EPILEPSY

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Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "EPILEPSY Newsletter'' which contains latest and interesting news in the field of Neuropsychiatry.

This issue contains:

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Diagnostic yield of continuous video-electroencephalography for evaluating events concerning for seizures in children aged 1–24 months

INTRODUCTION

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The paroxysmal, rhythmic, and repetitive events (PRREs) during infancy can sometimes indicate a medical emergency, requiring immediate evaluation to determine if they are seizures. These events in young infants can involve changes in mental status, vital signs, or various abnormal, repetitive, and rhythmic behaviors. While many of these behaviors may be normal for neurodevelopment and typical child behavior, some might be seizures. Rapid identification and treatment of seizures in infants is essential.[1] Diagnosing epilepsy solely from the description of PRRE semiology or video recordings of these events can often be unreliable.[2] Each year, a substantial number of young patients are admitted to hospitals for the characterization of PRREs using continuous video-electroencephalography (cVEEG). Utilizing cVEEG for this purpose has become the standard of care in these cases.[3] Developing a system to identify candidates who would most urgently benefit from a cVEEG admission for PRRE characterization would be highly advantageous.[1] This study aimed to assess the effectiveness of cVEEG monitoring in diagnosing events suggestive of seizures in children aged 1–24 months.

Children who are more likely to be diagnosed with epilepsy after cVEEG admission can be identified by their unique patient traits, PRRE characteristics, and the presence of EEG interictal abnormalities.

METHODS

A single-center retrospective chart review was conducted among 243 patients, encompassing all children aged 1–24 months who were admitted for PRRE capture and characterization with cVEEG. The review included demographic information, birth and family history, known brain injuries, event semiology, duration, frequency, and interictal EEG features. Odds ratios for predicting seizures were calculated for each of these factors. The primary objective was to determine whether the target PRRE identified during the initial cVEEG admission was confirmed as a seizure.

RESULTS

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During the initial cVEEG admission, 160 participants (65.8%) had their target event of concern captured. Among these, 41 patients (25.8%) were confirmed to have seizures, while the majority (n=119) were diagnosed with non-epileptic events. Variables that predicted seizure likelihood during the initial cVEEG admission included event duration (>1 minute), frequency (≥3 occurrences per week), and the presence of abnormal interictal findings. For patients not diagnosed with epilepsy during the initial admission, the likelihood of a subsequent epilepsy diagnosis was associated with specific PRRE semiology (motor active or motor passive), longer event duration (>1 minute), and abnormal interictal EEG features from the initial cVEEG. Prediction tools and scoring systems for assessing risk in infants with suspected seizures due to PRREs are detailed, and a multivariable model to differentiate seizures from non-seizure events, based on combined patient characteristics and interictal EEG findings from the initial PRRE characterization, as presented in Figure 1.

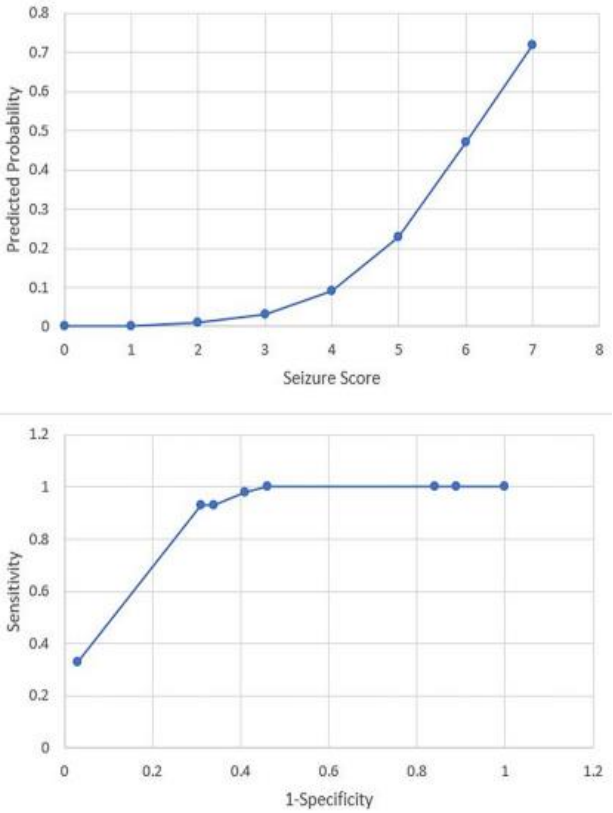

Figure 1. A higher seizure score was linked to a higher likelihood that a paroxysmal, rhythmic, and repetitive event (PRRE) constituted a seizure in patients aged 1 to 24 months who presented for an initial hospitalisation for event characterization using continuous video-electroencephalography.

