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Case Report

Epileptic spasms as the presenting seizure type in a patient with a new "O" of TORCH, congenital Zika virus infection

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ABSTRACT

Congenital TORCH infections are a significant cause of epileptic spasms, an infantile epileptic encephalopathy, through disruptions to several pathways in neurodevelopment. Congenital Zika virus has a similar neurotropism to other TORCH agents, and leads to microcephaly, severe neurodevelopmental impairment, and high rates of early onset seizures. Here we report a child with confirmed congenital Zika virus who developed extensor epileptic spasms and hypsarrhythmia associated with a loss of early developmental milestones. Early treatment led to resolution of epileptic spasms and improved developmental trajectory, though the child continues to have ongoing focal seizures and prominent developmental impairment. Congenital Zika virus infection requires close monitoring as early identification of epileptic spasms is likely important in long term developmental outcome.

1. Introduction

Congenital Zika virus infection is responsible for an epidemic of children with microcephaly and severe neurodevelopmental impairment [1]. Mouse models show that the Zika virus exerts a tropism for neural progenitor cells, and acts through direct neurotoxicity and by disrupting the differentiation, maturation, and migration of developing neurons [2]. This leads to a wide spectrum of abnormal brain development that can involve severe microcephaly, abnormal gyral patterning, widespread abnormalities of cortical organization, and more rarely isolated focal dysplasias. The sequelae of congenital Zika virus infection are broad, and include diffuse hypertonia and hyperreflexia, irritability, and epilepsy [3]. The rates of seizures in congenital Zika virus infection range from 9 to 54%, with seizure subtypes including focal and generalized seizures and more recently descriptions of epileptic spasms in as many as 20% of children [4]. The classification of epilepsy and EEG findings in congenital Zika infection has been limited, though a case series shows interictal abnormalities and abnormal backgrounds occur in more than half of children, while 29% meet criteria for hypsarrhythmia variant [5]. Here we present a child with confirmed congenital Zika infection who develops epileptic spasms to better illustrate the range of cerebral pathology seen in this disease and how that correlates with epilepsy and electrographic findings.

2. Case report

A Mexican woman who had recently traveled to the United States gave birth at 39 weeks gestation to a female with a head circumference of 28.6 cm (Z-score −4.5). The pregnancy was complicated by delayed head growth noted on an ultrasound at 6 months gestation. The delivery was spontaneous and uncomplicated, with APGARs of 8 and 9 and a birth weight of 2.55 kg (6th percentile). The neonate had apneas which required a brief observation in neonatal intensive care, but these resolved and she was discharged by day 3. While the mother denied illnesses during pregnancy, she reported screening positive for Zika virus exposure in Mexico. Initial screening of the newborn using RT PCR for Arbovirus virus RNA was negative, but Zika IgM antibodies were detected on capture ELISA and the diagnosis was confirmed using the plaque reduction neutralization test, with Zika antigen titers >1260:1 (positive >320:1).

An ultrasound at 2 weeks revealed ventriculomegaly and bilateral calcifications in the gray–white junction (Fig. 1A,B). Ophthalmologic evaluation showed bilateral chorioretinal lacunae. Brain MRI at 3 months confirmed reduced brain size with polymicrogyria, predominantly involving bilateral frontal perisylvian and parietal cortical regions (Fig. 1C,D,E). Numerous foci of cerebral calcifications in bilateral subcortical white matter and gray–white interfaces were also apparent. Clinically, she fed well in the neonatal period with only mild hypertonia and periods of irritability. At 6 weeks, her head circumference was 31.7 cm (Z-score −4.4). Her examination revealed mild irritability, developing appendicular hypertonia, poor tracking, and leftward gaze preference. By 4 months, her appendicular hypertonia was more prominent, though by that time she had developed a social smile, displayed tracking improving head control,

