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Case Report

Rhythmic high-amplitude delta with superimposed spikes (RHADS): a treatment dilemma

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Abstract

Pathognomonic EEG patterns have been described in genetic conditions such as Angelman and Rett syndromes. EEG patterns along the ictal-interictal continuum have been increasingly recognized with the greater availability of continuous EEG monitoring; however, treatment decisions may be difficult with unpredictable clinical implications. Rhythmic High-Amplitude Delta Activity with Superimposed (Poly) Spikes (RHADS) has been described as a particular EEG pattern in POLG1 Alpers Syndrome. The balance between treating subclinical seizures and managing encephalopathy in these patients is challenging.

Keywords: ictal-interictal; POLG; RHADS; Alpers syndrome; occipital seizure

Introduction

Alpers' disease is a childhood onset, rare mitochondrial disorder. A triad of refractory seizures, psychomotor regression, and hepatopathy recognizes it. The clinical course is characterized by recurrent status epilepticus; the most frequent cause of death is liver failure.

Rhythmic High-Amplitude Delta Activity with Superimposed (poly) spikes (RHADS) is a pathognomonic electroencephalography (EEG) signature that may facilitate the recognition of Alpers' disease, thus avoiding antiseizure medication that can trigger liver failure.

This case presentation addresses the early recognition of this EEG pattern in patients with suspected neurometabolic/genetic conditions. It discusses the difficulties in managing this pattern as an ictal-interictal continuum pattern.

Case description

A 16-month-old patient was admitted for febrile status epilepticus and profound hypoglycemia in March 2023.

Seizures were described as staring, limpness, pallor, abnormal breathing, and limb twitching.

Despite an escalation of midazolam infusion and administration of levetiracetam, seizures persisted. Adding lacosamide and phenytoin was effective; midazolam was gradually weaned.

When not sedated, seizures were characterized by eye deviation to the left, arrest of crying, loss of tone, and trunk flexion. Seizures were controlled by optimizing phenytoin. One week later, a non-epileptic, hyperkinetic movement disorder developed.

The patient was discharged after three (3) weeks with significant cortical visual impairment attributable to an occipital lobe injury.

Past medical and family history

The patient was born to non-consanguineous parents after an uneventful pregnancy. Vaccines were up-to-date.

Before hospitalization, the patient had recently started cruising, standing by walking the hands up the body. The patient's speech, language, and social milestones were appropriate.

Since early adulthood, the patient's maternal grandmother had episodic hypoglycemia. The maternal uncle was diagnosed with type 1 diabetes mellitus at 9 years of age. His comorbidities included anxiety, mood disorder, and pervasive developmental disorder. A paternal male cousin experienced a similar event at 18 months old.

Diagnostic assessment

Neuroimaging (Fig. 1)

MRI head revealed gyral swelling with cortical and subcortical diffusion in both occipital/temporal regions, ventrolateral thalami, and splenium of the corpus callosum. No lactate peaks were observed in M.R. spectroscopy.

Three (3) weeks later, the swelling improved, with mild brain volume loss.

EEG findings

Description of ictal-interictal continuum (IIC) pattern (Fig. 2)

Continuous, bilateral independent, rhythmic, very high-amplitude delta activity with overlying fast activity, spikes, sharp waves, and polyspikes (rhythmic delta activity with fast activity and spikes/sharp waves—RDA + FS) was observed over the posterior quadrants (maximal occipital). Over the right occipital region, (O2), amplitudes reached 880 Mv; left occipital (O1), 600 μV (midline central, (Cz), reference) {Normal amplitude 20–150 μV}; frequency fluctuated (0.75–1 Hz O1 and 1–1.5 Hz O2). No clinical

