Motor Abnormalities and Epilepsy in Infants and Children With Evidence of Congenital Zika Virus Infection

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Initial reports of congenital Zika virus (ZIKV) infection focused on microcephaly at birth with severe brain anomalies; the phenotype has broadened to include microcephaly that develops after birth and neurodevelopmental sequelae. In this narrative review, we summarize medical literature describing motor abnormalities and epilepsy in infants with evidence of congenital ZIKV infection and provide information on the impact of these conditions. Specific scenarios are used to illustrate the complex clinical course in infants with abnormalities that are consistent with congenital Zika syndrome. A search of the English-language medical literature was done to identify motor abnormalities and epilepsy in infants with evidence of congenital ZIKV infection by using Medline and PubMed, Embase, Scientific Electronic Library Online, Scopus, the OpenGrey Repository, and the Grey Literature Report in Public Health. Search terms included “Zika” only and “Zika” in combination with any of the following terms: “epilepsy,” “seizure,” “motor,” and “cerebral palsy.” Clinical features of motor abnormalities and epilepsy in these children were reviewed. Thirty-six publications were identified; 8 were selected for further review. Among infants with clinical findings that are consistent with congenital Zika syndrome, 54% had epilepsy and 100% had motor abnormalities. In these infants, impairments that are consistent with diagnoses of cerebral palsy and epilepsy occur frequently. Pyramidal and extrapyramidal motor abnormalities were notable for their early development and co-occurrence. Prompt identification of potential disabilities enables early intervention to improve the quality of life for affected children. Long-term studies of developmental outcomes and interventions in children with congenital ZIKV infection are needed.
Initial reports of the sequelae of congenital Zika virus (ZIKV) infection were focused on the most severe and clinically apparent physical finding of microcephaly at birth.\(^1\) On brain neuroimaging, anomalies included decreased brain volume, ventriculomegaly or hydrocephaly, calcifications in the basal ganglia and junction between cortical and subcortical white matter, hypoplasia of the cerebellum or brainstem, and cortical malformations (eg, polymicrogyria) predominantly of the frontal lobes but also seen more diffusely in severely affected infants.\(^2,3\) Clinical signs included irritability, hypertonia, hemiparesis, extrapyramidal movements (such as dystonia and dyskinesia), epileptic seizures, and dysphagia.\(^4,5\)

Although the prenatal and postnatal neuroimaging phenotype related to congenital ZIKV infection has been examined extensively,\(^2,5,11-12\) the clinical characteristics and presence of co-occurring neurodevelopmental conditions among affected infants with brain anomalies as well as their trajectory over time have been less well described.\(^2,5,11-12\) A pattern of anomalies beyond microcephaly, including neurologic findings, has emerged, constituting a broader phenotypic definition of congenital Zika syndrome.\(^4\) On the basis of the apparent predilection of ZIKV for neural progenitor cells demonstrated in animal models and human early-stage cortical organoids\(^13-19\) and the reported neuroimaging findings, a number of neurologic abnormalities could be expected dependent on the extent and location of the damage. In this review, we focus on 2 major neurodevelopmental conditions described in children with congenital ZIKV infection, specifically motor abnormalities that are consistent with a clinical diagnosis of cerebral palsy (CP) and epilepsy.

CP refers to a group of nonprogressive disorders of movement, posture, or muscle tone that are attributable to damage or disturbances that occurred in the developing fetal or infant brain.\(^20-22\) The prevalence of CP from population-based surveillance in Europe is \(\sim\) 2 per 1000 live births.\(^23,24\) In the United States, the birth prevalence of spastic CP from population-based surveillance in metropolitan Atlanta, Georgia, of births from 1985 to 2002, remained stable at \(\sim\) 2 per 1000 1-year survivors.\(^25\) Epilepsy is a neurologic disorder that is characterized by recurrent, unprovoked seizures.\(^26,27\) The estimated incidence of new-onset epilepsy is 4 to 5 per 10000 people per year and, after exclusion of febrile seizures, is highest in infancy.\(^28-30\)

CP is often accompanied by additional neurologic disturbances and disorders, including epilepsy.\(^31\) Estimates of the frequency of the co-occurrence of epilepsy among individuals with CP vary widely, from 15% to 62%, depending on the type and severity of CP as well as the study population.\(^32-38\) The estimated frequency of co-occurring epilepsy among 8-year-old children with CP in 4 surveillance areas in the United States was 41%.\(^39\) Severe motor impairment often presents clinically as spastic quadriplegia, and epilepsy is reported to be more common in children with spastic quadriplegia\(^40\) than with other subtypes of CP;\(^40,41\) however, this finding is not universal.\(^39\)

