CORRESPONDENCE

Epilepsy Profile in Infants with Congenital Zika Virus Infection

TO THE EDITOR: Congenital Zika virus (ZIKV) infection may have severe clinical consequences, including dysmorphic features, orthopedic abnormalities, ophthalmologic and auditory lesions, microcephaly, and hydrocephalus.[1] When ZIKV infection is acquired in utero, it may be associated with epilepsy, and we characterized aspects of this complication in a study performed at our referral center. Patients who were referred to our center had congenital or acquired microcephaly, were asymptomatic or symptomatic newborns who were born to mothers who had confirmed or suspected ZIKV infection during pregnancy, had calcifications (not related to other in utero infections) that were detected by means of neuroimaging studies, or had an unexplained developmental delay and lived in geographic regions where ZIKV infection was epidemic (see Table S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org).

Our study included 141 infants, 54.6% of whom were girls, who had congenital ZIKV infection that was confirmed by laboratory analysis. The mean age of the patients was 9 months (range, 1 to 14). Serum samples obtained from the infants and their mothers and samples of cerebrospinal fluid obtained from the infants were tested by means of quantitative reverse-transcriptase–polymerase-chain-reaction assay for the detection of the ZIKV genome and by an IgM antibody capture determined by enzyme-linked immunosorbent assay. In all the infants, structural brain abnormalities were detected by means of neuroimaging studies. The study was approved by the institutional review board of our referral center, and written informed consent was obtained from the parents of the infants.

The study protocol included a clinical evaluation every other month and immediate assessment in case of the development of unexpected clinical complications. The parents were interviewed with the use of a questionnaire that addressed clinical variables associated with epilepsy. Medical records, electroencephalography (EEG), video EEG, and videos from the families of the patients that documented seizures corroborated this information. Seizures were classified according to the guidelines of the International League against Epilepsy.

The prevalence of epilepsy in this cohort was 67%, and the mean age of the infants at the onset of epilepsy was 4.9 months. Data from the parents of the infants indicated that the seizures occurred during the first 6 months of life in 74% of the infants. At the onset of epilepsy and during follow-up, the main seizure types were epileptic spasms (in 72% of the infants), focal motor seizures (in 21%), and tonic seizures (in 4%) (Table 1). A single seizure type was documented in 77% of the infants.

All infants with epilepsy received antiepileptic drugs, and 56% received polytherapy. The last

THIS WEEK'S LETTERS

Table 1. Clinical and Electroencephalographic Findings Associated with Congenital Zika Virus Infection.

Variable	Study Cohort (N=141)
	no./total no. (%)
Prevalence of epilepsy	95/141 (67)
Seizure type*	
Epileptic spasms	68/95 (72)
Focal motor	20/95 (21)
Tonic	4/95 (4)
Tonic–clonic	2/95 (2)
Myoclonic	1/95 (1)
Use of antiepileptic drugs	95/141 (67)
Monotherapy†	42/95 (44)
Polytherapy	53/95 (56)
Two antiepileptic drugs	42/53 (79)
Three antiepileptic drugs	11/53 (21)
Electroencephalographic features	
Abnormal background	84/89 (94)
Abnormal or absent sleep patterns	83/84 (99)
Diffuse slowing	73/84 (87)
Asymmetry with slowing over one hemisphere	3/84 (4)
Epileptiform activity	73/89 (82)
Multifocal epileptiform discharges	32/73 (44)
Focal epileptiform discharges	37/73 (51)
Generalized epileptiform discharges	4/73 (5)
Hypsarrhythmia	8/73 (11)
Burst-suppression pattern	6/73 (8)

* Seizure types were classified according to the guidelines of the International League against Epilepsy.
† In nine children who were receiving monotherapy, the antiepileptic drug was switched because the first drug was ineffective.

evaluation showed that remission was achieved in 62 infants (65%); of these infants, 24 received monotherapy (39%) and 38 received polytherapy (61%). The use of vigabatrin, levetiracetam, valproate, and phenobarbital appeared to be associated with improved seizure control.

The main EEG patterns detected in the patients are listed in Table 1. The presence of a classic or modified hypsarrhythmia or a burst-suppression pattern was associated with drug-resistant epilepsy. All patients with hypsarrhythmia had clinical spasms that were characteristic of the West syndrome. A burst-suppression pattern was not associated with tonic seizures. Remission occurred in one patient in the group of patients with a burst-suppression pattern or hypsarrhythmia.

The prevalence of epilepsy in this referral center–based cohort was higher than in previous series in which the prevalence ranged from 9 to 50%.[1-4] In our study, patients had early-onset, often drug-resistant, epilepsy. The background was abnormal in most EEGs, as previously observed.[5] However, some EEG features, such as a burst-suppression pattern and hypsarrhythmia, were predictive of severe epilepsy. Epilepsy may complicate congenital ZIKV infection.

Hélio van der Linden, Jr., M.D.
Dr. Henrique Santillo Rehabilitation and Readaptation Center
Goiânia, Brazil

Maria D. Carvalho, M.D.
Oswaldo Cruz University Hospital
Recife, Brazil

Vanessa van der Linden, M.D.
Association for Assistance of Disabled Children
Recife, Brazil

Kalyne M. Lacerda, M.D.
Oswaldo Cruz University Hospital
Recife, Brazil

André Pessoa, M.D.
Hospital Infantil Albert Sabin
Fortaleza, Brazil

Mara L. Carneiro, M.D.
Dr. Henrique Santillo Rehabilitation and Readaptation Center
Goiânia, Brazil

Marli T. Cordeiro, M.D.
Centro de Pesquisas Aggeu Magalhães Fiocruz
Recife, Brazil

Kette D. Valente, M.D., Ph.D.
Hospital das Clínicas da Faculdade de Medicina
da Universidade de São Paulo
São Paulo, Brazil
kette.valente@hc.fm.usp.br

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

1. van der Linden V, Pessoa A, Dobyns W, et al. Description of 13 infants born during October 2015–January 2016 with congenital Zika virus infection without microcephaly at birth — Brazil. MMWR Morb Mortal Wkly Rep 2016;65:1343-8.
2. Moura da Silva AA, Ganz JS, Sousa PD, et al. Early growth and neurologic outcomes of infants with probable congenital Zika virus syndrome. Emerging Infect Dis 2016;22:1953-6.
3. Schuler-Faccini L, Ribeiro EM, Feitosa IM, et al. Possible association between Zika virus infection and microcephaly — Brazil, 2015. MMWR Morb Mortal Wkly Rep 2016;65:59-62.
4. Alves LV, Cruz DDCS, van der Linden AM, et al. Epileptic seizures in children with congenital Zika vírus syndrome. Rev Bras Saude Mat Inf 2016;16:Suppl 1:S27-S31.
5. Carvalho MDCG, Miranda-Filho DB, van der Linden V, et al. Sleep EEG patterns in infants with congenital Zika virus syndrome. Clin Neurophysiol 2017;128:204-14.
DOI: 10.1056/NEJMc1716070