DISCUSSION

The study concluded that cVEEG is a valuable and effective method for characterizing events and diagnosing epilepsy.[1] Video-EEG monitoring is best used for patients who require detailed event characterization or seizure localization before epilepsy surgery. When there was uncertainty about diagnosing epilepsy or identifying the cause of paroxysmal episodes, ictal video-EEG recording was the most reliable method for making an accurate diagnosis. For specific populations, such as the elderly, where seizures may present with unusual semiology and occur infrequently, video-EEG can be especially helpful in confirming an epilepsy diagnosis.[4]

CONCLUSION

In summary, distinctive PRRE, EEG, and patient characteristics can help identify children who were more likely to have seizure events before their initial cVEEG admission. Continuous video-EEG remains a crucial and effective tool for event characterization and diagnosing epilepsy.

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Single-Channel Seizure Detection and Clinical Validation of Seizure Sites Using the CHB-MIT Dataset

INTRODUCTION

For individuals with refractory epilepsy, the single-channel method offers a significant potential for wearable seizure detection on long-term EEG recordings when combined with clinical classification of the most prominent seizure sites.

Epilepsy is a chronic neurological disorder affecting 0.64% of the global population. Around one-third of individuals with epilepsy experience refractory epilepsy. Electroencephalography (EEG) is a crucial first step in diagnosing epilepsy, and long-term EEG monitoring is vital for managing seizures and developing effective treatment plans. Although automated seizure detection has advanced significantly, its practical use for patients with refractory epilepsy remains limited due to the reliance on multiple EEG channels. The use of numerous electrodes can be uncomfortable for patients and adds significant computational complexity, especially during extended monitoring periods. Recent research into machine and deep learning-based seizure detection methods has explored using four EEG channels placed behind the ear, showing that a reduced number of channels can be effective for automated seizure detection in long-term wearable EEG recordings. However, these methods are often concentrated on detecting seizures primarily in areas near the temporal lobes.[1] Single-channel EEG monitoring offers a convenient solution for patients using wearable devices for extended periods. Employing just one channel can significantly improve comfort and lower complexity during long-term EEG monitoring. A recent study introduced a wearable EEG device, called ear-EEG, which fits in the ear and has shown effectiveness in detecting electroencephalographic seizure patterns in the temporal lobe.[2] This study developed a patient-specific deep learning approach for single-channel seizure detection, utilizing long-term scalp EEG recordings from the Children's Hospital Boston-Massachusetts Institute of Technology (CHB-MIT) dataset, along with neurologists' validation of the spatial seizure characteristics for each individual patient.

METHODS

The researchers chose four EEG channels from the full montage: Fp1-F3, Fp2-F4, P7-O1, and P8-O2. P7-O1 and P8-O2 were selected for their proximity to behind-the-ear positions, while Fp1-F3 and Fp2-F4 were chosen for their placement on the forehead. They identified 13 cases

where seizure locations could be detected by either one or more of these channels. For these 13 patients, they developed seizure detectors for 18-channel, 4-channel, and single-channel configurations. Neurologists reviewed the specific seizure locations for each patient and selected one of the four channels—two near the ear and two on the forehead—based on seizure re-annotation.

RESULTS

In a segment-level evaluation of patient-specific seizure detectors, the 18-channel system demonstrated high performance with a sensitivity of 98.66±1.19%, specificity of 98.47±2.71%, accuracy of 98.47±2.69%, and an AUC of 98.56±1.81% across 13 cases. Among these, chb02 and chb04 achieved the highest accuracy at 99.97±0.03% and 99.97±0.02%, respectively, with sensitivity and specificity values of 98.12±3.25% and 99.97±0.03%, and 98.18±2.52% and 99.97±0.02%, respectively. In contrast, chb15 had the lowest accuracy at 90.33±8.93%, with sensitivity and specificity of 96.20±5.32% and 90.24±9.13%, respectively. The 18-channel system correctly detected 5.9±4.6 seizures, missed 0 seizures, and had 2.4±4.4 false alarms per average recording duration of 7.0±4.1 hours. All patients showed 100% sensitivity, but chb11

Table 1. The mean ± standard deviation of the 13 instances represents the performance of patient-specific seizure detectors for ictal-interictal categorization (segment-level) and seizure detection (event-level).

