon eucalyptus should not be used in children under three years old.[95]

Treatment

Most patients with WNV infection do not require treatment since illness is typically mild and self-limiting. Among patients with severe disease, supportive care is the mainstay of management. Several disease-targeted therapies have been used with variable results (Table 3). Our literature search identified four pediatric cases describing treatment outcome. Two of these patients presented with AFP and were treated with intravenous immune globulin (IVIG); one recovered fully, while the other recovered with only a residual foot drop.[59,96] Two other children presented with encephalitis following chemotherapy. One was treated with ribavirin and had full recovery, while the fourth patient died despite treatment with IVIG, corticosteroids, and Omr-IgG-am, which is an IVIG containing WNV antibodies.[65,97]

Omr-IgG-am was produced after a 2001 report of an adult patient with WNE who had a dramatic response to IVIG produced in Israel, incidentally found to contain high titers of WNV-specific antibodies, while the IVIG from other geographic locations assessed had none.[98] The drug has subsequently been used in other cases (Table 3) and in a clinical trial comparing it to Polygam, manufactured in the United States, and to placebo (Table 4). The trial, however, was terminated early due to low enrollment and expiration of the Omr-IgG-am product. The preliminary data showed no difference in severity of outcomes among the treatment and control groups.[57] Similarly, transfusion with fresh frozen plasma with WNV IgG has been postulated to ameliorate or prevent clinical disease in two cases, but there have not been any controlled trials.[36,40]

A monoclonal antibody known as MGAWN1 was developed to target the viral E protein, which is vital for fusion with the host cell. The antibody was found to be safe in a phase I trial, but the phase II trial to determine efficacy was terminated early due to poor enrollment.[99,100] Other pharmacologic treatments that have been used include nonspecific antiviral agents and immunomodulators such as ribavirin, interferon alfa-2b, and corticosteroids.

Prognosis

Children with WNND have a better prognosis then older adults, with a fatality rate of 1% compared with 14% in older adults.[7] Some of this difference may be due to a lower rate of comorbidities in the pediatric population, and a lower incidence of encephalitis among children, given that WNE generally has a poor outcome, even when controlling for age.[116] That being stated, children who do develop WNE remain at risk of death or severe neurological sequelae.[7] While data specific to the pediatric

TABLE 2.
Diagnostic Criteria for Neuroinvasive Arboviral Disease, Adapted From the Council of State and Territorial Epidemiologists Position Statements. Both Clinical and Laboratory Criteria Must Be Present[91]

Clinical criteria	• Fever AND • Meningitis, encephalitis, acute flaccid paralysis, or other acute signs of central or peripheral neurological dysfunction, AND • Absence of a more likely clinical explanation	
	Confirmed	Probable
Laboratory criteria	• Isolation of virus or identification of viral antigen or nucleic acid from tissue or bodily fluid OR • Four-fold or greater increase in virus-specific quantitative antibody titers in paired sera OR • Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies OR • Virus-specific IgM antibodies in CSF and a negative result for other endemic arbovirus IgM antibodies in CSF	• Virus-specific IgM antibodies in CSF or serum with no other testing

Abbreviations:
CSF = cerebrospinal fluid
CTX = chemotherapy

TABLE 3.
Treatment and Outcome of WNV Infections in Children and Adults. Partially Adapted From the CDC Literature Review for Providers[101]

Therapy	Clinical Presentation	Outcome
Pediatric cases		
IVIG[59,96]	2 AFP	1 full recovery, 1 residual foot drop
RBV[97]	1 WNE post-CTX	Full recovery
IVIG+CS+WNIG[65]	1 WNE post-CTX	Death
Adult cases		
IVIG[33,39,102]	2 AFP	1 no change, 1 partial recovery
	2 WNE postorgan transplant	2 full recovery
WNIG[103-108]	10 WNE	7 full recovery, 3 deaths
	2 postorgan transplant	1 full recovery, 1 death
	1 post-CTX	Death
	1 CLL, not receiving CTX	Full recovery
	6 no pertinent medical history	5 full recovery, 1 death
	2 AFP	2 full recovery
	1 myalgia after organ transplant	Death
IFN[3,109-111]	1 WNE	Full recovery
	2 WNE + unspecified weakness	2 partial recovery
	1 WNE + AFP	Death
	3 WNE	1 full recovery, 2 partial recovery
CS[112,113]	1 WNE	Partial recovery
	1 WNE + AFP	Partial recovery
WNP+WNIG[40]	1 asymptomatic postorgan transplant	Remained asymptomatic
IVIG+IFN[36]	2 organ donor-derived WNE	2 deaths
IVIG+WNP+IFN[36]	1 organ donor-derived WNE	Full recovery
IVIG+RBV[36]	1 organ donor-derived, fever with urinary tract infection, no neurological symptoms	Did not develop neurological symptoms

