



# 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 highly specific EEG pattern in POLG1 Alpers Syndrome.
- The balance between treating subclinical seizures and managing encephalopathy in these patients is challenging.

## Keywords

Ictal-interictal, POLG mutation, RHADS EEG pattern, Alpers Syndrome, Focal occipital seizure onset

## Introduction

Rhythmic High-Amplitude Delta Activity with Superimposed (poly)spikes (RHADS) is a pathognomonic electroencephalography (EEG) signature that may facilitate the recognition of Alpers' disease and allow timely avoidance of anti-seizure medication that can trigger liver failure.

The aims of this case presentation are:

- 1) To address the early recognition of this EEG pattern in patients with suspected genetic or neurometabolic conditions.
- 2) To discuss the difficulties in managing patients with RHADS on continuous EEG/ICU monitoring as an ictal-interictal continuum pattern.

Level of Clinical Evidence: 4

## Case Description

A 16-month-old female was admitted to the pediatric intensive care unit for management of febrile status epilepticus and profound hypoglycemia in March 2023 [1].

Seizures were described as staring with limpness of her body, pallor, abnormal breathing and limbs twitching.

The patient experienced frequent subclinical and clinical seizures. The clinical events witnessed were described as sudden eye opening, staring, and eye deviation of unclear laterality occasionally associated with bradycardia. Midazolam

infusion was escalated, and loading doses of levetiracetam were administered; however, she continued to experience seizures. The addition of lacosamide and phenytoin was effective, and midazolam was gradually weaned.

When she was no longer sedated, her seizures were characterized by eyes deviation to the left, arrest of crying, loss in tone, and neck and trunk flexion. Seizures were controlled by optimizing the phenytoin dose. One week after presentation, she developed a persistent non-epileptic, hyperkinetic movement disorder involving her limbs.

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

## Past medical and family history

Before hospitalization, her development was mildly

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delayed. At 16-months-old, she had recently started cruising but stood up from the floor by walking her hands up her body, suggesting functional gross motor weakness. Her speech, language, and social milestones were appropriate.

Her maternal grandmother had a history of hypoglycemia of unclear etiology since early adulthood. 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, not otherwise specified. A paternal male cousin experienced a similar event at 18-months-old; managed for febrile status epilepticus, lost developmental skills, and took time to recover to baseline.

## Diagnostic Assessment

### Investigations

**Neuroimaging:** Initial MRI of the head revealed gyral swelling with cortical and subcortical diffusion in both occipital/temporal regions, fornices, ventrolateral thalami, and splenium of the corpus callosum. No lactate peaks were observed in these areas in MR spectroscopy.

Three (3) weeks later, improvement was noted in this swelling, with mild brain volume loss.

#### EEG findings

**Description of ictal-interictal continuum (IIC) pattern:** Continuous bilateral independent rhythmic very high-amplitude delta activity with overlying fast activity, spikes, sharp waves, and polyspikes (RDA+FS) were observed over the bilateral posterior quadrants and maximal over the occipital areas. Over the right occipital region, (O2), this reached amplitudes of 880mV and left occipital (O1) to 600  $\mu$ V (midline central, (Cz), reference). Frequency fluctuated, generally 0.75-1 Hz over O1 and 1-1.5 Hz over O2. No definite evolution was observed. No clinical signs were associated with this pattern.

**Description of electrographic seizures:** There was an evolution of the rhythmic delta activity with a change in frequency from < 1 Hz to 1.5 Hz, and morphology to sharply contoured delta activity with intermixed spikes then polyspikes and wave at 1.5-2 Hz until ictal offset. The 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 non-motor onset with staring, autonomic symptoms; decreased awareness):** The patient initially opened her eyes with minimal blinking. It was unclear whether her eyes deviated in a particular direction. The electrographic onset occurred at O1 and evolved in morphology, frequency, and field involvement. The EKG rate decreased from baseline HR (100-110 bpm) to 60 bpm for up to 30 seconds 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; no left ventricular hypertrophy or dilation.

CSF lactate - 2.9 mmol/L

Creatine kinase - 189 IU/L

**Ultrasound abdomen:** The liver parenchyma was homogeneous in echotexture, with no focal abnormalities identified, and was not enlarged. Normal color and spectral Doppler blood flow within the hepatic veins, portal vein, and hepatic artery.

### Treatment of seizures

During continuous EEG monitoring, it was noted that increasing the midazolam infusion had no effect on the persistent bi-occipital pattern observed, leading the team to hypothesize that this may be along the ictal-interictal continuum. Phenytoin loading and optimization had the greatest effect on seizure activity.

Due to the possible concern of an underlying mitochondrial neurological condition, sodium valproate was avoided when escalating anti-seizure treatment.

### Follow-Up

**Hospitalizations:** She presented at 19-months with a 1-day history of left arm jerking movements and was otherwise well at her neurological baseline. A routine EEG showed that epilepsy partialis continua (EPC) correlated with left arm jerks.

Repeat MRI showed progression of cerebral volume loss, most pronounced in the occipital lobes, with some gyriiform T2 hyperintensities. Prominent hippocampal atrophy and patchy T2 hyperintensities in the thalami were also noted. No abnormal peaks were identified using the MR spectroscopy.

Her liver enzyme level was also elevated, thought to be related to phenytoin. Phenytoin was weaned off, and ursodiol was started.

**Development:** At 21 months of age, five months after her initial hospitalization, she was able to sit up, support her head, started crawling and pulling to stand, but not walking. She used her hands to reach (impaired by low vision), transfer, and feed herself. She could say three words, was interactive, and was bonded with her parents.

Her vision remained suboptimal, with a binocular visual acuity of 20/540. She reacted appropriately to the sounds.

