

Clinical Reasoning: Pediatric Seizures of Unknown Cause

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Abstract

We describe a neonate and a 14-month-old child presenting with seizures that were not (completely) controlled with antiepileptic medications. There were no signs of infection, and electrolytes and neuroimaging were normal. In the neonate, pyridoxine was administered followed by cessation of seizures, and a diagnosis of pyridoxine-dependent epilepsy (PDE-ALDH7A1, a neurometabolic disorder of lysine metabolism) was genetically confirmed. The 14-month-old child received a genetic diagnosis of PDE-ALDH7A1 after abnormalities in the metabolic investigations. Both children were treated with pyridoxine and adjunct lysine reduction therapy (LRT). Seizures were controlled completely, but both children are developmentally delayed. During her second pregnancy, the mother of the neonate was started on pyridoxine treatment because of the risk of PDE-ALDH7A1. After delivery, pyridoxine treatment was continued in the neonate, who did not show any clinical symptoms. Molecular analysis identified the familial variants consistent with the diagnosis of PDE-ALDH7A1. Adjunct LRT was initiated. This child has never experienced seizures, and development has been completely normal thus far (age 2.9 years), despite the shared genotype with their sibling with developmental delays (DDs). In conclusion, in neonates, infants, and children presenting with seizures of unknown origin with partial or no response to common antiepileptic medications, the diagnosis of PDE-ALDH7A1 or other pyridoxine-responsive genetic epilepsies should be considered, prompting a trial of pyridoxine as “diagnostic therapeuticum.” The digital application *Treatable-ID* (treatable-id.org) can support clinicians in the early diagnosis of treatable conditions in patients presenting with DD/intellectual disability of unknown cause.

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Section 1

Case 1

A female neonate, born after an unremarkable pregnancy as the first child to nonconsanguineous parents, presented at the age of 8 days with poor intake, irritability, and abnormal breathing.¹ After a cyanotic event with jerking of the left arm, she was transferred to a tertiary care hospital. Episodes of rhythmic lip pursing and rhythmic waist flexion and extension, accompanied by a scream and mild bilateral hand tremor, developed into a status epilepticus. Following the protocol, benzodiazepines, phenytoin, and phenobarbital were administered, which abated, but did not resolve the seizures. Brain CT, magnetic resonance imaging, and spectroscopy and angiography (MRI/MRS/MRA) were unremarkable. Electroencephalography (EEG) did not capture seizures.

Questions for Consideration for Case 1 With Status Epilepticus:

1. What is the differential diagnosis?

2. What kind of investigations would you initiate at this point?

Case 2

A 14-month-old girl was seen at the outpatient clinic for recurrent generalized seizures. Her medical history included normal psychomotor development but several seizure episodes since the age of 8 months and one pediatric intensive care unit admission with status epilepticus. Brain MRI and interictal EEG were normal, lumbar puncture showed no signs of infection, and electrolytes were within normal limits. Her parents had not wanted to start anti-epileptic medication yet, except for rectal midazolam as rescue medication.

Questions for Consideration for Case 2:

1. What is the differential diagnosis for her seizures?
2. Would you initiate investigations at this point? If so, which ones?

GO TO SECTION 2

Section 2

Case 1

The differential diagnosis for neonatal seizures in this patient includes electrolyte disturbance, CNS infection, inherited metabolic disorder, epilepsy syndrome, and benign convulsions. Cerebral bleeding, infarction, malformation of cortical development, and hypoxic-ischemic encephalopathy are highly unlikely given the normal neuroimaging.

At 10 days of age, a video EEG did not capture electrographic seizures but did show excessive discontinuity in wakefulness and non-REM sleep, with periods of sharply contoured alpha/theta frequency interrupted by background attenuation, reflecting moderate to severe encephalopathy. Following 100-mg intravenous pyridoxine and phenobarbital administration, complete cessation of seizures and improvement on EEG were noted. Oral pyridoxine 30 mg/kg/d in 2 dosages was then continued. Targeted single gene testing revealed compound heterozygous variants in *ALDH7A1* c.834G>A (p.Val278=) and c.1489+5G>A (both previously reported²), confirming the diagnosis of pyridoxine-dependent epilepsy (PDE-*ALDH7A1*). She had borderline gross motor and speech delay.

Adjunct lysine reduction therapy (LRT) was initiated at the age of 1.7 years: a protein-restricted diet with an amino acid mixture (AAM; GlutarAde Essentials) and arginine supplementation (150 mg/kg once per day). However, taste issues caused poor adherence.

After LRT initiation, steady developmental progress was reported, but speech remained delayed. Biochemically, plasma α -aminoadipic semialdehyde (α -AASA) (measured first at age 4.9 years) has always been elevated and varied between 18.9 and 70.8 μ M (reference <3.1 μ M). At the age of 3.7 years, a Wechsler Preschool and Primary Scale of Intelligence (WPPSI) showed a full-scale Intelligence Quotient (FSIQ) of 87, thus within normal limits. At the age of 8.8 years, she is a year behind her peers. She attends mainstream classes with an individualized educational plan for math, language arts, and writing with special education support 3.5 h/d. Since the initiation of pyridoxine, she has remained seizure-free.