Abbreviations:
AFP = acute flaccid paralysis
CLL = chronic lymphocytic leukemia
CS = corticosteroids
CTX = chemotherapy
IFN = interferon alFa-2b
IVIG = intravenous immunoglobulin
RBV = ribavirin
WNE = West Nile encephalitis
WNIG = high titer WNV-IVIG
WNP = plasma with WNV IgG

population regarding the likelihood of full recovery after WNE are unavailable, long-term outcomes have been studied in patients of all ages. Following the WNV outbreak in New York City in 1999, only 37% of patients with WNE had full recovery one year later.[117] The largest study to date examining long-term outcomes found that the majority of patients with West Nile fever or meningitis without encephalitis did not have any neurological deficits one to three years after infection. However, 86% of patients with WNE had an abnormal neurological examination, most frequently involving abnormal tandem gait, motor weakness, and hearing loss. At 10 years postinfection, 20% of patients had died, all but one of whom had been diagnosed with encephalitis.[116] The clinical course of WNND generally seems to be monophasic, although cases of recurrent weakness in AFP have been reported.[118]

Future directions

Vaccination

Much of the current research into WNV therapy is focused on the development of vaccines. While equine vaccines are commercially available, there is currently no equivalent for humans. A number of vaccines have been evaluated in various phases of clinical trials. One recombinant vaccine in particular, ChimeriVax-WN02, has been found safe and effective in two phase II clinical trials among healthy adults.[119] However, due to the relatively low incidence and sporadic nature of WNV outbreaks, completing later phase clinical trials can prove difficult.[120]

TABLE 4.
Therapeutic Trials for Human WNV Infections

Trial	Number Per Treatment Group	Clinical Presentation	Outcome
IVIG vs. WNIG vs. placebo[114]	11 IVIG, 33 WNIG, 11 placebo	WNE or AFP	No significant difference among treatment groups (early termination, incomplete data published)
MGAWN1 vs. placebo[100]	4 MGAWN1, 6 placebo	Unavailable data	MGAWN1: improvement (2), death (2) Placebo: improvement (3), death (1)
IFN vs. placebo[115] (Abstract poster)	15 IFN, 8 placebo	WNE	Significantly greater improvement in treated group than control (Incomplete data)

Abbreviations:
AFP = acute flaccid paralysis
IFN = interferon alfa-2b
IVIG = intravenous immunoglobulin
MGAWN1 = recombinant humanized monoclonal antibody
WNE = West Nile encephalitis
WNIG = high titer WNV-IVIG

Targeted therapies

Regarding therapeutic options for those infected with the virus, several viral components have been identified as potential targets for drug development. A number of these approaches have proven successful in other viruses and show promise in treating WNV. Nucleoside inhibitors targeting RNA-dependent RNA polymerase have proven efficacious in human immunodeficiency virus, herpesvirus, and hepatitis B and C.[121] Favipiravir is a nucleoside inhibitor already licensed in Japan to treat influenza and has demonstrated efficacy in mouse models infected with lethal doses of WNV, but has not yet been trialed in humans with WNV.[122] The development status of this and numerous other compounds are detailed elsewhere and provide promise for the future pharmacologic treatment and prevention of severe disease.[121]

Conclusions

While pediatric WNND is an uncommon manifestation of a relatively common viral infection, further research is needed given its potential poor prognosis with tendency toward permanent neurological deficits or even death. Larger studies evaluating risk factors for the development of neuroinvasive disease in children and the potential transmission via pregnancy, breast milk, and organ transplantation are needed. Moreover, the development of effective vaccine and treatment may help prevent fatalities and neurological disability among thousands of individuals affected by WNND worldwide. Practitioners should consider WNND in the differential diagnosis of meningoencephalitis or AFP, especially during periods of high mosquito activity.

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