The onset of seizures among persons with CP is usually during the first year of life and can occur as early as the neonatal period. The treatment of seizures is more difficult among children with co-occurring CP, often requiring multiple medications, and some seizures are refractory to treatment.\(^33-35,41\) Therefore, the outcomes in children with CP and epilepsy are often poor, with requirements for ongoing, complex medical care and rehabilitative services.\(^42\)

Both motor abnormalities and epilepsy have been reported to occur and co-occur in infants with laboratory or clinical evidence of congenital ZIKV infection and a phenotype that is consistent with congenital Zika syndrome.\(^5,12\)

An integrated examination of the characteristics of motor abnormalities, epilepsy, or both has not been done. In this review, we summarize the literature on these 2 outcomes and assess the basis for equating the motor phenotype to CP. Additionally, clinical scenarios are provided for 3 infants to illustrate the complex medical and neurodevelopmental issues that occur in infants with Zika-related motor abnormalities and epilepsy.

**METHODS**

**Literature Review**

A comprehensive search of the English-language medical literature was done to identify reports of motor abnormalities and epilepsy in infants with evidence of congenital ZIKV infection by using Medline and PubMed, Embase, Scientific Electronic Library Online, Scopus, the OpenGrey Repository, and the Grey Literature Report in Public Health. The end search date of April 30, 2017, was used for all sources with the exception of the Grey Literature Report in Public Health, which discontinued data collection at the end of 2016. These sources were searched from the year of inception: 1946, 1974, 1997, 1997, and 1999, respectively. Search terms included “Zika” only and “Zika” in combination with any of the following terms: “epilepsy,” “seizure,” “motor,” and “cerebral palsy.” Suspected congenital ZIKV infection was characterized as having (1) laboratory evidence of infection if the infants or their mothers had nucleic acid or antibody testing results for ZIKV that were positive, or (2) clinical evidence if the infants had physical findings that were consistent with congenital Zika syndrome\(^5\) (without or with a history...
of maternal symptoms) and were either not tested or Zika-specific testing results were negative. Two authors (M.Y-A., C.A.M.) reviewed 36 publications for information specific to these outcomes. All publications were assessed for the following informative characteristics: individual-level data on the occurrence of motor impairment and/or epilepsy, number of cases, age beyond the neonatal period, and laboratory evidence of congenital ZIKV infection.

**Case Scenarios**

Case scenarios of 3 infants that illustrate the early medical and developmental course in some infants and young children with evidence of congenital ZIKV infection were selected from clinical cohorts managed by 2 authors (A.P., V.v.d.L.). These scenarios provide a more complete clinical picture of infants with congenital Zika syndrome than is found in most published reports. They describe the neurologic complications in the context of the myriad health concerns for these infants as well as show the evolution of the clinical findings. The authors reviewed the 3 infants’ medical records, including neuroimaging and EEGs, to develop the 3 clinical scenarios.

**Study Oversight**

The inclusion of case scenarios was approved by the Ethics and Research Committee of the Hospital Infantil Albert Sabin in Fortaleza, Ceará, Brazil, and the Oswaldo Cruz University Hospital (CAAE5283316.8.0000.5192) in Recife, Pernambuco, Brazil. Parental informed consent was obtained for each of the 3 case patients. On review by the human subjects contact for the National Center on Birth Defects and Developmental Disabilities of the Centers for Disease Control and Prevention, this work was deemed human subjects research; the Centers for Disease Control and Prevention was not engaged.

**RESULTS**

**Literature Review**

As of April 30, 2017, the majority of published reports of infants with laboratory or clinical evidence of congenital ZIKV infection were from Brazil, where infants had been identified under the screening and reporting protocol for all newborns in Brazil. This protocol was developed by the Brazilian Ministry of Health (MoH) and was first instituted in November 2015; however, the protocol was modified over time. Of the 36 publications on ZIKV infection that were identified in the literature search as possibly containing information on motor impairment or epilepsy, only 13 contained specific information on 1 of these outcomes, and 8 of those publications (Table 1) met 1 or more of the informative characteristics. All 8 publications concerned infants born in the country of Brazil.

