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Case Report

Focal epilepsy features in a child with Congenital Zika Syndrome

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ABSTRACT

Zika virus (ZIKV) is a mosquito-borne, single-stranded DNA flavivirus that is teratogenic and neurotropic. Similar to the teratogenic effects of other TORCH infections, ZIKV infection during pregnancy can have an adverse impact on fetal and neonatal development. Epilepsy is detected in 48–96% of children with Congenital Zika Syndrome (CZS) and microcephaly. Early epilepsy surveillance is needed in children with prenatal ZIKV exposure; yet, most ZIKV-endemic regions do not have specialist epilepsy care. Here, we describe the demographic, clinical, imaging, and EEG characteristics of a 2-year-old child with CZS and microcephaly who presented with focal epileptiform activity, suboptimal growth, and severe neurodevelopmental delays. Administration of a brief seizure questionnaire by allied health professionals to the patient's caregiver helped to characterize the child's seizure semiology and differentiate focal from generalized seizure features. A telemedicine EEG interpretation platform provided valuable diagnostic information for the patient's local pediatrician to integrate into her treatment plan. This case illustrates that CZS can present with focal epilepsy features and that a telemedicine approach can be used to bridge the gap between epilepsy specialists and local care providers in resource limited ZIKV-endemic regions to achieve better seizure control in children with CZS.

1. Introduction

Zika virus (ZIKV) is a mosquito-borne, single-stranded DNA flavivirus that is teratogenic and neurotropic [1]. ZIKV in pregnant women can infect the fetus through vertical transmission, particularly in the first trimester before a protective zone of mature villous trophoblasts has been established in the uteroplacental circulatory system [2–4]. After crossing the placental barrier, ZIKV directly targets neural progenitor cells, which can lead to cell cycle dysregulation, cell cycle arrest, and apoptosis [5]. Similar to the teratogenic effects of other TORCH infections, ZIKV infection during pregnancy can have a substantial negative impact on fetal and neonatal brain development, which increases epilepsy risk [6]. Congenital Zika Syndrome (CZS) is characterized by severe microcephaly, thin cerebral cortices with subcortical calcifications, macular scarring and focal pigmentary retinal mottling, congenital contractures, and marked early hypertonia and symptoms of extrapyramidal involvement [7]. Focal brain malformations can be found concurrent with microcephaly and in the absence of microcephaly [8]; these include focal cortical dysplasia, polymicrogyria, decreased frontal lobe mass, and/or calcifications within the basal ganglia [4,8]. Epilepsy is detected in 48–96% of children

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with CZS and microcephaly [9–13]. Epilepsy rates are substantially lower in normocephalic children with prenatal ZIKV exposure (3%), although still elevated relative to the general population [14].

Early diagnosis and treatment of epilepsy is essential in CZS, as seizures can predispose children to a lifetime of neurodevelopmental and social deficits [15]. Language and motor delays are commonly found in children with ZIKV-associated epilepsy [16,17], which may necessitate intensive early intervention services. In children with CZS and microcephaly, seizure onset is typically within the first few months of life [12,13]. Electroencephalographic (EEG) findings include abnormal background rhythms, hypsarrhythmia, and focal or multifocal epileptiform discharges [12]. Given that CZS may be associated with generalized, focal, or mixed seizures, EEG is essential for guiding treatment. However, most ZIKV-endemic regions do not have access to EEG or epilepsy specialist care [18]. Here, we introduce a telemedicine approach to epilepsy care that can be used to bridge the gap between epilepsy specialists and local pediatricians in ZIKV-endemic regions. We describe how this approach augmented the care and treatment of a 2-year-old child with CZS and microcephaly.

2. Case report

A two-year-old Afro-Caribbean female presented with microcephaly during a ZIKV outbreak in Grenada, West Indies. Her mother was recruited from a public health center as part of a larger study investigating the impact of *in utero* Zika virus exposure on neurodevelopment [14]. The mother provided written informed consent to support her child's participation in the study and also consented to publication of this case study.

2.1. Serum testing

The mother had serum drawn at 24 (±2) weeks gestation. Prenatal serology was positive for flavivirus and negative for alphavirus infection using IgM antibody captured enzyme-linked immunosorbent assay (MAC-ELISA) [19]. A plasmonic-gold (pGOLD) platform (Nirmidas Biotech, Palo Alto, CA) for measuring IgG against ZIKV and dengue virus (DENV) antigens was used to distinguish these possible flaviviral infections, with IgG avidity used to determine the timing of exposure [20]. The pGOLD IgG immunoassay has demonstrated sensitivity and specificity to ZIKV greater than 90% and 98%, respectively, in the convalescent phase [20]. Maternal pGOLD IgG immunoassay results were positive for ZIKV and DENV antibodies. IgG avidity testing showed ZIKV exposure within the prior 6 months and more remote DENV infection (i.e., prior to pregnancy). The infant had serum drawn at 2 months of age. Results from the pGOLD IgG immunoassay were positive for ZIKV and negative for DENV.