During her second pregnancy, the mother of case 1 started with prenatal pyridoxine treatment (100 mg/d) at 16 weeks' gestation because of the risk of PDE-*ALDH7A1*. After an unremarkable delivery, pyridoxine treatment (30 mg/kg/d) was initiated in the female neonate, who did not show any clinical symptoms. Biomarker analysis revealed plasma pipercolic acid (PA) of 26.4 μ mol/L (reference <5.2 μ mol/L) and α -AASA of 30.0 μ mol/L (reference <1.6 μ mol/L). Molecular analysis identified the familial variants consistent with the diagnosis of PDE-*ALDH7A1*. Adjunct LRT (protein-restricted diet and arginine supplementation) was initiated at day 16 of life; AAM was started at birth but discontinued due

to insurance denial and costs. At age 2.9 years, her speech/language and motor skills are age appropriate. She has never experienced seizures.

Case 2

The differential diagnosis in this 14-month-old girl with recurrent seizures, normal neuroimaging, and no signs of infection or electrolyte disturbance includes a genetic (epilepsy syndrome) and inherited metabolic disorder.

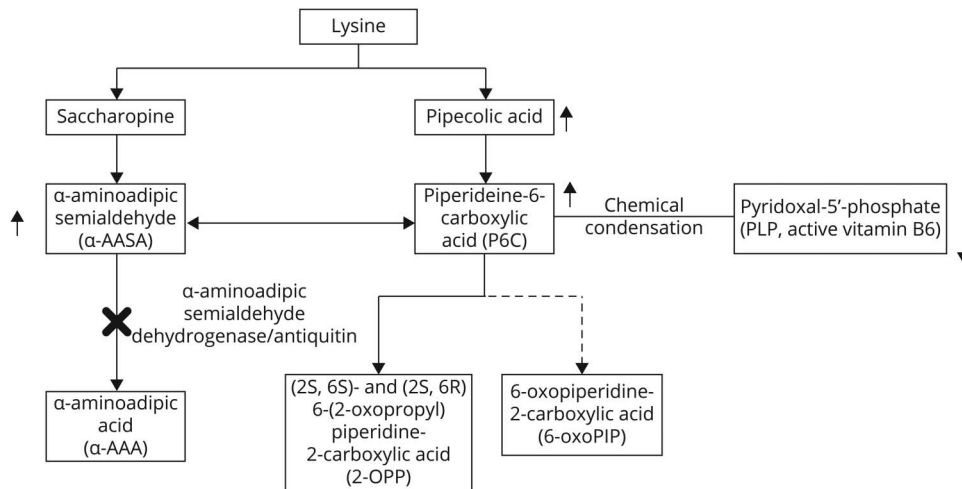
Metabolic investigations were performed in blood, urine, and CSF and showed increased PA in CSF and increased urine α -AASA. Molecular analysis (GenBank accession# NM_001182.4) revealed previously unreported (gnomAD and ESP) compound heterozygous variants c.632G>A (p.Cys211Tyr) predicted as likely pathogenic and c.1415+10T>C p.? shown in vitro to cause nonsense-mediated RNA decay. Pyridoxine was initiated from the age of 14 months, arginine supplementation of 250 mg/kg/d at age 5.9 years, and a lysine-restricted diet (protein intake 1.2 gram/kg/d) at age 6.5 years. AAM was refused by the patient. After LRT initiation, α -AASA decreased by 10-fold. The WPPSI at age 6.2 years showed an IQ of 83, and the Wechsler Intelligence Scale for Children (fourth edition) showed a FSIQ of 76 at age 7.3 years. She is enrolled in regular education, and after LRT initiation, subjective improvements (improved focus and energy and better social interactions) were noted by mother and teachers. Since the start of pyridoxine, the patient has experienced no further seizures (current age 9 years).

Discussion

Pyridoxine-dependent epilepsy due to α -AASA-dehydrogenase deficiency (PDE-*ALDH7A1*) is a neurometabolic disorder of the lysine degradation pathway. Because of the deficiency of the enzyme α -AASA-dehydrogenase, accumulation of α -AASA and its cyclic form Δ -1-piperideine-6-carboxylate (Δ 1-P6C) occurs, leading to an inactivation of pyridoxal-5-phosphate (PLP), the active form of vitamin B6.³ Recently, new biomarkers (2S,6S- and 2S,6R-oxopropylpiperidine-2-carboxylic acid [2-OPP] and 6-oxopiperidine-2-carboxylic acid [6-oxoPIP]) have been discovered (Figure 1).⁴ PDE-*ALDH7A1* is characterized by seizures, and most patients suffer developmental delay (DD) or intellectual disability (ID). Typically, PDE-*ALDH7A1* presents in the neonatal period; however, atypical, late-onset presentations occur as well, usually milder and with better neurodevelopmental outcomes.^{5,6}