Segment-level evaluation	Detector	18-channel	4-channel	Single-channel	Single-channel (Publicly available annotation)
	Sensitivity (%)	98.66±1.19	97.31±3.78	96.76±3.97	96.39±2.75
	Specificity (%)	98.47±2.71	97.72±3.61	98.19±1.82	94.92±8.38
	Accuracy (%)	98.47±2.69	97.73±3.59	98.18±1.83	94.93±8.35
	AUC (%)	98.56±1.81	97.51±2.94	97.47±2.77	95.62±4.20
Event-level evaluation	**Sensitivity (%)**	100.00±0.00	97.05±9.23	99.62±1.39	97.69±6.96
	FAR (/h)	0.30±0.47	0.40±0.77	0.22±0.34	0.16±0.26
	Latency (s)	2.1±6.7	3.5±4.8	3.3±5.5	8.0±9.4
	Correctly detected seizure	5.9±4.6	5.8±4.4	5.8±4.3	5.8±4.4
	Missed seizure	0.0±0.0	0.2±0.4	0.1±0.3	0.2±0.4
	False alarm	2.4±4.4	2.9±6.1	1.0±1.2	1.2±2.1

and chb15 had false alarm rates (FAR) of 1.43/h and 1.14/h, respectively. For the 4-channel detectors, the segment-level performance metrics included a sensitivity of 97.31±3.78%, specificity of 97.72±3.61%, accuracy of 97.73±3.59%, and an AUC of 97.51±2.94%, averaged over the 13 cases. The chb04 and chb05 had the highest accuracy at 99.92±0.07% and 99.92±0.06%, with sensitivity and specificity of 93.75±10.83% and 99.92±0.07%, and 99.69±0.70% and 99.92±0.06%, respectively. Conversely, chb15 showed the lowest accuracy at 87.93±10.51%, with sensitivity and specificity of 92.80±9.47% and 87.86±10.79%,

respectively. The 4-channel system had a mean of 5.8±4.4 correctly detected seizures, 0.2±0.4 missed seizures, and 2.9±6.1 false alarms during an average recording time of 7.0±4.1 hours. The chb11 and chb15 recorded FARs of 2.51/h and 1.57/h, while chb17 had the lowest sensitivity at 66.67% but no false alarms. The single-channel detectors performed with a sensitivity of 96.76±3.97%, specificity of 98.19±1.82%, accuracy of 98.18±1.83%, and an AUC of 97.47±2.77% on average over the 13 cases. The highest accuracy was seen in chb02 and chb11, both at 99.94±0.02%, with sensitivity and specificity of 99.75±0.44% and 99.94±0.02%, and 100% and 99.94±0.02%, respectively. On the other hand, chb23 had the lowest accuracy at 93.92±8.54%, with sensitivity and specificity of 87.49±21.67% and 93.96±8.61%, respectively. The single-channel detectors detected an average of 5.8±4.3 seizures correctly, missed 0.1±0.3 seizures, and had 1.0±1.2 false alarms during a mean EEG recording length of 7.0±4.1 hours. No case had an FAR exceeding 1/h. Specifically, chb02 had the highest FAR of 0.88/h with 100% sensitivity, while chb15 had the lowest sensitivity at 95% with an FAR of 0.07/h. Detailed results for the 18-, 4-, and single-channel detectors across the 13 cases were summarized in Table 1.

DISCUSSION

This study found that single-channel seizure detectors achieved an average sensitivity greater than 99% and a false alarm rate (FAR) of less than 0.3 per hour, comparable to multi-channel detectors. Recent research has explored patient-specific automated wearable seizure detection using 4-channel behind-the-ear scalp EEG recordings combined with deep learning and machine learning techniques for real-time seizure identification during long-term EEG monitoring. You et al. reported an average sensitivity of 94.2% and a FAR of 0.29 per hour using variational autoencoder-based methods.[3] In contrast, Swinnen et al. reported 98.3% sensitivity and a FAR of 0.91 per hour with their SVM-based methods, highlighting the convenience of behind-the-ear EEG monitoring, especially for patients requiring continuous observation.[4] Additionally, recent studies have investigated the feasibility of long-term wearable seizure detection using a single-channel EEG sensor, Epilog. Frankel et al. showed that epileptologists could accurately identify seizures in single-channel EEG recordings when sensors were positioned near seizure onset sites, achieving an accuracy exceeding 80%.[5]