**Motor Abnormalities**

Among case reports, case series, and cohort study, the predominant neurologic findings in newborns and young infants with brain anomalies that are consistent with congenital ZIKV infection are extreme irritability, hyperreflexia and hypertonia with spasticity, hypertonia, or a combination of hyper- and hypertonia. Five of the 6 case series were helpful in further defining the motor phenotype (Table 1). In a case series, Botelho et al evaluated 4 infants with clinical evidence of congenital ZIKV infection on the basis of maternal symptoms and infant neuroimaging with standardized assessments of psychomotor development at ages 3 and 4 months. All displayed 2 or more of the following clinical features: hypertonia, hyperreflexia, and muscle spasms or irritability, including 1 infant who also had seizures. Their performance on the Test of Infant Motor Performance was atypical: all 4 infants had a deficit in their manual function, 2 had a visual function deficit, and 3 had dysphagia. Del Campo et al reported 83 infants with microcephaly. Among those infants, 62 (75%) had hypertonia, 23 (28%) had excessive posturing, 17 (21%) had increased deep-tendon reflexes, and 14 (17%) had spasticity. A persistence of primitive reflexes was documented in 8 infants >3 months of age. ZIKV-specific immunoglobulin M (IgM) was tested in the cerebrospinal fluid (CSF) of 14 infants, and 12 had positive results. In a third case series of 35 infants, Schuler-Faccini et al documented hypertonicity and/or spasticity in 13 (37%), hyperreflexia in 7 (20%), and tremors in 4 (11%). Some of the infants in this series were also included in the case series reported by Del Campo et al (L. Schuler-Faccini, MD, PhD, personal communication, 2017), and these infants cannot be separated out on the basis of reported data. In a case series, Moura da Silva et al recognized a combination of signs and symptoms that were pyramidal (described as hypertonia, hyperreflexia and clonus, and persistent primitive reflexes) and extrapyramidal (described as flaccid tone and symmetric dyskinesia present while awake) in 27 of 48 (56%) infants who had clinical evidence of congenital Zika syndrome. The majority of the 48 infants had microcephaly at birth, and the neurologic phenotype tended to emerge in the second or third month of life. Six infants did not have congenital microcephaly; however, 3 of the 6 infants developed microcephaly postnatally. van der Linden et al described the occurrence of postnatal microcephaly because of a prenatal insult in 13 infants with laboratory-confirmed ZIKV infection. All 13 infants had ZIKV-specific IgM detected in CSF, serum, or both and neuroimaging findings associated with microcephaly,
including cortical malformations, intracranial calcifications, and ventriculomegaly. All had a decrease in head circumference (HC) over time, with most developing microcephaly before 1 year of age. Hypertonia was noted in all infants, and 2 had hemiparesis (1 left-sided and 1 bilaterally). Four infants had no grasp ability in 1 hand. A persistence of the asymmetric tonic neck reflex was present in 12 of 13 infants, and symptoms that were consistent with dyskinesia or dystonia were also present in 12 of the infants; 10 had dysphagia. Finally, in a cohort study in Rio de Janeiro, Brasil et al examined 49 newborn infants of 58 women who tested positive for ZIKV during pregnancy by real-time, reverse-transcription polymerase chain reaction (PCR) assay in blood, urine, or both. Of the 49 infants, 21 were reported to have neurologic signs and symptoms, such as hypertonia, hyperreflexia, spasticity, and abnormal posturing. One infant had hemiparesis. Four additional infants were noted to have abnormal neurologic symptoms without further specification; among 25 infants whose mothers were symptomatic, 18 (72%) had the symptoms documented.

### TABLE 1 Studies Selected to Describe Motor Abnormalities and Epilepsy in Infants and Children With Evidence of Congenital ZIKV Infection

