

# West Nile Encephalitis Incidence 'Quite Large'

BY BRUCE JANCIN

VAIL, COLO. — West Nile virus has very quickly become the most important cause of arbovirus encephalitis in the United States.

West Nile virus (WNV) first appeared in the Western Hemisphere in New York City in 1999. Yet today the overall frequency of West Nile encephalitis in the United States approaches that of herpes simplex encephalitis, Dr. Kenneth L. Tyler observed at a conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver

"If you account for the fact that most West Nile cases are concentrated in the summer months and in certain geographic areas, whereas herpes of course is year-round and not with any geographic predilection, in some of those areas the relative incidence of West Nile encephalitis



then special MRI techniques such as flare or fast-spin often are required.

The cerebrospinal fluid (CSF) can provide a clue to the diagnosis of WNV meningitis and encephalitis. Unlike in the classic picture of CNS viral infections, where the CSF shows lymphocytic pleocytosis, Dr. Tyler demonstrated in a study of 250 patients with WNV meningitis or encephalitis that 37% of encephalitis patients and 45% of meningitis patients had polymorphonuclear leukocytes as the predominant cell type in their CSF, and the polys often persisted for a week or more (*Neurology* 2006;66:361-5). The CSF contained normal glucose levels, elevated protein, and a mean of about 226 cells/mm<sup>3</sup>.

**In central states, the incidence of WNV encephalitis is at least 25-fold greater than that of herpes encephalitis.**

DR. TYLER

Another diagnostic clue is that the CSF of a patient with WNV CNS disease often appears highly reactive, "almost like a cancer," according to Dr. Tyler.

Studies within the last year indicate the recovery phase following symptomatic WNV infection may be more prolonged than originally thought, even in patients with West Nile fever rather than neurologic disease. In a not-yet-published 108-patient Texas study, 60% of patients reported persistent symptoms of weakness, fatigue, memory deficits, personality change, new-onset depression, or walking difficulties after 1 year; 42% had continued complaints after 5 years.

However, in a more rigorous longitudinal study using validated test instruments, Dr. Mark Loeb of McMaster University, Hamilton, Ont., and coinvestigators found that recovery from the physical, mental, mood, and fatigue symptoms of WNV took about 1 year on average, with patients having neuroinvasive disease taking slightly longer than those with West Nile fever (*Ann. Intern. Med.* 2008;149:232-41).

Acute flaccid paralysis is a poliomyelitislike disorder marked by the acute onset of rapidly progressive asymmetric flaccid weakness. Nearly 90% of affected patients reach their maximum involvement in less than 24 hours.

"I've seen patients who were fine in the morning and quadriplegic in the evening. That's how rapidly it can progress," Dr. Tyler said.

Acute flaccid paralysis is predominantly a lower motor neuron phenomenon. The paralyzed limbs typically have decreased or absent reflexes but preserved sensation. Cranial nerve involvement is a feature in 70% of cases. Among the more common manifestations are dysphagia, extraocular eye movements, facial paralysis, and vocal cord paralysis. ■

# Researchers Close in on Key Factors in West Nile Disease

BY BRUCE JANCIN

VAIL, Colo. — The genetics of symptomatic West Nile infection has become a hot area of investigation with implications spilling over into clinical care.

Infection with West Nile virus (WNV) adheres to the typical arbovirus pyramid: Roughly 80% of human infections are entirely asymptomatic, 20% result in the nasty and debilitating febrile illness called West Nile fever, and about 1 in 150 infections lead to severe CNS disease. The question is, what's different about those 20% or so who develop symptomatic infections? Dr. Kenneth L. Tyler asked at a conference on pediatric infectious diseases sponsored by the Children's Hospital, Denver.

One factor may be the patients' age. In the 2002 Chicago-area outbreak, the incidence of WNV encephalitis was less than 5 cases per 100,000 among 45- to 59-year-olds, triple that in 60- to 74-year-olds, and more than the 30 per 100,000 among individuals aged 75 years and older, he said.