#### Treatment

**Anti-seizure 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 once a day, Coenzyme Q10 40 mg twice daily, Vitamin E 100 international units once a day.

Ursodiol 60 mg twice a day.

She was followed by a multidisciplinary team, including pediatric neurology, biochemical genetics, gastroenterology, ophthalmology, and early intervention programs.

## Discussion

We present the case of a 16-month-old girl who presented with febrile status epilepticus and hypoglycemia, with a developmental and family history suggestive of an underlying genetic condition with neurological effects. Her maternal family history was significant for impaired glucose control, and she had a history of delayed walking, with evidence of proximal myopathy. In addition to focal non-motor seizures with behavioral arrest, autonomic symptoms, and tonic motor symptoms, the patient developed a hyperkinetic movement disorder.

Continuous EEG monitoring showed bi-occipital rhythmic high-amplitude delta activity with superimposed (poly)spikes (RHADS), pathognomonic of Alpers' disease. This finding led us to avoid sodium valproate when treatment was escalated. Additionally, this pattern along the ictal/interictal continuum, did not improve despite the escalation of anti-seizure treatment, and the patient became exceedingly sedated and drowsy. Therefore, a team decision was made for acute antiseizure treatment solely when this pattern evolved.

A pattern on the IIC does not qualify as an electrical seizure or status epilepticus, but there is a reasonable chance that it may contribute to impaired alertness, causing other clinical symptoms, and/or contributing to neuronal injury [1]. The IIC pattern identified here was a rhythmic delta activity averaging 1.0 Hz that occurred persistently over a 10-second period with an additional modifier of (poly)spikes. It did not qualify as an electrical seizure or status epilepticus, as a diagnostic anti-seizure drug trial was ineffective.

The diagnostic criteria for mitochondrial encephalopathy is described as a clinical triad of refractory seizures, psychomotor regression, and hepatopathy. In the absence of hepatopathy, this pathognomonic "RHADS" EEG finding may be useful for diagnosing the early stages of Alpers syndrome. In one study, the incidence of RHADS was described in 18 of 29 patients (62.1%) with Alpers syndrome [2-4]. RHADS and slowing were the most common factors identified in the occipital region (57.1%), followed by impairments in the frontal lobe (28.6%) and temporal (14.3%) regions. Gamma oscillations were described in four patients in this series using the corresponding wavelet transform method, with the time-frequency spectra exhibiting spectral blobs at approximately 30-80 Hz in association with the corresponding spikes. This finding supports the idea that RHADS is a type of epileptic phenomenon. This pattern progressively consisted of fewer spikes within the semi-rhythmic delta activity in the follow-up EEG's for our patient.

In this case, the other confounder was the initial hypoglycemia and supportive findings of occipital lobe injury. However, the EEG presentation of hypoglycemia involves low-frequency and middle-amplitude delta-to-theta activity [5]. Thus, the recognition of a very high-amplitude rhythmic delta activity was a crucial finding that led the team to explore other possibilities.

The occipital cortex has the highest metabolic activity in the brain; thus, it is vulnerable to impaired respiratory chain function. Specifically, the magnitude of respiratory chain deficiency has been found to be more pronounced in interneurons, with the loss of inhibitory neural networks playing a role in seizure development [6,7]. Severe respiratory chain defects and loss of interneurons were prominent in the occipital lobes, contributing to the vulnerability of the occipital lobes in this patient subset.

Extrapyramidal features, including dystonia, Parkinsonism, and tardive dyskinesia, have been described in patients with *POLG* mutations [8]. The mechanisms underlying movement disorders in *POLG* are not fully understood; however, one retrospective UK 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 in comparison 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 anti-seizure drugs when this pattern evolved in frequency, morphology, and/or 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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Not applicable.

## Ethical Compliance

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

## Authors Contribution

All authors contributed to the preparation of this report and approved the final version of the article.

## Declarations of Interest

None.

## References

1. Hirsch LJ, Fong MWK, Leitinger M, et al. (2021) American clinical neurophysiology society's standardized critical care EEG terminology: Version. *J Clin Neurophysiol* 38: 1-29.
2. Wolf NI, Rahman S, Schmitt B, et al. (2009) Status epilepticus in children with Alpers' disease caused by *POLG1* mutations EEG and MRI features. *Epilepsia* 50: 1596-1607.

3. van Westrhenen A, Cats EA, van den Munckhof B, et al. (2018) Specific EEG markers in POLG1 Alpers' Syndrome. *Clin Neurophysiol* 129: 2127-2131.
4. Li H, Wang W, Han X, et al. (2021) Clinical attributes and electroencephalogram analysis of patients with varying Alpers' syndrome genotypes. *Front Pharmacol* 12: 669516.
5. Sejling AS, Kjær TW, Pedersen-Bjergaard U, et al. (2015) Hypoglycemia-associated changes in the electroencephalogram in patients with type 1 diabetes and normal hypoglycemia awareness or unawareness. *Diabetes* 64: 1760-1769.
6. Iizuka T, Sakai F, Kan S, et al. (2003) Slowly progressive spread of the stroke-like lesions in MELAS. *Neurology* 61: 1238-1244.
7. Hayhurst H, Anagnostou ME, Bogle HJ, et al. (2019) Dissecting the neuronal vulnerability underpinning Alpers' syndrome: A clinical and neuropathological study. *Brain Pathology* 29: 97-113.
8. Luoma P, Melberg A, Rinne JO, et al. (2004) Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: Clinical and molecular genetic study. *Lancet* 364: 875-882.
9. Papandreou A, Rahman S, Fratter C, et al. (2018) Spectrum of movement disorders and neurotransmitter abnormalities in paediatric POLG disease. *J Inher Metab Dis* 41: 1275-1283.

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