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Authors</th>
<th>No. Cases</th>
<th>Age at Follow-up</th>
<th>Pyramidal Signs Described</th>
<th>Extrapyramidal Signs Described</th>
<th>Seizures Described</th>
<th>Other Findings Described</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case series</td>
<td>Botelho et al64</td>
<td>4</td>
<td>3–4 mo</td>
<td>Hypertonia, hyperreflexia</td>
<td>None described</td>
<td>Present in 1 infant but not described</td>
<td>Irritability, abnormal vision, dysphagia, developmental testing abnormal</td>
</tr>
<tr>
<td>Case series</td>
<td>Del Campo et al66</td>
<td>83</td>
<td>0–10 mo</td>
<td>Hypertonia, excessive posturing, increased deep tendon reflexes, spasticity, persistence of primitive reflexes</td>
<td>Dystonia in 1 of 83 infants</td>
<td>Seizures present but not described in this publication</td>
<td>Strabismus, nystagmus, arthrogryposis, features consistent with FBDS</td>
</tr>
<tr>
<td>Case series</td>
<td>Moura da Silva et al5</td>
<td>48</td>
<td>Birth to 8 mo</td>
<td>Hypertonia, hyperreflexia, clonus, persistence of primitive reflexes</td>
<td>Fluctuating tone, asymmetric dyskinesia of the extremities absent during sleep</td>
<td>Abnormal brain activity without epileptiform discharges, focal and multifocal epileptiform discharges</td>
<td>Irritability, dysphagia, clubfoot, arthrogryposis, late-onset microcephaly, FBDS</td>
</tr>
<tr>
<td>Case series</td>
<td>van der Linden et al12</td>
<td>13</td>
<td>5–12 mo</td>
<td>Hypertonia, hemiparesis, no grasp, persistence of asymmetric tonic neck reflex</td>
<td>Dystonia, dystonia</td>
<td>Present in 7 infants but not described</td>
<td>Dysphagia, irritability during first mo of life</td>
</tr>
<tr>
<td>Case series</td>
<td>Schuler-Faccini et al10</td>
<td>35</td>
<td>Ages not given</td>
<td>Hypertonia and/or spasticity, hyperreflexia</td>
<td>None described</td>
<td>Present in 3 infants but not described</td>
<td>Irritability, clubfoot, arthrogryposis</td>
</tr>
<tr>
<td>Case series</td>
<td>Alves et al63</td>
<td>106</td>
<td>29–299 d</td>
<td>None described</td>
<td>None described</td>
<td>Spasms, generalized tonic-clonic seizures, partial seizures; average age of onset is 192 d</td>
<td>None described</td>
</tr>
<tr>
<td>Case series</td>
<td>Carvalho et al61</td>
<td>37</td>
<td>1–5 mo</td>
<td>None described</td>
<td>None described</td>
<td>Diffuse low voltage, background asymmetry and modified hypersrrhythmia with or without burst; focal frontal or occipital spikes and/or sharp waves, multifocal spikes and/or sharp waves; electrographic seizures without clinical findings; abnormal EEGs without clinical seizures</td>
<td>None described</td>
</tr>
<tr>
<td>Prospective cohort</td>
<td>Brasil et al62</td>
<td>49 of 117 live births</td>
<td>First mo of life</td>
<td>Hypertonia, hyperreflexia, spasticity and abnormal posturing, hemiparesis</td>
<td>None described</td>
<td>Present in 1 infant, abnormal EEGs in 2 infants</td>
<td>Abnormal neurologic findings, not specified in 4 of 49 infants</td>
</tr>
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FBDS, fetal brain disruption sequence.
in the second trimester. The infants described in these 5 studies have nonprogressive disorders of movement, posture, and muscle tone, and thus fit the definition of CP.

Epilepsy

In 3 of the 4 case series included above, estimates of the frequency of epileptic seizures after congenital ZIKV infection varied from 24 of 48 (50%), 3 of 35 (9%), and 7 of 13 (54%), respectively (Table 1). Among 27 of 48 infants with clinical evidence of congenital ZIKV infection who underwent EEG and were reported on by Moura da Silva et al, abnormal brain activity without epileptiform discharges was seen in 48%, whereas the remainder had focal or multifocal epileptiform discharges. In the case series reported by Schuler-Faccini et al, 3 of 35 (9%) infants had clinically recognized seizures with clinical evidence of congenital Zika infection. van der Linden et al reported that 7 of the 13 (54%) infants with late-onset microcephaly had documented seizures in the first year of life. In another series, Alves et al focused solely on epilepsy and reported that among 106 infants with ZIKV-specific IgM (65 infants) or clinical features of congenital Zika syndrome (41 infants), ~38% (40 infants) had epileptic seizures. The median time of first report of seizure activity was 192 days of life. Among the 40 infants, >43% of incidents were characterized as spasms; another 22.7% were generalized tonic-clonic seizures, 20.5% were partial seizures, and 4.5% were other types of seizures. Recently, Carvalho et al reported the sleep EEG patterns of 37 infants aged 1 to 5 months with microcephaly. The patterns showed different types of abnormalities, primarily interictal epileptogenic activity and hypersrrhythmia. Four of the 37 infants who did not have clinically apparent epilepsy also had abnormal EEG patterns. Thirty-two of the 37 infants had positive serology results for ZIKV-specific IgM, 1 infant tested negative, and 4 test results were not available.