CONCLUSION

The single-channel detectors achieved an average sensitivity exceeding 99% and a false alarm rate (FAR) of less than 0.3 per hour, matching the performance of multi-channel detectors. Additionally, re-annotating well-characterized seizures can enhance the performance of single-channel detectors, especially in reducing false alarms and latency. The researchers propose that combining single-channel detection with neurologists' identification of key seizure locations offers significant potential for developing wearable devices designed for long-term seizure monitoring in patients with refractory epilepsy.

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Comparison of the interictal epileptic activity burden in children with genetic drug-resistant epilepsy before and after a standardized treatment with pulsatile corticoid therapy

INTRODUCTION

In addition to lowering the IEA burden, PCT was shown to raise sleep spindle rates, which are critical for cognitive performance.

Drug-resistant epilepsy affects approximately one-third of children with epilepsy. Despite its clinical significance, treating drug-resistant epilepsy remains challenging. Corticosteroids, such as adrenocorticotropic hormone (ACTH) and synthetic preparations, have been widely used since the 1950s to manage infantile spasms, demonstrating effectiveness. In patients with West Syndrome, a form of epileptic encephalopathy characterized by infantile spasms, intramuscular ACTH and oral corticosteroids have been shown to reduce seizures significantly, sometimes leading to complete seizure freedom, and improve electroencephalogram (EEG) findings.[1] However, ACTH can cause significant side effects, including hypercortisolism, cardiac hypertrophy, and electrolyte imbalances.[2] Thus, studies therefore suggest a standardized approach for pulsatile cortisone therapy (PCT) that involves a block design with intervals of hospitalization and high-dose intravenous dexamethasone. Unlike oral steroids, PCT enhances the bioavailability of dexamethasone and allows for patient monitoring throughout the treatment. To our knowledge, there is no systematic prospective study examining the effectiveness of PCT in children with genetic drug-resistant epilepsy. It is also unclear whether PCT might positively impact sleep physiology, such as sleep spindles.[1] A recent study found that a localized decrease in sleep spindles among patients with focal epilepsy was associated with poorer cognitive functioning.[3] This study assessed the burden of interictal epileptic activity (IEA)—measured as the percentage of EEG time with interictal epileptiform discharges (IEDs)—in children with genetic drug-resistant epilepsy both before and after undergoing a standardized PCT.

METHODS

In this retrospective study, children with drug-resistant epilepsy underwent a standardized PCT protocol involving cycles of high-dose intravenous dexamethasone (20 mg/m² body surface area). The final analysis included 24 children. Each patient was hospitalized for 3 days per PCT cycle, and EEGs were recorded both before the treatment began (baseline) and during hospitalization around every second cycle. EEG recordings were taken during both sleep and wakefulness. The study compared the IEA burden before and after PCT. Secondary outcomes included the rate of sleep spindles, seizure frequency, and subjective assessments obtained through a standardized interview.

RESULTS

The IEA burden significantly decreased in EEG recordings after PCT compared to baseline (baseline: 5.4% vs. after PCT: 1.5%, p=0.001, d=−0.41) (Figure 1A). Four patients achieved complete freedom from IEA burden, showing no IEDs or bursts after PCT. Patients who experienced a reduction in seizure frequency had a significantly greater decrease in IEA burden compared to those who did not show a reduction in seizures (IEA burden reduction: 86.7% vs. 5.9%, p=0.025, d=−0.72) (Figure 1A). Spindle rates slightly increased after PCT compared to baseline (baseline: 1.0/min vs. after PCT: 1.6/min, p=0.081, d=0.27) (Figure 1B). Fast spindle rates significantly increased after PCT compared to baseline (baseline: 0.8/min vs. after PCT: 1.5/min, p=0.045, d=0.36), while slow spindle rates showed no significant change (baseline: 0.3/min vs. after PCT: 0.3/min, p=0.407, d=0.04) (Figure 1B). Out of the 24 patients, seizure frequency data were unavailable for four due to a lack of objective clinical symptoms. Among the remaining 20 patients, 17 (85%) showed improvement in seizure frequency, and three (15%) did not. One patient became seizure-free. Quality of life improved for 19 of 24 children (79.2%), and sleep quality improved for 13 of 16 children (81.3%) following PCT. No patient experienced an increase in seizure frequency. No serious adverse effects, such as severe infections or significant weight gain, were reported during PCT. Nineteen patients (79.2%) experienced mild adverse effects including sleepiness (n=10), mood swings (n=9), stomach ache (n=3), restlessness (n=2), reduced appetite (n=2), bloating (n=3), diarrhea (n=1), increased appetite (n=1), weakness (n=1), fever (n=1), muscle pain (n=1), joint pain (n=1), difficulty falling asleep (n=1), and microcytic anemia (n=1). Two patients had elevated blood glucose levels (>140 mg/dL) at admission, but glucose levels normalized during hospitalization.