2.2. Birth and delivery

The mother was 30 years of age at the time of delivery. Her pregnancy was uncomplicated, with no reported alcohol, drug, or tobacco use. The patient was born full-term via normal vaginal delivery. Meconium aspiration was noted and resuscitative assistance was provided. One-minute APGAR score was 2, 5-minute score was 3, and 10-minute score was 8. Facial dysmorphism was observed. Head circumference was 30 cm at birth ($z = -3.5$) [23]. Reflex testing was performed at 2 months of age with grasping, sucking, and plantar reflexes present and Moro and Galant reflexes absent.

2.3. Growth and development

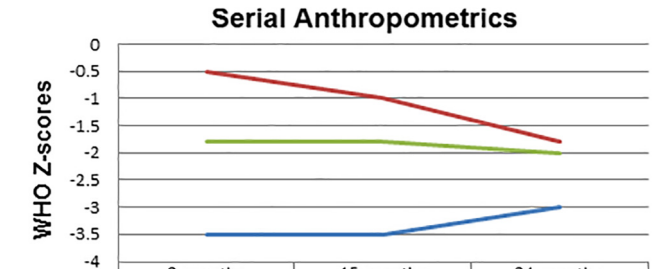
Suboptimal growth was observed on serial anthropometric assessments (Fig. 1) using WHO standards [21]. A neurological exam was performed at 16 months of age. Strabismus was observed. Babinski reflex was present. Motor examination showed significant global hyperreflexia and global hypertonia, which were more pronounced in the left upper and lower limbs. The Intergrowth-21st Neurodevelopmental Assessment (INTER-NDA) package was used to assess vision, motor functions, language skills, cognitive skills, and social/behavioral functions at 24 months of age [22]. Her scores across all domains were in the profoundly delayed range (<3rd percentile), with skills at approximately the level of a 5-month-old. She was unable to visually track or reach for objects but could hold her head up in prone position and was able to emotionally respond to faces.

2.4. Neuroimaging

Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain were clinically acquired at 13 months and showed dilation of ventricles, with more pronounced volume loss in the right hemisphere, particularly in the frontoparietal lobes, as well as lissencephaly and agyria, predominantly in the frontal lobes (Fig. 2A–C).

2.5. Epilepsy profile

The patient has no known family history of epilepsy. Seizure onset was at 3 months of age. She was diagnosed with epilepsy based on the presence of at least 2 unprovoked seizures occurring more than 24 hours apart and started on carbamazepine (10 mg/kg/day) [23]. Her mother described features of the patient's seizures with prompting from the Pediatric Epilepsy Screening Questionnaire (PESQ), a screening tool used to identify seizures and distinguish focal from generalized features in resource-limited settings [24]. The PESQ was administered at 15, 24, and 27 months of age by allied health research staff in the patient's local health center. At 15 months, the patient's mother reported non-motor (behavioral arrest/staring spells) and motor (tonic-clonic) seizures of unknown onset that were occuring at a frequency of one to three times weekly, with a maximum of three episodes in a day. This was communicated to her local pediatrician and her dosage of carbamazepine was increased to 25 mg/kg/day. Serum concentrations were not acquired because this service was not locally available. She had a period of seizure freedom for several months. At



	2 months	15 months	24 months
HC	-3.5	-3.5	-3
Weight	-0.5	-1	-1.8
Length	-1.8	-1.8	-2

Fig. 1. Serial anthropometric assessment. Head circumference (HC), weight, and height were standardized for age using World Health Organization growth charts. Head circumference remains well below normal limits for age. Weight remains within normal limits at 2 and 15 months but declines to the lower end of the normal range by the age of 24 months. Length remains at the lower end of the normal range from 2 to 24 months.

