Zika virus

What the neurologist wants to know

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Just as *Neurology*® Without Borders launched in late January, news coverage about the Zika virus epidemic in Latin America with Brazil at ground zero began to reach the popular press.^{1–4} Photographs of devastated parents and microcephalic, dysmorphic infants have captured the public's attention. Recent articles in the *New England Journal of Medicine*⁵ and *Lancet*^{6–8} among others have outlined some of what is known about the epidemiology of this arbovirus and how we believe it made its way from Africa (identified in 1947) to Southeast Asia (mid-20th century) to Micronesia (2007) to French Polynesia (2014) and most recently to Latin America in 2015.⁹

Arrival of the Zika virus into a tropical climate with ample mosquito vectors and large populations of nonimmune individuals, many of whom live in crowded, urban spaces without air conditioning or screens to limit exposure to the aggressive, indoor daytime bites of the *Aedes*, has resulted in ~500,000 infections since April 2015.¹⁰ Clinical suspicion of a microcephaly epidemic in Brazil and 2 cases of RT-PCR–diagnosed Zika in microcephalic neonates led to the initiation of a registry of incident microcephaly with ~4,000 cases reported in the past 9 months. Officials are careful to point out that causality has not been definitively established though Zika virus has been detected in amniotic fluid and fetal brain tissue of some affected fetuses. The role, if any, of the coincident outbreaks of dengue and Chikungunya remains unclear. So what is known about the impact of Zika on the nervous system?

NEUROBIOLOGY Basic science. Zika was first identified in 1947 in the Zika (meaning “overgrown”) Forest of Uganda in rhesus monkeys during a yellow fever investigation. Initial reports of Zika were published in the *Transactions of the Royal Society of Tropical Medicine & Hygiene* in 1952 and the Royal Society has made the full text of these early articles freely available online until February 29, 2016.¹¹ This early work clearly delineated viral tropism to brain in intraperitoneally infected mice with the virus crossing the blood–brain barrier and infecting both neurons and glia. Intracytoplasmic inclusions, which were

then referred to as virus factories, are now known to be the result of the virus hijacking the process of autophagy for its own replication.^{12–14} Another potential mechanism for the neurodevelopmental anomalies associated with Zika is the amplification of centrosomes due to the dual role of some proteins in autophagy and centrosome stability. In mice, increased numbers of centrosomes causes delayed mitosis, increased apoptosis, neural stem cell disorientation, premature neuronal differentiation, and decreased numbers of progenitor cells—all of which could result in microcephaly.¹⁵

Clinical findings. Previous studies of Zika in Africa and Southeast Asia characterized it as an endemic virus causing self-limited infections with fevers, myalgias, arthralgias, a maculopapular rash, and conjunctivitis that largely affected children, with 80% of infections being asymptomatic.¹² When Zika spread to French Polynesia in 2007 concurrently with an outbreak of dengue, reports of neurologic and autoimmune phenomena began to surface. Guillain-Barre syndrome (GBS) incidence reached 20 times the number of expected cases based upon the population size and a retrospective review suggested a similar magnitude increase in neurologic fetal anomalies in infants born in 2014–2015.¹⁶ A report from the European Centre for Disease Prevention and Control indicated that in addition to increased numbers of GBS cases, Zika was thought to be associated with encephalitis, meningoencephalitis, facial paralysis, and myelitis.¹⁷

CLINICAL MANAGEMENT CSF is not required for diagnosis, but definitive diagnosis can be challenging. RT-PCR may only be positive during active viremia, which is as brief as the 3rd–5th day postinfection. Immunoglobulin M (IgM) and neutralizing antibody levels are low early in the disease and these as well as plaque reduction neutralization testing (PRNT) can cross-react with dengue. There is no vaccine and treatment is limited to supportive care with the notable advice that aspirin and nonsteroidal anti-inflammatory drugs be avoided in possible Zika infection due to the common

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co-occurrence of dengue and the difficulty distinguishing the 2 infections—these medications are avoided in dengue due to the increased risk of bleeding associated with their use.¹⁰

Ultrasound can be diagnostic of fetal Zika infection as early as 18–20 weeks of gestational age. Key findings beyond microcephaly (occipitofrontal circumference of <3rd percentile for age, sex, and gestational age) include intracranial and intraocular calcifications, corpus callosal and vermian dysgenesis, an enlarged cisterna magna, severe unilateral ventriculomegaly, agenesis of the thalami, cataracts, and neuronal migration disorders, including lissencephaly and pachygyria.¹⁰

US GUIDELINES The Centers for Disease Control and Prevention (CDC) is recommending that pregnant woman postpone travel to any Zika-infected regions.^{18,19} A travel history should be obtained from all pregnant women and pregnant women who have traveled to a Zika-affected area and who have also experienced 2 or more clinical symptoms of Zika within 2 weeks of their travel should be tested through local health authorities or the CDC as no commercial testing is available. Amniocentesis for RT-PCR may aid in diagnosis and decision-making.

Where there is evidence of potential maternal Zika exposure, live births should undergo placental histopathology, as well as cord blood for RT-PCR, IgM, and neutralizing antibodies and PRNT for both Zika and dengue. Similar tissue assessments are warranted in tissue recovered from fetal losses. Surviving infants should undergo cranial ultrasound, ophthalmologic assessments, and hearing screens with repeat hearing evaluations at 6 months even if initial hearing at birth appears normal.

EPIDEMIOLOGY The incubation period in humans is unknown but in other primates it is ~10 days.⁹ The infection is amplified via humans with mosquito-human-mosquito transmission well-established. Perinatal²⁰ and sexual transmission²¹ are also described and virus is detectable in saliva, urine, semen, and breast milk.^{22,23} There are concerns that Zika could be transmitted iatrogenically via blood products, although no such cases have been reported to date.²⁴

FROM A LOCALIZED PROBLEM TO A GLOBAL THREAT: WHAT LIES AHEAD? The United Nations health agency held a meeting on January 28, 2016, and the WHO is similarly meeting on February 1, 2016. Global attention is coming none too soon for the thousands of Zika-affected children. Bogoch et al.⁷ used *Aedes* habitat and volume of air travel to model the risk of spread of Zika from Latin America to the rest of the Americas and concluded that 22.7

million people in the United States live in regions with possible year-round transmission. These are gross underestimates if unconfirmed reports from Brazil on January 28, 2016, that Zika transmission by the *Culex* is now occurring are substantiated.²⁵ *Culex* mosquitoes, which also carry West Nile Virus, are 20 times more common than *Aedes* and are distributed in broad swaths of North America. This global health issue may soon become all too local for US pediatric neurologists and neonatologists.

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