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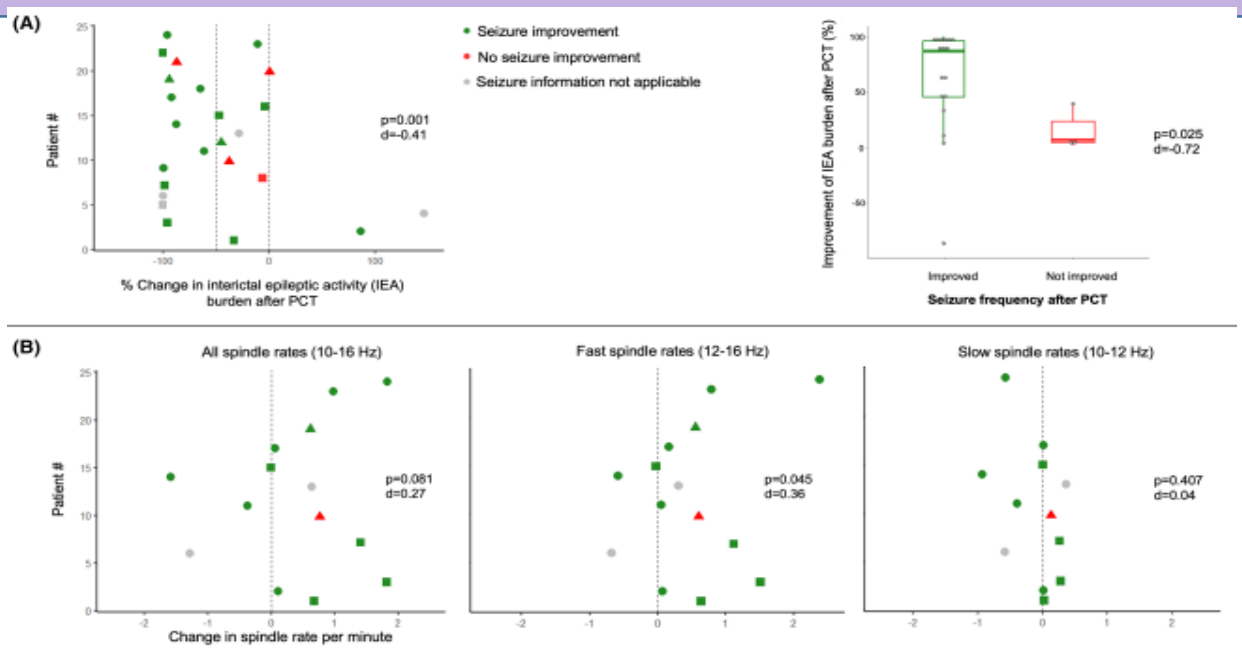

Figure 1. (A) After PCT, there was a noticeable decrease in the IEA burden, shown as a percentage change. A decrease in the IEA burden was shown by percentage changes below zero, while an increase in the IEA burden was indicated by percentage changes above zero. Individuals who experienced fewer seizures per seizure demonstrated a much greater decrease in IEA burden. (B) After PCT, there was no difference in all and slow spindle rates, but fast spindle rates, as seen in the change in rate per minute in N2, were dramatically increased. Every triangle, dot, and square symbolises a single patient. Patients with developmental and epileptic encephalopathy syndromes with gradual neurological deterioration were depicted by a triangle, patients with localised epilepsy by a dot, and patients with generalised epilepsy by a square.