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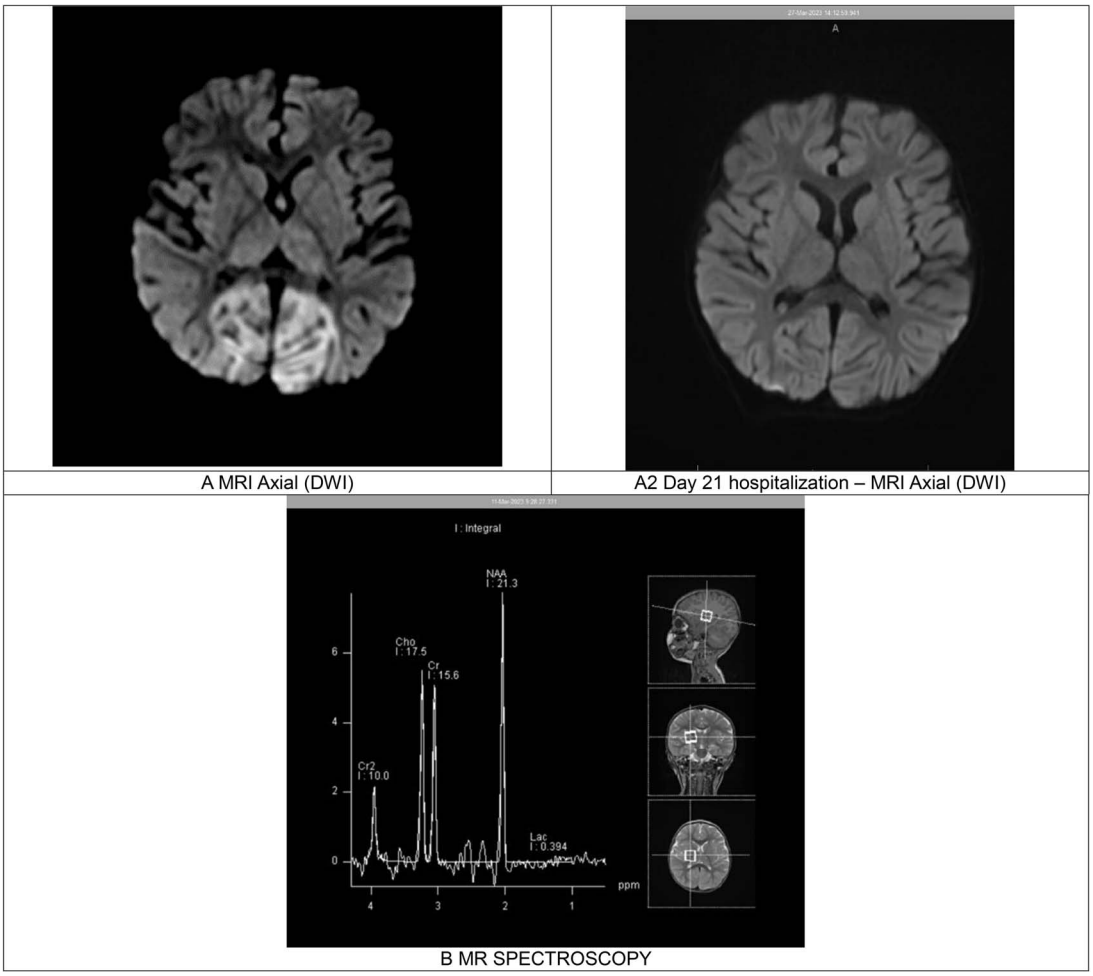

Figure 1. Neuroimaging Findings. A1-2: gyral swelling with cortical and subcortical diffusion in both occipital/temporal regions seen initially in comparison to repeat imaging 21 days after. B: No abnormal lactate peak was identified on MR spectroscopy.

signs were associated with this pattern; no change in pattern with antiseizure drug loading.

Description of electrographic seizures

This pattern evolved with a change in frequency (<1 Hz to 1.5 Hz) and morphology (sharply contoured delta activity with intermixed spikes, then 1.5–2 Hz polyspikes and wave) until ictal offset. Electrographic onset was either left occipital, right occipital, or bi-occipital, with bilateral field involvement. Diffuse background attenuation was observed at the end of the seizure.

Description of clinical seizures (focal unaware, non-motor onset with staring, autonomic symptoms)

The patient opened their eyes with minimal blinking and unclear deviation. The electrographic onset occurred at O1 and evolved in morphology, frequency, and field involvement. The EKG rate decreased from 100–110 bpm to 60 bpm for up to 30 s with field involvement of O2.

Etiological investigations

Whole Exome Sequencing (WES): heterozygous for two pathogenic mutations in the POLG gene: C.3483-4_3497 del, splicing; c2243G > C, p.Trp748Ser.

Supportive investigations

Echocardiogram: normal biventricular systolic function

CSF lactate—2.9 mmol/l

Creatine kinase—189 IU/l

Ultrasound abdomen: Homogenous liver parenchyma, no focal abnormalities, no enlargement. Normal color and spectral Doppler blood flow within the hepatic, portal veins, hepatic artery.

Treatment of seizures

During continuous EEG monitoring, increasing the midazolam infusion did not affect the persistent bi-occipital pattern, leading to the hypothesis that this may be along the ictal-interictal continuum. Once the appropriate phenytoin drug level was achieved, seizure frequency decreased. Seizures resolved after optimizing phenytoin maintenance and adding lacosamide. Continuous EEG recording was discontinued when seizure freedom for 48 h was achieved.

Due to the concern of a mitochondrial neurological condition, sodium valproate was avoided.

