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Enhanced Epilepsy Surveillance and Awareness in the Age of Zika

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Zika virus (ZIKV) is a flavivirus transmitted primarily through the bite of an infected mosquito, through sexual activity without a condom, and probably through blood transfusion and exposure to other bodily fluids.[1] Prior to 2015, ZIKV disease outbreaks occurred in areas of Africa, Southeast Asia, and the Pacific Islands. Since 2015, out- breaks have occurred in the Americas.[1] In general, ZIKV infection produces no clinical symptoms in many individuals or a mild, self-limiting illness characterized by rash, fever, myalgia, arthralgia, headaches, and/or non- purulent conjunctivitis.[1]

However, congenital ZIKV infection has been established as a cause of microcephaly and other severe brain anomalies.[2] Clinically, craniofacial disproportion, irritability, hypertonia, hemiparesis, extrapyramidal movements (eg, dystonia and dyskinesias), dysphagia, arthrogryposis, clubfeet, and chorioretinal defects have all been reported in ZIKV-exposed infants.[3,4] Radiographically, decreased brain volume, intracerebral calcifications, diffuse cortical malformation and atrophy, ventriculomegaly, white matter attenuation, and/or cerebellar and brainstem hypoplasia have also been described.[3,4] Pathologically, ZIKV appears to target human neural progenitor cells, causing increased cell death and cell-cycle dysregulation, which is thought to disrupt neuronal development and migration.[5]

In two 2016 case series reports, both seizures and epilepsy were reported in some infants with probable congenital ZIKV infection.[3,4] In a case series of 48 infants from Brazil with probable congenital ZIKV syndrome, 50% reportedly had clinical seizures.[3] All 48 infants

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had abnormal radiographic findings, with 91% having intracerebral calcifications, 88% having cortical malformations, and 77% having ventriculomegaly. Among 27 infants who had electroencephalographic monitoring, 30% had focal and 22% had multifocal interictal epileptiform discharges, suggesting an underlying hyperexcitable brain.[3] In another case series[4] of 13 infants in Brazil with laboratory evidence of congenital ZIKV infection, all had cortical malformations, all had subcortical and or/basal ganglia intracerebral calcifications, 92% had decreased brain volume, and 83% had ventriculomegaly on neuroimaging. Seven (54%) were diagnosed as having epilepsy.[4]

Other congenital central nervous system infections with similar radiographic abnormalities have also been associated with the development of epilepsy. For instance, in a case series[6] of 19 children with previous congenital cytomegalovirus infection, 17 (89%) had abnormal brain neuroimaging (eg, intracerebral calcifications, ventriculomegaly, white matter abnormalities, and/or cortical malformations, such as schizencephaly or polymicrogyria), and epilepsy eventually developed in 7 (41%) of these 17 (at a mean [range] age of 20.7 [2–37] months). These findings are not surprising, as both brain infections (eg, meningoencephalitis) and perinatal brain structural injuries are established risk factors for epilepsy.[7]

These findings suggest the need to examine how and to what extent congenital ZIKV infection and resulting brain abnormalities are associated with seizures and/or epilepsy. Answering these questions is important; epilepsy is associated with considerable morbidity and costs, and early recognition and treatment of epilepsy may mitigate some adverse outcomes associated with developmental delay.[7] Because seizure symptoms vary, diagnoses are usually based on history from caregivers and not clinical examination. Because the public and some health care professionals may not recognize seizures in infants and young children, cases of ZIKV-associated epilepsy may be misdiagnosed or under-reported. Other symptoms not related to seizures, such as irritability, abnormal extrapyramidal movements, ab- normal gaze, and intermittent responsiveness associated with congenital ZIKV syndrome, may complicate recognition.

Enhancing seizure and epilepsy awareness and surveillance where active ZIKV transmission is occurring may help improve the identification of ZIKV-associated epilepsy in infants with congenital ZIKV exposure, allow for a fuller understanding of the ZIKV-associated epilepsy burden, and assist in planning and intervention efforts to ensure that those with ZIKV-associated epilepsy and their families receive appropriate treatment and support.[7] Local public health authorities in ZIKV-affected areas could partner with various epilepsy stakeholders to help increase awareness and establish custom epilepsy surveillance systems based on local preferences and available resources. For example, where currently omitted, questions regarding seizures and epilepsy could be added toexisting ZIKV disease surveillance systems. Questions regarding congenital ZIKV infection also could be added to long-term disease surveillance systems that track epilepsy burden or to surveys used in epidemiological studies on epilepsy. Additionally, a specific surveillance system examining the relationship between congenital ZIKV syndrome and seizures/epilepsy could be established (formal guidelines regarding public health surveillance are available at the US Centers for Disease Control and Prevention Surveillance Resource Center at https://

www.cdc.gov/surveillancepractice/guide.html). When such enhanced epilepsy awareness and surveillance efforts are established, their effectiveness should be formally evaluated to help establish best practices for ZIKV-affected areas.

Neurologists could be helpful to this effort in several ways. First, they could help educate local health care professionals in ZIKV endemic areas about seizure recognition and appropriate seizure management. Second, they could ask the parents/caregivers of any infant with new-onset seizures or epilepsy about prior potential ZIKV exposure. Finally, they should report any suspected ZIKV- associated neurologic conditions (including epilepsy) to their state or local public health departments.

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