DISCUSSION

PCT not only reduced the epileptic seizure burden but also improved sleep physiology. This study represents the first objective assessment of corticosteroids' effects on sleep physiology, specifically through sleep spindles, in children with genetic drug-resistant epilepsy. Sleep spindles, which are physiological oscillations characteristic of N2 sleep, were notably increased, especially the fast spindles (12–16 Hz), by the end of PCT. This was significant because sleep spindles were crucial for cognitive functions such as learning and memory.[4] Moreover, fast spindles have been shown to be more predictive of cognitive function compared to slow spindles.[5] Thus, PCT might not only reduce the IEA burden but also positively influence sleep physiology and cognitive function.

CONCLUSION

PCT was observed to not only mitigate the pathophysiology of epilepsy but also enhance sleep-related physiological metrics that were crucial for cognitive function. This study could provide a foundation for integrating PCT into clinical practice, given its demonstrated effectiveness and minimal side effects.

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Epileptic Spasms as the Initial Seizure Manifestation in a Case of Congenital Zika Virus Infection in a Newborn with TORCH Syndrome

INTRODUCTION

Early detection of epileptic spasms was likely crucial for long-term developmental outcomes, hence thorough monitoring was necessary for congenital Zika virus infection.

Congenital Zika virus infection has led to an epidemic of children suffering from microcephaly and severe neurodevelopmental disabilities. The consequences of this infection are extensive and include widespread hypertonia, hyperreflexia, irritability, and epilepsy.[1] Seizure rates in congenital Zika virus infection vary from 9% to 54%, encompassing both focal and generalized seizures. Recently, epileptic spasms have been reported in up to 20% of affected children.[2] Research on the classification of epilepsy and electroencephalogram (EEG) findings in congenital Zika virus infection has been limited. However, a case series indicates that over half of affected children exhibit interictal abnormalities and abnormal EEG backgrounds, while 29% meet the criteria for the hypsarrhythmia variant.[3] This report presented a child with confirmed congenital Zika virus infection who developed epileptic spasms, aiming to highlight the spectrum of cerebral pathology associated with the disease and its correlation with epilepsy and EEG findings.

CASE PRESENTATION

A woman delivered a female infant at 39 weeks gestation, with a head circumference of 28.6 cm. The pregnancy was complicated by delayed head growth observed in an ultrasound at 6 months. The delivery was spontaneous and uncomplicated, with APGAR scores of 8 and 9 and a birth weight of 2.55 kg (6^{th} percentile). The neonate initially required brief observation in the neonatal intensive care unit for apnea, which resolved, allowing discharge by day 3. Although the mother did not report any illnesses during pregnancy, she did test positive for Zika virus exposure. Initial tests on the newborn, including RT-PCR for Zika IgM antibodies, confirmed the diagnosis with Zika antigen titers of N1260:1 (positive N320:1). An ultrasound at 2 weeks showed ventriculomegaly and bilateral calcifications at the gray-white matter junction (Figure

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1A, B). Ophthalmological evaluation revealed bilateral chorioretinal lacunae. A brain MRI at 3 months demonstrated reduced brain size with polymicrogyria, predominantly in the bilateral frontal perisylvian and parietal cortical areas (Figure 1C, D, E), along with numerous foci of cerebral calcifications in the bilateral subcortical white matter and gray-white matter interfaces. Clinically, the neonate fed well but exhibited mild hypertonia and irritability. At 6 weeks, her head circumference was 31.7 cm, and she displayed mild irritability, appendicular hypertonia, poor visual tracking, and a leftward gaze preference. By 4 months, her appendicular hypertonia was more pronounced, although she had developed a social smile, improved tracking, head control, and intermittent rolling. However, at this stage, the mother observed the onset of pronounced startle-like episodes with bilateral arm extension, which clustered. There was also a noted reduction in responsiveness, including decreased eye contact, social smiling, and increased sleep disruptions. An EEG revealed frequent multifocal discharges, primarily over the right occipital and bitemporal regions, with slow waves exceeding 300 μV over the right hemisphere and a BASED score of 4, indicating hypsarrhythmia (Figure 2A). Clinical extensor epileptic spasms (ES) were observed, corresponding with high-amplitude slow waves followed by background attenuation (arrow, Figure 2B). Treatment with vigabatrin was initiated and increased to the target dose, resulting in a decrease in the frequency and severity of spasms. After two weeks, the EEG showed no slow waves over 200 μV (BASED score 3) and resolution of hypsarrhythmia, although subtle spasms persisted. The addition of topiramate to the vigabatrin regimen led to a reduction in clinical spasms and improved cooing and sound responsiveness, though spastic quadriplegia remained prominent. A follow-up EEG at 16 months (Figure 2C) displayed sleep spindles in stage II sleep and resolution of hypsarrhythmia but revealed focal epileptiform activity and regional slowing in the right parietal region.