Follow-up

Hospitalizations

The patient presented at 19 months with a 1-day history of left arm jerking, otherwise well at neurological baseline. Epilepsia partialis continua (EPC) correlated with left arm jerks.

Repeat MRI showed progression of cerebral volume loss, pronounced in the occipital lobes. No abnormal peaks were identified on M.R. spectroscopy.

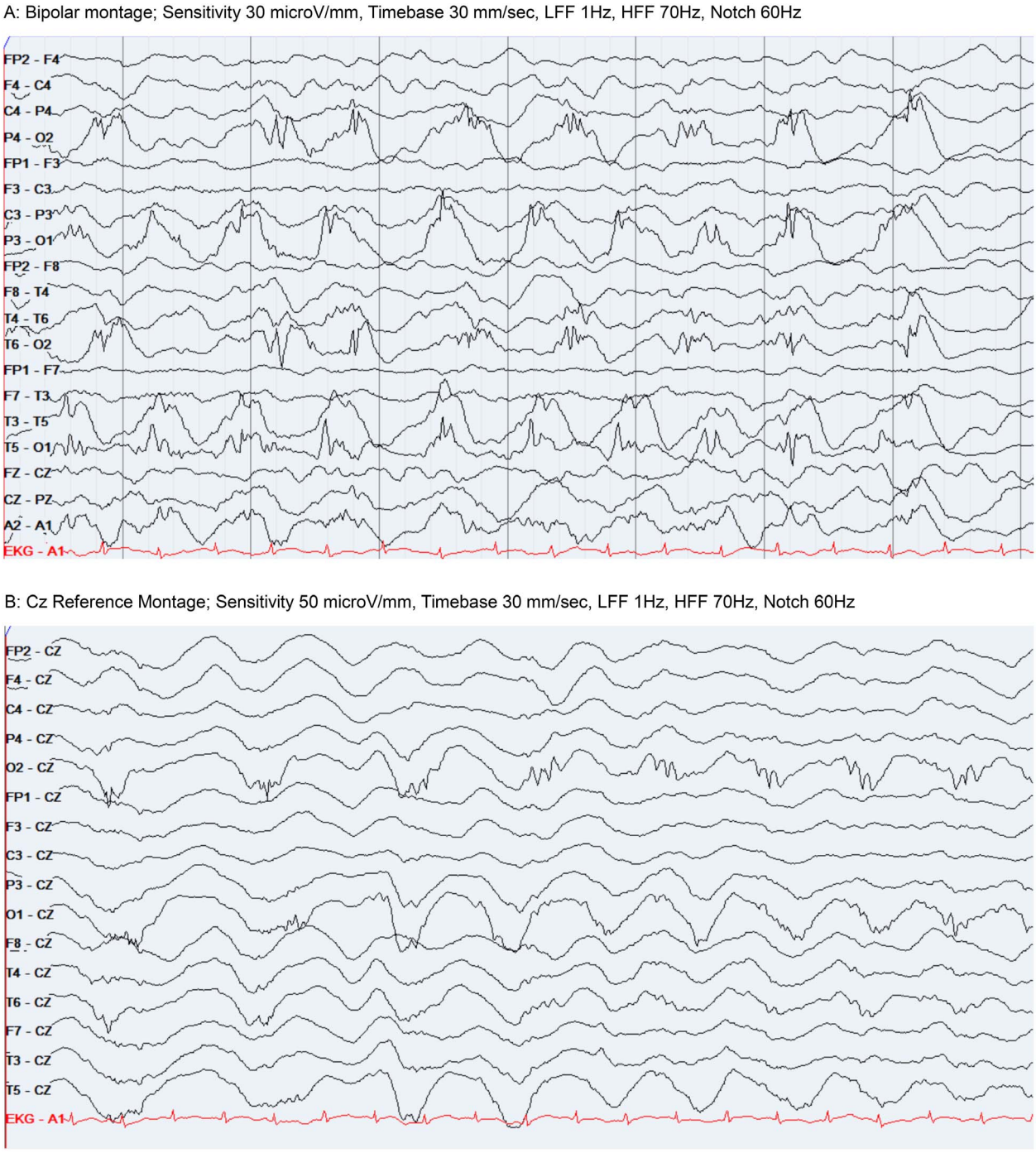

Figure 2. Rhythmic High-Amplitude Delta Activity with Superimposed Spikes (RHADS) EEG pattern. (**A**) Bipolar montage; Sensitivity 30 microV/mm, Timebase 30 mm/s, LFF 1 Hz, HFF 70 Hz, Notch 60 Hz. (**B**) Cz Reference Montage; Sensitivity 50 microV/mm, Timebase 30 mm/s, LFF 1 Hz, HFF 70 Hz, Notch 60 Hz.