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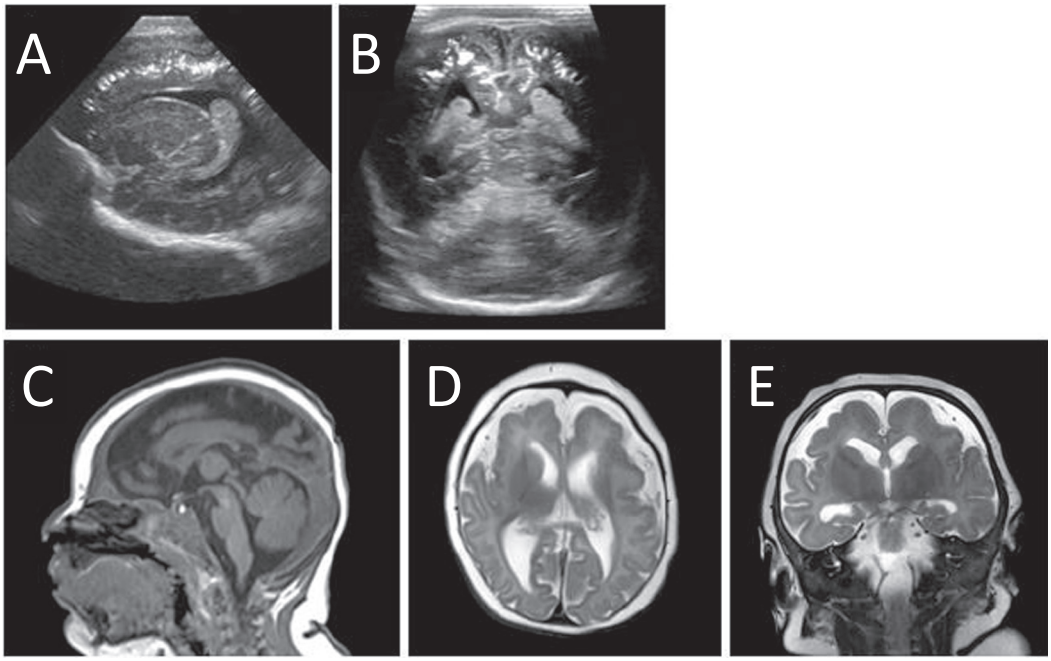

Fig. 1. (A,B) Cranial ultrasound at 1 week. A: parasagittal and B: coronal views through the anterior fontanelle demonstrating extensive punctate calcifications in the periventricular and subcortical white matter. (C–E) C: Sagittal MPR image demonstrating small cranium relative to face, and small supratentorial structures relative to brainstem and cerebellum. Axial (D) and coronal (E) T2-weighted images showing small cerebral hemispheres with reduced white matter volume, *ex vacuo* dilation of lateral ventricles, and extensive bilateral polymicrogyria most prominent in the anterior and superior frontal lobes.

and the ability to roll intermittently. However, at this time her mother noted onset of pronounced startle-like episodes, with bilateral arm extension, which would cluster. Around this time her mother had also noted a reduction in overall responsiveness in the patient, with reduced eye contact, social smiling and laughing, and greater sleep disruptions.

An EEG demonstrated abundant multifocal discharges that were most frequent over right occipital and bitemporal regions, with independent slow waves exceeding 300 μV over the right hemisphere with a BASED score of 4 [6], meeting criteria for hypsarrhythmia (Fig. 2A). There were also numerous clinical extensor epileptic spasms (ES) corresponding with a high amplitude slow wave followed by background