"Neurologic West Nile disease is relatively unheard of in infants, children, and young adults," observed Dr. Tyler, professor of neurology, medicine, and microbiology at the University of Colorado Health Sciences Center, Denver.

A Centers for Disease Control and Prevention study comparing risk factors for development of WNV encephalitis versus West Nile fever in seropositive individuals showed that in addition to advanced age, other significant risk factors for encephalitis in a multivariate analysis were alcohol abuse, which conferred a 7.5-fold increased risk, and diabetes, with a 4.1-fold greater risk (*Clin. Infect. Dis.* 2006;42:1,234-40).

There are also genetic factors involved. The first genetic risk factor to be identified for symptomatic WNV infection was a deletion mutation in the cell surface protein called chemokine receptor 5 (CCR5). In a meta-analysis involving 619 WNV-seropositive individuals, in-

vestigators at the National Institute of Allergy and Infectious Diseases demonstrated that homozygotes for the CCR5 delta 32 mutation had a fourfold increased risk of symptomatic disease (*J. Infect. Dis.* 2008;197:262-5).

CCR5 is important in guiding trafficking of inflammatory lymphocytes into the CNS, where they can help clear the WNV. Studies conducted in excellent mouse models of WNV infection clearly demonstrate that in the presence of the delta 32 mutation, far fewer of these lymphocytes are present in brain tissue, reflecting inhibition of the cell-mediated host immune response to the viral pathogen, the neurologist explained.

In an unusual twist, more than a dozen years ago AIDS researchers discovered that CCR5 is the primary coreceptor used by HIV to infect cells. Homozygosity for CCR5 delta 32 was shown to confer powerful protection against HIV infection in exposed individuals. So the same mutation that protects an individual against acquiring HIV predisposes to neuroinvasive WNV disease, he said.

CCR5 antagonists, both monoclonal antibodies and small molecules, are a promising new class of investigational HIV drugs in active development, but it will be extremely important to protect patients on these drugs from bites by WNV-carrying mosquitoes.

Most recently, investigators at Washington University, St. Louis, have shown that Toll-like receptor 3 (TLR3), a viral sensor that's part of the innate immune system, protects against WNV infection in mice (*J. Virol.* 2008;82:10,349-58).

TLR3, when functioning normally, results in generation of high levels of inflammatory cytokines, including tumor necrosis factor- $\alpha$  and interleukin-6, in the periphery to help control WNV infection. But TLR3 expression is often reduced in the elderly, which may account for their increased propensity for severe WNV infection. The TLR3 findings provide a therapeutic rationale for studies of interferon alpha-n3 (Alferon). ■

# Polio Vaccine Guidelines Updated

The final dose of the standard four-dose vaccination series with inactivated poliovirus should be administered at 4 years of age or older after a minimum interval of 6 months after the third dose, according to updated recommendations from the Advisory Committee on Immunization Practices.

In addition, the committee advises using the minimum age of 6 weeks for the first dose and the minimum interval of 4 weeks between the following two doses "only if the vaccine recipient is at risk for imminent exposure to circulating poliovirus."

This condensed vaccination schedule is not advisable in other situations because shorter intervals and an earlier

start date lead to lower seroconversion rates. The normal four-dose schedule for inactivated poliovirus vaccine (IPV) sets doses at ages 2 months, 4 months, 6-18 months, and 4-6 years (*MMWR* 2009;58:829-30).

ACIP also clarified the poliovirus vaccination schedule that should be used with the combination vaccine DTaP-IPV/Hib (Pentacel). When four doses of DTaP-IPV/Hib are administered at ages 2, 4, 6, and 15-18 months, ACIP recommends using an additional fifth booster dose of IPV (Ipol) or DTaP-IPV (Kinrix) at age 4-6 years, with a minimum interval of at least 6 months between the fourth and fifth dose.

—Jeff Evans