Motor Abnormalities and Epilepsy

Reports of the co-occurrence of motor abnormalities and epilepsy in infants with laboratory or clinical evidence of congenital Zika syndrome are not easily gleaned from the current literature, which is characterized by case series reporting percentages of selected features. In two studies, Brasil et al and van der Linden et al provide this information on an individual basis. Only 1 newborn was reported to have overt seizures and 2 additional infants to have an abnormal EEG among newborns born to 58 women in the Rio de Janeiro cohort study. In the second report, among 13 infants with laboratory-confirmed congenital Zika infection, just more than half (n = 7) had hypertonia or dyskinesia and/or dystonia co-occurring with epilepsy.

CASE SCENARIOS

Case summaries of 3 infants with laboratory or clinical evidence of congenital ZIKV infection were selected by the authors (A.P., V.v.d.L.) as illustrative of the early and complex medical and developmental courses in some affected infants and young children. This includes the progressive development of symptoms of both pyramidal and extrapyramidal system damage and the need for multiple anticonvulsants for seizure control. They are not representative of all infants with neurologic signs or symptoms attributed to in utero exposure to ZIKV (see Fig 1).

Case A is a girl who was born in October 2015 in the Northeast Region of Brazil (Supplemental Video 1). Her mother had a skin rash associated with itching in the first month of pregnancy. At 27 weeks’ gestation, obstetric ultrasonography revealed microcephaly. Delivery occurred at 39 weeks’ gestation with a birth weight of 2685 g. Her HC was 28.5 cm (~3 SDs below the mean for gestational age and sex) and was classified as severe microcephaly. The infant also displayed craniofacial disproportion, closed anterior fontanelle, and redundant skin or rugae of the scalp. Laboratory testing results of CSF were negative for ZIKV RNA by PCR; virus-specific IgM results were positive for ZIKV and negative for dengue virus. Test results for toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis (TORCH) infection were negative. Brain computed tomography (CT) scans revealed a diffuse bilateral reduction of cerebral parenchyma, ventriculomegaly, cortical underdevelopment, and multiple calcifications predominantly in the basal ganglia and cortical and/or subcortical white-matter regions. On MRI at age 4 months, the CT scan findings were confirmed, and in addition, the corpus callosum was noted to be hypoplastic. On ophthalmologic assessment, the newborn had chorioretinal atrophy of the macula of the right eye. The auditory evaluation was normal.

Clinically, since birth, she has displayed extreme irritability and hyperexcitability. She was treated for gastroesophageal reflux and esophagitis. At 3 months of age, a worsening of irritability was associated with seizures characterized by asymmetric spasms isolated or in clusters. Her EEG at that time revealed no electrographic seizure activity but did reveal multifocal epileptiform discharges, and she was treated with phenobarbital. She showed improvement with less irritability, hyperexcitability, and crying, and her seizures were controlled. Two months after she was started on phenobarbital, the seizures returned and remained partially controlled at 5 months of age. She has been treated with phenobarbital, valproic acid, levetiracetam, vigabatrin, and topiramate.
At the age of 14 months, she continued to have severe microcephaly, with an HC of 34 cm (>8 SDs below the mean). She had arrested development with a marked delay of motor skills, no interaction with the environment, and poor head control. She had abnormal pyramidal and extrapyramidal signs, including hypertonia and hyperreflexia of all 4 extremities, a persistence of primitive reflexes, and dystonic movements of the limbs and mouth. A radiograph of the hips was normal, revealing no signs of dislocation.

Case B is a boy who was born in November 2015 in the Northeast Region of Brazil (Supplemental Video 2). His mother had no history of skin rash or other symptoms of ZIKV infection during pregnancy. All obstetric ultrasonography was normal. The delivery occurred at 39 weeks’ gestation, and he weighed 2770 g. The HC was 32 cm (normal for gestational age and sex at 1.6 SDs below the mean). The infant had a normal examination at birth, without craniofacial disproportion or other dysmorphic features; however, per MoH screening protocol, he had a cranial ultrasonogram, which was normal. A CT scan of the brain was performed at 2 days of age, also per MoH screening protocol for infants with HCs of ≤32 cm, and revealed scattered punctate calcifications. Subsequent MRI at 7 days revealed polymicrogyria and heterotopia on the right side with mild bilateral ventriculomegaly and calcifications in the cortical and/or subcortical white-matter regions. Test results for TORCH infection were negative. Results of laboratory testing of CSF were negative for ZIKV RNA by PCR; virus-specific IgM results were positive for ZIKV and negative for dengue viruses.