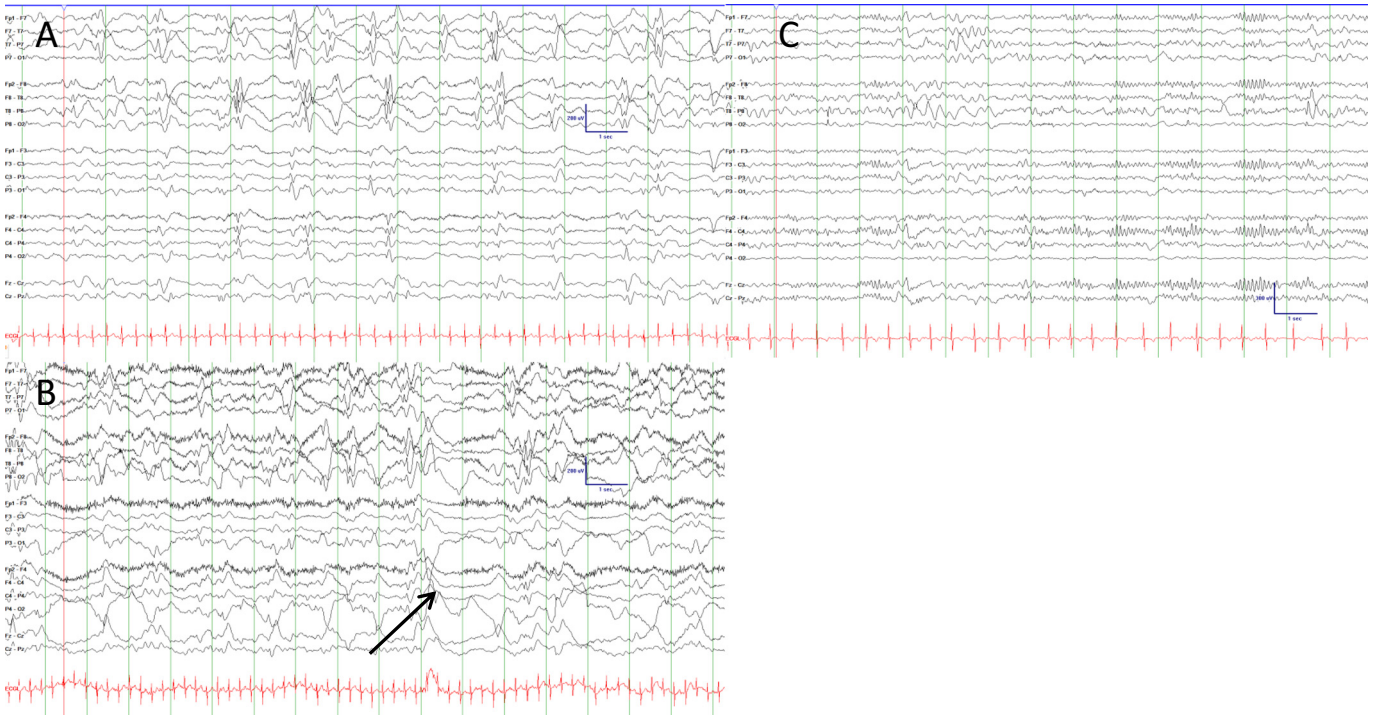

Fig. 2. (A,B) EEG at 4 months of age, bipolar montage. A: Background activity in sleep displays multifocal spikes with most frequent discharges over the temporal regions. Background activity abnormal with high amplitude slow waves reaching 300 μV over the right hemisphere and lack of normal features of sleep. B: Clinical spasms seen in the awake state (arrow) with a high amplitude slow wave maximally over the right temporal region followed by diffuse attenuation. The background is disorganized with prominent delta slowing. (C) EEG at 16 months of age in sleep shows resolution of background encephalopathy but epileptiform activity over the right parietal region (P8).

attenuation (arrow, Fig. 2B). The patient was started on vigabatrin and escalated to goal dose with reduced frequency and severity of spasms. After two weeks of therapy, the EEG exhibited no independent slow waves over 200 μV (BASED score 3) and resolution of hypsarrhythmia, but subtle spasms persisted. Clinical spasms relented on a combination of vigabatrin and topiramate, and she regained the ability to coo and attend to sound, though had prominent spastic quadriplegia. Follow-up EEG at 16 months of age (Fig. 2C) shows sleep spindles in stage II sleep and resolution of hypsarrhythmia but focal epileptiform activity and regional slowing over the right parietal region.

3. Discussion

ES, or infantile spasms, result from several symptomatic causes, including developmental malformations and intrauterine insults, with imaging of these cases sufficient to identify more than half of symptomatic causes. Malformations of cortical development (MCDs) contribute to 8% of ES cases, and they have lower rates of response to treatment [7,8]. Congenital infections such as the TORCH etiologies are implicated in the development of ES. Intracranial calcifications are common in TORCH infections, and their presence is associated with higher rates of epilepsy [9]. Congenital cytomegalovirus (CMV) infection not only frequently leads to intracranial calcifications, but also is commonly associated with microcephaly and MCD that share many features with congenital Zika virus infection. Yet infantile spasms have been linked with CMV infections with otherwise normal imaging as well, indicating additional pathways of cortical dysfunction.

Zika virus appears to mimic the vertical transmission and widespread organ toxicity of the TORCH infections and through its tropism for the developing brain disrupts multiple pathways in neurodevelopment. Congenital Zika virus infection is able to recapitulate a wide variety of malformations of brain development by direct infection of neuroprogenitor cells triggering apoptosis and leading to abnormal proliferation (microcephaly) and of glial cells, particularly astrocytes, thereby disrupting migration (polymicrogyria and focal dysplasia) [10]. Non-specific inflammatory effects such as necrosis, activated microglia and calcium deposition frequently occur in congenital Zika infection, and these changes correlate with persistence of the virus in the CSF of Rhesus Monkeys [11]. Therefore while hypsarrhythmia patterns in Zika virus mirror the most frequent patterns described in MCDs more broadly, the underlying etiology is more complex and may reflect ongoing injury. The electrographic pattern in this case reveals multifocal epileptogenic activity that is maximal in the perisylvian regions, correlating with the regions of most prominent cortical malformation. While treatment led to both clinical and electrographic background improvement, she continues to have occasional focal seizures that have been intractable to medications.

In this case, the congenital Zika virus had been identified and the etiology of the MCD clear, though maternal infections often go unnoticed and the sequelae of TORCH infections may be more subtle. The recognition of Zika virus as the etiology of ES may well be relevant for treatment: There appears to be better efficacy with vigabatrin in cases of ES due to MCDs [12], and viral reactivation from immunomodulating agents such as steroids or ACTH has been documented with CMV and may be a concern with Zika as well.

4. Conclusions

We report this case to expand the etiologic basis for epileptic spasms to include another neurotropic virus, to demonstrate the range of pathology seen in congenital Zika virus infection, and to show that appropriate antiepileptic treatment can resolve background epileptic encephalopathy even in severe cases. This case supports more rigorous monitoring for epileptic spasms in children with congenital Zika virus infection, and illustrates the importance of screening for infectious etiologies in ES.

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