The secondary PLP depletion is overcome by pharmacologic doses of pyridoxine, which can control seizures throughout a lifetime and is a "diagnostic therapeuticum." As clearly illustrated by these cases, pyridoxine should be trialed in any neonate or child whose epilepsy is uncontrolled by common antiepileptic medications. A pyridoxine trial should be initiated directly on suspected diagnosis while taking the

Figure 1 Lysine Metabolism and Pyridoxine-Dependent Epilepsy Because of α -AASA-Dehydrogenase Deficiency (PDE-ALDH7A1)



necessary precautions because intravenous administration can cause apnea. Even in the absence of a direct positive effect, this should be followed by biochemical and molecular confirmation of PDE-ALDH7A1 because pyridoxine does not affect disease biomarkers. This is important for counseling reasons as well, as illustrated by the sibling of case 1.

In addition to PDE-ALDH7A1, the differential diagnosis of pyridoxine-responsive seizures includes other neurometabolic conditions, such as neonatal/infantile hypophosphatasia (TNSALP deficiency), hyperprolinemia type II deficiency, PLP-binding protein (PLPBP) deficiency, and pyridoxamine 5'-phosphate oxidase (PNPO) deficiency. This is not surprising given that PLP acts as a cofactor for more than 140 enzymatic reactions, many of which in the CNS. Even in the absence of response to pyridoxine, the effect of PLP should be evaluated as PNPO deficiency responds only to this B6 vitamin.⁷

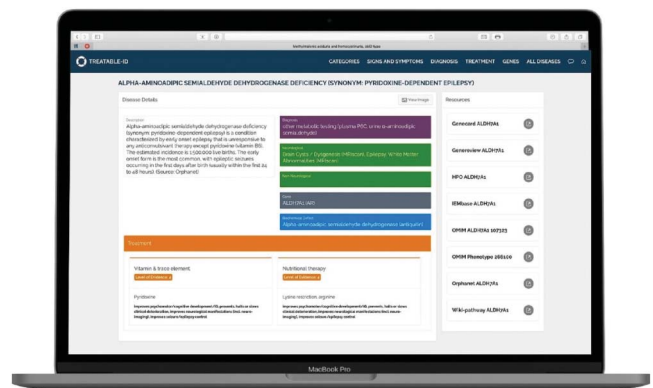
Although individually rare, early identification of IMDs underlying neonatal epilepsy is crucial because there may be implications for treatment. A 2-tiered metabolic algorithm with focus on diagnosis of treatable IMDs ($n > 70$) was proposed by van Karnebeek et al.⁸

Despite adequate seizure control with pyridoxine treatment, PDE-ALDH7A1 outcomes are poor because at least 75% of patients suffer DD/ID.^{6,9} Adjunct LRT can improve neurodevelopmental outcomes in many patients because of lowering of neurotoxic intermediates of the lysine degradation pathway.¹⁰⁻¹² LRT includes a lysine-restricted diet, as substrate limitation, and arginine supplementation, as arginine and lysine compete for transport across the blood-brain barrier via a cationic transporter.¹³ LRT seems to be most beneficial for neurodevelopmental outcome when started as early as possible, emphasizing the importance of early recognition

of PDE-ALDH7A1.^{1,9} As for our case 2, subjective improvements were noted after adjunct LRT initiation, and the sibling of case 1, who started LRT very early, has a normal neurodevelopment so far, despite having the same genetic variant as their sibling with DDs. Prenatal pyridoxine treatment might have influenced neurodevelopmental outcome, although cases have been described of poor outcome despite the prenatal treatment.¹⁴ Consensus guidelines for the diagnosis and management of patients with PDE-ALDH7A1 are available and have been updated in 2021.¹⁵ The international PDE registry serves as the basis for PDE-ALDH7A1 research (pdeonline.org).

To support clinicians in keeping track of all these developments, we performed a literature review in 2021. The

Figure 2 Pyridoxine-Dependent Epilepsy Page in Treatable-ID



Treatable-ID (treatable-id.org) is a freely accessible digital tool to help improve early recognition and intervention for treatable metabolic disorders presenting with ID based on our comprehensive review. ID = intellectual disability.

knowledge on 116 treatable IDs was translated into the digital Treatable ID app (freely available via treatable-id.org or as native App via Google Play or Apple Store) (Figure 2).¹⁶

In conclusion, in neonates, infants, and children presenting with seizures of unknown origin with partial or no response to common antiepileptic medications, the diagnosis of PDE-ALDH7A1 or other pyridoxine-responsive genetic epilepsies should be considered, prompting a trial of pyridoxine as *diagnostic therapeuticum*. Pyridoxine therapy does not affect the diagnostic potential of the disease biomarkers, so samples for biochemical analysis should be taken after initiation of treatment. In addition, molecular analysis of *ALDH7A1* should be initiated. If PDE-ALDH7A1 is confirmed, LRT should be started as adjunct therapy to optimize neurodevelopmental outcomes. If PDE-ALDH7A1 is ruled out, other genetic causes of B6 responsiveness should be investigated.

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Appendix (continued)

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