The infant demonstrated neurodevelopmental delay after 4 months of age and began displaying asymmetric movements of the upper limbs at that time. At 5 months of age, she...
age, asymmetric spasms occurring in clusters began. An EEG at that time revealed a mild slowing of background activity without epileptic discharge. On ophthalmologic assessment, examinations of the anterior and posterior segments of the eye were normal. The auditory evaluation was normal. An EEG at 11 months revealed focal epileptic discharge with centroparietal spikes in the right hemisphere in addition to the background slowing. Valproic acid controlled the seizure activity. At 13 months of age, he began vomiting the medication, which resulted in the return of the seizures; he was placed on levetiracetam, which led to good control of seizures.

At 15 months, he had microcephaly, with an HC >2 SDs below the mean for gestational age and sex at 44 cm. He had good interaction with the environment and normal ocular movements. He had bilateral hemiparesis predominantly on the left side, with hypertonia and hyperreflexia in both lower extremities and the left arm and dystonic movements of the left hand. There was no persistence of primitive reflexes. He was able to sit without support but not able to walk. A radiograph of the hips was normal, revealing no signs of dislocation. This case was included but not fully described in a previous case series.12

Case C is a boy who was born in November 2015 in the Northeast Region of Brazil (Supplemental Video 3). His mother had an itchy skin rash but no additional symptoms of ZIKV infection during the first trimester of pregnancy. The obstetric ultrasonogram at 34 weeks’ gestation was read as normal. The infant was born at 39 weeks’ gestation, and he weighed 2700 g. The HC was 30 cm (>3 SDs below the mean for gestational age and sex). He had craniofacial disproportion, redundant scalp skin, a short neck, and retrognathia. A CT scan in the first month of life revealed microcephaly, cortical and subcortical calcifications, cerebral cortex thinning, a marked dilatation of the lateral ventricles, and overlapping cranial sutures. Since the first days of life, he displayed hyperexcitability, hypertonia, hyperreflexia, irritability, extremity tremors, and strabismus. Testing for ZIKV was not available for the mother or her infant during this time. Test results for TORCH infections were negative.

At 9 months of age, he presented with spasms and irritability. An initial EEG revealed multifocal discharges; a video EEG was suggestive of mild-to-moderate dysfunction of the basal cerebral rhythms associated with focal epileptiform activity in the left-frontotemporal region. He had onset of seizures at 9 months and was started on valproic acid with eventual control of the seizures and lessened irritability. After the onset of epileptic seizures, a repeat brain CT scan revealed increased ventricular dilatation. The ophthalmologic evaluation revealed increased bilateral optic nerve cupping and rarefaction of retinal pigments. The auditory evaluation revealed possible hearing loss. At 10 months of age, microcephaly remained, and he had poor visual contact and incomplete head control. He was unable to sit, even with support, and had no crawling or voluntary use of his limbs. He had a positive Babinski sign and a persistence of primitive reflexes, such as grasp and asymmetric tonic neck reflex. Pyramidal signs included bilateral spastic hemiparesis with hyperreflexia predominately in the upper limbs with extrapyramidal signs of dystonia in the upper limbs. This case was included but not fully described in a previous case series.66

**FIGURE 1** Continued

Case patient A at age 1 month. A noncontrast CT scan of the brain (axial section) reveals bilateral subcortical, basal ganglia, and midbrain calcifications (shown by the small arrows). C, Case patient A at age 14 months. A noncontrast CT scan of the brain (axial section) reveals ventriculomegaly (shown by the “V”) and subcortical calcifications (the small arrow). D, Case patient A at age 3 months. An EEG reveals slow background activity with generalized epileptiform discharges, including polyspike and wave morphology. 5 of them are seen across the entire brain, although slightly more prominent on the left (shown by the first circle), and polyspike and slow-wave epileptiform discharge are visible across the entire brain (the second circle). E, Case patient A at age 14 months. A photograph reveals abnormal posturing consistent with spasticity, including flexed elbows, clenched fists, and extension at the hips and knees with dorsiflexion at the ankles. Backward extension of the head and body is consistent with opisthotonus. F, Case patient B at age 1 month. A noncontrast CT scan of the brain (axial section) reveals scattered punctate calcifications (shown by the small arrows). G, Case patient B at age 14 months. A noncontrast CT scan of the brain (axial section) reveals bilateral asymmetric ventriculomegaly (shown by the “V”). H. Case patient B. A newborn’s photograph reveals a slightly sloped forehead but otherwise normal appearance. I, Case patient B at age 11 months. An EEG reveals focal epileptic discharge with central and parietal spikes in the right hemisphere (shown by the circle) in addition to background slowing. J, Case patient B at age 1 month. An MRI of the brain (axial section) reveals polymicrogyria on the right (shown by the large arrow). K, Case patient B at age 12 months. A photograph reveals an engaged child with obvious microcephaly but no additional craniofacial abnormalities. L, Case patient C at age 1 month. A noncontrast CT scan of the brain (axial section) reveals bilateral cortical and subcortical calcifications (shown by the small arrows) and cortical atrophy (the large arrow). M, Case patient C at age 1 month. A noncontrast CT scan of the brain reveals ventriculomegaly (shown by the “V”), subcortical calcifications (the small arrow), and an irregular skull shape. N, Case patient C at age 3 months. A photograph reveals flexion in the hips and pelvis, scissoring of the legs, and flexed elbows, consistent with increased tone. O, Case patient C at age 11 months. An EEG reveals left-sided, predominantly posterior, focal epileptiform discharges (shown by the dashed boxes).