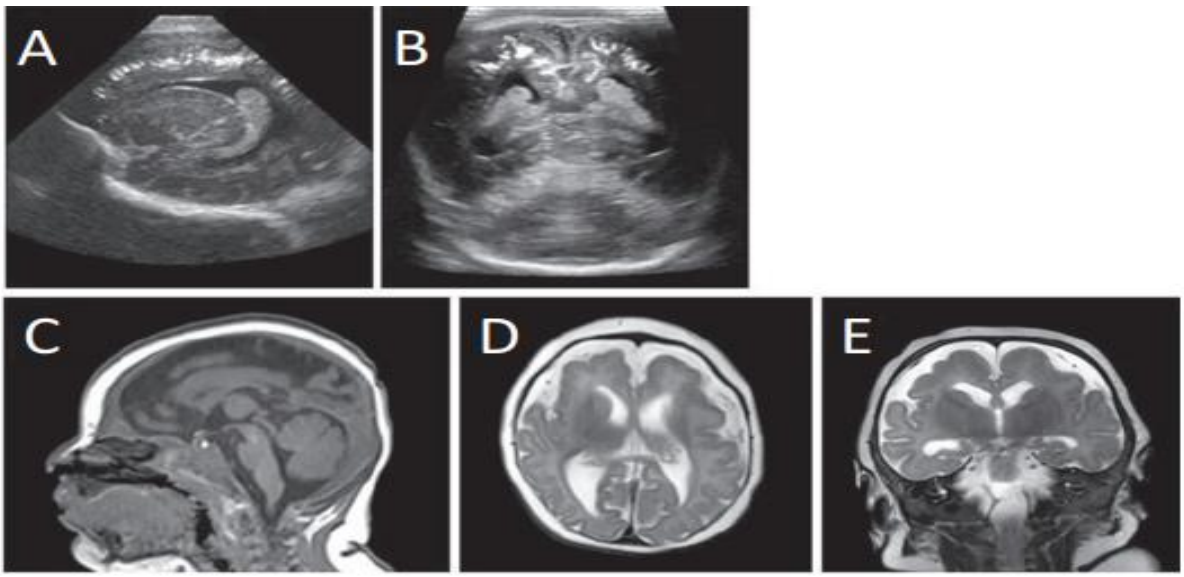

Figure 1. Cranial ultrasonography at one week (A, B). The periventricular and subcortical white matter show significant punctate calcifications in A's parasagittal and B's coronal images via the anterior fontanelle. (C–E) C: Sagittal MPR picture showing tiny supratentorial structures in relation to the brainstem and cerebellum, as well as a small skull in relation to the face. Axial (D) and coronal (E) T2-weighted scans displaying significant bilateral polymicrogyria, primarily in the anterior and superior frontal lobes, and tiny cerebral hemispheres with decreased white matter volume and ex vacuo dilatation of lateral ventricles.

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DISCUSSION

Congenital infections, including those classified under TORCH, are known to contribute to the development of epileptic spasms. Intracranial calcifications are frequently observed in TORCH infections and were linked to increased rates of epilepsy.[4] 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).[5] In this instance, congenital Zika virus infection was confirmed as the cause of the malformations of cortical development (MCD), even though maternal infections from TORCH pathogens can often be asymptomatic, and the consequences may manifest more subtly. Identifying Zika virus as the cause of epileptic spasms (ES) could be crucial for treatment decisions. Vigabatrin has shown greater effectiveness in treating ES associated with MCDs,[6] and viral reactivation, including from cytomegalovirus (CMV), has been observed with the use of immunomodulating agents like steroids or ACTH, and there was a potential concern that similar reactivation could occur with Zika virus.

CONCLUSION

This case emphasized the understanding of epileptic spasms by including another neurotropic virus as a potential cause. It highlighted the diverse range of pathology associated with congenital Zika virus infection and demonstrated that effective antiepileptic treatment can address even severe cases of background epileptic encephalopathy. The case underscores the need for thorough monitoring for epileptic spasms in children with congenital Zika virus infection and shown the importance of screening for infectious causes of epileptic spasms.

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