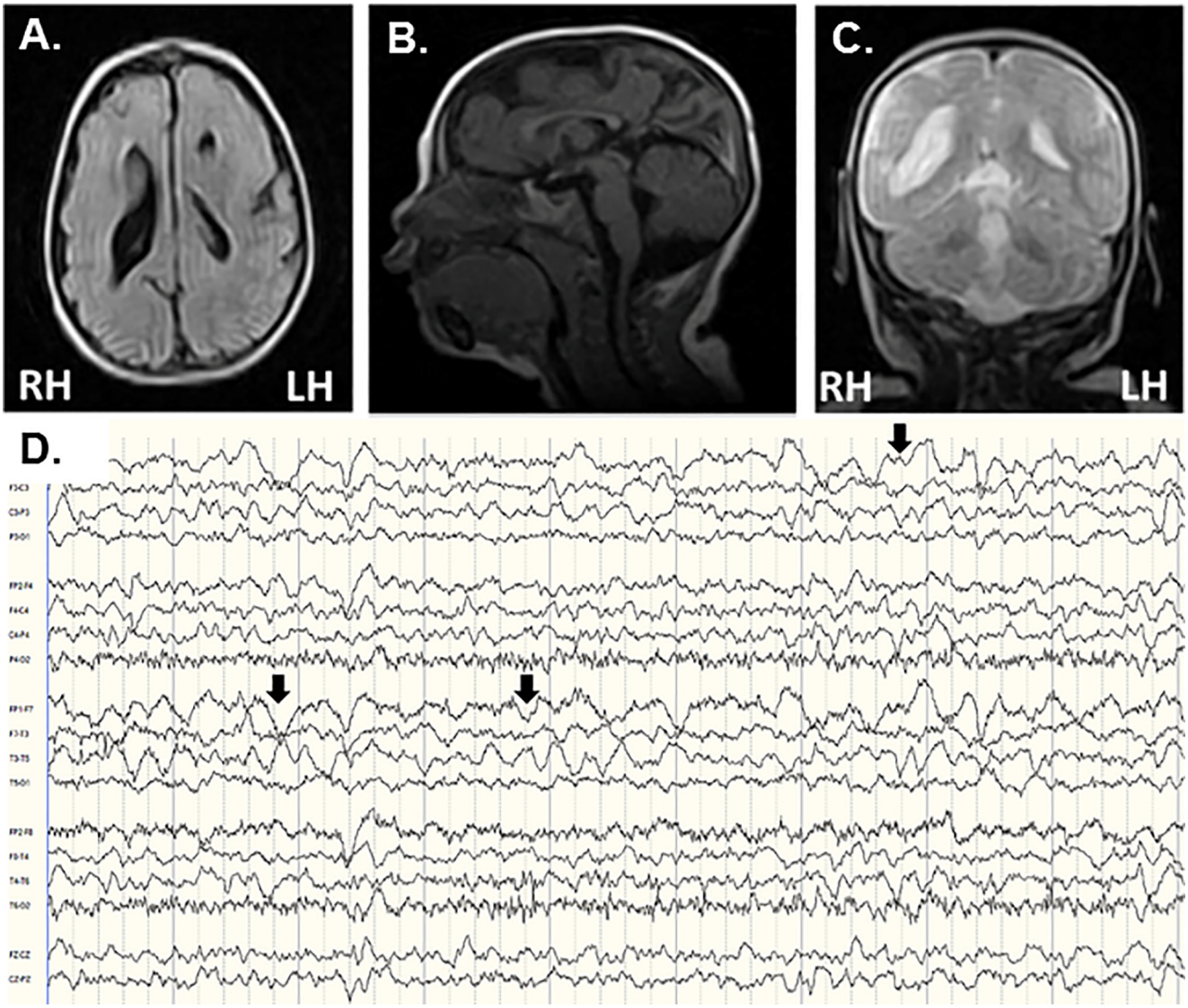


Fig. 2. Magnetic resonance imaging (MRI) at 13 months (A–C). A: FLAIR axial view demonstrating enlarged lateral ventricles, predominantly in the right hemisphere. B: T1-weighted mid-sagittal view demonstrating intact corpus callosum and brain stem. C: T2-weighted coronal view demonstrating enlarged lateral ventricles and reduced cerebral volume, predominantly in the right hemisphere. D: Electroencephalography (EEG) at 16 months showing focal slowing (arrows) in left hemisphere.

27 months, her mother reported a cluster of breakthrough focal to bilateral tonic-clonic seizures (shaking of one side only at onset), which was communicated to the patient's pediatrician. She was transitioned to levetiracetam (two doses of 10 mg/kg/day). Good seizure control was achieved and maintained as of 36 months of age.