**DISCUSSION**

Viruses that are neurotropic (ie, have an affinity for and capability of infecting nerve cells) can cause a variety of neurologic abnormalities depending on the types and location of the cells that are infected and the extent of the infection.69 The brain pathology and early neurodevelopmental findings of congenital ZIKV
infection share some of the features of neurodevelopmental conditions that are associated with intrauterine TORCH infections, specifically symptomatic congenital cytomegalovirus infection and congenital rubella syndrome, both of which are caused by neurotropic viruses.

Among infants with evidence of congenital ZIKV infection and features of congenital Zika syndrome in the reviewed publications, documented motor abnormalities are indicative of both pyramidal and extrapyramidal involvement. Because the terms used to describe motor dysfunction varied considerably, a direct comparison of abnormalities was not possible. Nevertheless, some indication of hypertonia and other signs of pyramidal involvement ranged from 37% in the report by Schuler-Faccini et al10 to 100% in the 2 smallest series reported by van der Linden et al12 and Botelho et al,44 and 42.9% in the cohort study from Brasil et al.82 The frequency of extrapyramidal signs was less well documented in these series; in 3 reports, Moura da Silva et al,5 van der Linden et al,12 and Del Campo et al66 specifically described extrapyramidal signs, and 1 of those reports12 noted that 12 of 13 (92.3%) infants had extrapyramidal findings of dyskinesia or dystonia.

Although the term “cerebral palsy” is rarely used in describing Zika-affected infants and children, probably because of the clinical practice of deferring this diagnosis until age 2 to 3 years,31 the description of abnormal neurologic findings in the published reports is consistent with a diagnosis of CP. Of particular interest is the clinical presentation of a large proportion of infants displaying dyskinetic or dystonic movements in the reports by Moura da Silva et al12 and van der Linden et al.12 Dyskinetic CP is described as changes in muscle tone (hypertonia fluctuating with hypotonia) and the presence of multiple degrees of involuntary movements.79 This CP type is not common; in 1 report of children with CP from multiple sites across the United States, dyskinetic and spastic-dyskinetic CP subtypes combined occurred in only 5.8% of 8-year-old children compared with spastic subtypes overall, which were identified in 77% of children.79 On the basis of a report from European CP registries, dyskinetic CP was often severe and frequently associated with epilepsy and intellectual disability, and the degree of epilepsy and intellectual disability increased with the severity of motor impairment.78 Therefore, motor abnormalities in infants with congenital ZIKV infection are more likely to resemble a rare type of CP, and the co-occurrence of other neurologic conditions may be high.

Among the case series in which researchers report epilepsy,5,10,12,51,63 a variety of EEG abnormalities were found, with multifocal discharges being the most prevalent; onset in early infancy was also documented. Only 1 report documented the clinical types of seizures63; 17 of 40 (43%) seizures were described as spasms. Of note in these reports was the finding of abnormal brain activity without epileptic discharges5,51 and electrographic seizures without clinically apparent seizure manifestation.51 In the Rio de Janeiro cohort study,52 infants were evaluated as newborns, possibly before seizure activity was apparent. However, on the basis of published reports, we suggest that the prevalence of seizures increases with infant age and might not be associated with clinical findings.