Liver enzymes were also elevated; phenytoin was weaned off, and ursodiol was started.

Treatment

Antiseizure medications: lacosamide 10 mg/kg/day, levetiracetam 100 mg/kg/day, Topiramate 6.5 mg/kg/day.

Mitochondrial treatments: leucovorin 5 mg daily, ascorbic acid 50 mg daily, Coenzyme Q10 40 mg twice daily, Vitamin E 100 international units daily.

Ursodiol 60 mg twice daily.

The patient was followed by pediatric neurology, biochemical genetics, gastroenterology, ophthalmology, and early intervention programs.

Development

At 21 months, five months after the initial hospitalization, the patient could sit independently, crawl, and pull to stand. The patient used their hands to reach, transfer, and feed. The patient could say three words, reacted appropriately to sounds, interacted, and bonded with parents.

The patient's vision remained suboptimal, with a binocular visual acuity of 20/540.

Discussion

We present the case of a 16-month-old patient with febrile status epilepticus and hypoglycemia, who later developed a hyperkinetic movement disorder. The maternal family history was significant for impaired glucose control. There was a history of delayed walking with proximal myopathy.

Continuous EEG monitoring showed bi-occipital rhythmic high-amplitude delta activity with superimposed (poly) spikes (RHADS), pathognomonic of Alpers' disease, and sodium valproate was avoided. This pattern, along the ictal/interictal continuum, did not improve despite the escalation of antiseizure treatment, and the patient became exceedingly sedated and drowsy. Therefore, acute antiseizure treatment was administered solely when this pattern evolved.

A pattern on the ictal/interictal continuum (IIC) does not qualify as an electrical seizure or status epilepticus but may contribute to impaired alertness and neuronal injury [1]. The pattern identified was a rhythmic delta activity averaging 1.0 Hz that occurred persistently over 10 s with an additional modifier of (poly)spikes. It did not qualify as an electrical seizure or status epilepticus, as a diagnostic antiseizure drug trial was ineffective.

Alpers syndrome is an early-onset neurodegenerative disorder caused by biallelic pathogenic variants in POLG, essential for mitochondrial DNA replication. Without hepatopathy, this pathognomonic "RHADS" EEG finding may help diagnose the early stages of Alpers syndrome [2, 3]. In one study, the incidence of RHADS was described in 18 of 29 patients (62.1%) with Alpers syndrome [4]. RHADS and slowing were commonly identified in the occipital region (57.1%), then the frontal (28.6%) and temporal (14.3%) regions. Using the corresponding wavelet transform method, gamma oscillations described in four patients showed time-frequency spectra exhibiting spectral blobs at 30–80 Hz associated with corresponding spikes, supporting the idea that RHADS is a type of epileptic phenomenon. This pattern progressively consisted of fewer spikes within the rhythmic delta activity in our patient's follow-up EEGs.

In this case, the other confounders were the initial hypoglycemia and occipital lobe injury. The EEG presentation of hypoglycemia involves low-frequency, middle-amplitude delta-to-theta activity [5]. Thus, recognizing a very high-amplitude rhythmic delta activity was crucial to exploring other possibilities.

The occipital cortex has the highest metabolic activity in the brain and is therefore vulnerable to impaired respiratory chain function [6]. The magnitude of respiratory chain deficiency is more pronounced in interneurons, with loss of inhibitory neural networks playing a role in seizure development [7], contributing to the vulnerability of the occipital lobes in this patient subset.

Extrapyramidal features have been described in patients with *POLG* mutations [8], but the underlying mechanisms are not fully understood. One retrospective U.K. study analyzing cerebral spinal fluid neurotransmitter profiles in pediatric patients with confirmed biallelic *POLG* mutations indicated that aberrant dopamine and serotonin metabolism may play a role [9].

Conclusion

The identification of the RHADS pattern was helpful in guiding investigations and management, especially in the absence of hepatopathy. This also led us to consider an underlying mitochondrial condition due to the very high-amplitude morphology of the bi-occipital delta activity compared to the lower amplitude delta/theta activity observed due to hypoglycemic brain injury. The balance between over-treatment of this ictal-interictal pattern (IIC) and the sedation effects of drugs administered was addressed early, with optimization of antiseizure drugs when this pattern evolved in frequency, morphology, and field involvement. The recognition of this IIC pattern as a pathognomonic finding of Alpers syndrome should be further highlighted in the literature.

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Author contributions

All authors contributed to preparing this report and approved the article's final version.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

All procedures performed in studies involving human participants were per the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent

The authors declare that this report does not contain any personal information that could lead to identifying the patient(s) and volunteers. Written informed consent was obtained from the patient/parent for the publication of the manuscript.

Guarantor

Dr Vanita Shukla.

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