2.6. Telemedicine electroencephalography (TeleEEG)

As part of a research epilepsy surveillance protocol [14], we utilized the microEEG® (www.biosignalgroup.com) monitoring system. This 26-channel system has been validated in newborns [25] and was designed for use in field applications and high-noise environments [26–28]. It is optimized for use with the Eze-Net headpiece, which conforms to the International 10/20 System. The headpiece was easy to apply by trained allied health research staff and was well tolerated by the patient. We recorded electrophysiological activity during wake and sleep states for a minimum of 20 min along with a video recording of patient behavior time-locked to the EEG recording. EEG data were transferred to a HIPAA compliant server for remote interpretation by 3 pediatric epileptologists (DD, GC, AP), using a standardized form. EEGs acquired at 15, 16, and 24 months showed bilateral, focal epileptiform activity in frontal regions and focal slowing in the left frontal region (Fig. 2D). No generalized epileptiform findings were present in any of the EEGs. These findings were communicated to the patient's local pediatrician.

3. Discussion

This case study illustrates how the diagnosis and treatment of a child with CZS and focal epilepsy were improved by the use of a seizure questionnaire and teleEEG platform in a resource-limited region. Epilepsy profiles in CZS are diverse [12]. The mechanisms by which prenatal ZIKV infection predisposes a child to seizures are not yet fully understood but have been investigated in mouse models, human stem cells, and cerebral organoids [29–30]. ZIKV initially targets astrocytes [29], a type of glial cell, in addition to targeting neuronal progenitor cells [30]. The virus reacts with the tips of glial processes of astrocytes primarily in the cortex, hippocampus, thalamus, and hypothalamus [29]. During later stages of infection, astrocytes release viral progeny, resulting in further spread in localized regions [29]. Additionally, through its induction

of cell death of neuronal progenitor cells, ZIKV can lead to cortical thinning and reduction of brain volume on neuroimaging [8,30]. These findings indicate that focal, potentially epileptogenic, brain malformations often co-occur with globally abnormal morphology. Our patient presented with more pronounced volume loss in the right hemisphere, and focal lissencephaly and agyria in the right anterior region, which raises the possibility of greater astrocytic release of viral progeny in anterior regions during critical stages of her prenatal cortical development.

Access to EEG and specialist epilepsy care is limited in many ZIKV-endemic regions [18], yet neurophysiological studies can provide valuable information to localize epileptiform activity and assist with differential diagnosis of a focal versus generalized epilepsy syndrome. The teleEEG platform that we utilized provided valuable clinical information for the patient's local pediatrician (TD) to integrate into her diagnosis and treatment plan and may be similarly accessible to non-specialty clinics in resource-limited regions, as long as there is a remote/virtual relationship with a consulting epileptologist. Use of a formal epilepsy questionnaire helped to prompt communication of seizure semiology and medication failures to the patient's physician. The questionnaire we utilized was developed for use in resourse-limited regions and designed to be administered by non-specialist allied health professionals [24]. It has high reliability and discriminative validity for differentiating focal from generalized seizures [24]. Given the variability of epilepsy profiles in children with CZS [12], the use of a screening questionnaire to assist in differentiating focal from generalized seizures is important for optimizing antiseizure medication, especially if EEG is not available or is cost-prohibitive. In our case study, the neurophysiological data was concordant with neuroimaging findings and parent-reported seizure features and increased confidence in diagnosis of a focal epilepsy syndrome.

Global neurodevelopmental delays and suboptimal physical growth were apparent in our patient at two years of age, which is a common finding among children with CZS and microcephaly [31]. However, there is a wide spectrum of neurodevelopmental outcomes in CZS, with evidence for normal neurodevelopment in some children, even if microcephaly is present [32]. Neurodevelopmental delays are common in children with CZS and severe and frequent seizures [13]. The presence of epilepsy is associated with lower cognitive ability in children with microcephaly, independent of CZS [33]. Development of fine motor skills (such as hand-eye coordination) and gross motor skills (such as the ability to walk and maintain endurance) are significantly delayed in children with CZS and uncontrolled seizures [13]. Additionally, previously acquired motor skills can regress with frequent seizures [34]. Early and effective treatment can improve developmental trajectories [35]. Although epilepsy has not been formally investigated as a risk factor for abnormal neurodevelopment in CZS, these findings suggest that optimizing antiseizure medication to obtain seizure freedom can minimize the adverse impact of compromised neurodevelopment in children with CZS.

4. Conclusion

This case highlights the presence of focal seizures in a child with CZS and illustrates how a screening questionnaire and teleEEG platform can be used to augment epilepsy care in ZIKV-endemic regions, in close collaboration with epilepsy specialists.

Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SB reports support from Bio-Signal Group Co. and the following patents pending: 61/554,743; 13/284,886. None of the other authors have any conflicts of interest to disclose.

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