With congenital ZIKV infection, an early onset of involuntary movements and epilepsy are likely correlated to the severe degree of brain damage because of ZIKV exposure in utero. The projection of long-term neurodevelopmental sequelae of congenital ZIKV infection might not be valid at this point in time given the young age of most children who are affected by ZIKV and the recognition of co-occurring conditions (eg, epilepsy, sensory impairments [such as hearing and vision loss], and intellectual disability)55,80 at later ages. Additionally, the nature of the condition might change over time (eg, hypotonia develops into spasticity).81 However, initial prognostic factors might not predict outcomes for children with early indicators of CP. Among 29 children with congenital rubella who were without intellectual disability, 20 (69%) had abnormal tone or reflexes in early infancy; however, the percentage at 9 to 12 years of age had decreased to 10%.72 In addition, among 1-year-old children with CP of various origins who participated in the Collaborative Perinatal Project, 118 of 229 (52%) were free of motor disabilities at age 7 years, and the researchers found that certain types of CP, including ataxic and/or dyskinetic, were more likely to resolve.82 Nonetheless, the severity of brain pathology and abnormal neurologic findings in numerous reports raise the concern that many of the children with congenital ZIKV infection will have complex and potentially multiple developmental disabilities in addition to epilepsy and motor abnormalities. Moreover, infants and children who have 1 or both of these neurologic conditions are at risk for a number of medical conditions that can impair growth and development, such as malnutrition,83,84 and be life-threatening, such as swallowing and feeding difficulties21,85 and obstructive sleep apnea.86

Children with developmental disabilities, which include CP and epilepsy, require increased medical and rehabilitative services.87 The lifetime costs for a cohort of US children with CP born in 2003 was $11 billion, and the per-person lifetime cost approached $1 million.88 Medical costs for Medicaid-enrolled children with CP were 10 times higher than for Medicaid-enrolled
children without CP. In a study of the economic impact of epilepsy in the United States using medical expenditure data from 1996 to 2004, among children <18 years of age, the mean annual expenditure per child with epilepsy was $6379 compared with $1032 for a child without epilepsy. In general, economic costs related to managing epilepsy are higher in children than adults, in uncontrolled versus controlled epilepsy, and in children with disabilities versus without.

The findings in this review are subject to at least 4 limitations. First, the availability of testing for ZIKV infection in Brazil has been limited in some locations, especially in the early months of the epidemic in 2015, and many infants were reported on the basis of clinical findings alone. Second, the incomplete evaluation of infants, aggregate reporting of infants on the basis of 1 aspect of the phenotype, young age of case infants, inconsistent use of descriptive terminology, and small numbers in some studies limit the conclusions that can be drawn related to the co-occurrence of specific sequelae, such as CP and epilepsy. Third, this review was conducted by using publications from English-language journals only or those that provide English translations. It is likely that some descriptions of infants with congenital ZIKV infection were missed for this reason. And, finally, the narrative review process is a qualitative approach to critically analyze and summarize the published literature; however, this methodology has inherent limitations, such as selection bias and the inability to infer causality and consider complex interactions.

CONCLUSIONS
In this article, we highlight the occurrence and complexity of 2 neurologic conditions, movement abnormalities and epilepsy, that have been documented in infants with evidence of congenital ZIKV infection, some of whom have congenital Zika syndrome. Early recognition of the pattern of anomalies associated with congenital Zika syndrome allows clinicians to provide a timely assessment for co-occurring health conditions, such as epilepsy and CP, and their sequelae and to anticipate related problems.

The increasing number of infants and children who are affected by congenital ZIKV infection and survive with complex and difficult-to-manage health conditions, such as epilepsy and CP, will necessitate an expansion of available health care and laboratory capacity, educational and social services, and public health systems in countries that are affected by ZIKV. More data are needed to better understand the consequences and impacts of Zika-associated disabilities. Multidisciplinary systems of support engaging parents, health care providers, educational resources, and others within a community are needed to address factors that affect the quality of life for surviving children and their families. Improved public awareness of the possible profound and lifelong effects of ZIKV infection during pregnancy (ie, more than just microcephaly) is needed to garner support for the necessary programs and policies that can benefit infants who are affected by Zika as well as the larger population of children with special health care needs.

ADDENDUM
A recent publication has documented the health and developmental outcomes of a small series of children aged 19–24 months who were born with microcephaly and laboratory evidence of congenital Zika virus infection. As anticipated from earlier studies of affected infants, severe motor impairment consistent with cerebral palsy and epilepsy were predominant concerns in these children.

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ABBREVIATIONS
CP: cerebral palsy
CSF: cerebrospinal fluid
CT: computed tomography
HC: head circumference
IgM: immunoglobulin M
MoH: Ministry of Health
PCR: polymerase chain reaction
TORCH: toxoplasmosis, rubella, cytomegalovirus, herpes, and syphilis
ZIKV: Zika virus
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