Pyridoxine-Dependent Epilepsy as a Cause of Neonatal Seizures

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ABSTRACT

Pediatric seizures are a common reason for emergency department visits. The highest risk of seizures in children is during the neonatal period. A low index of suspicion is important to facilitate the early assessment, workup, and treatment of inborn errors of metabolism to optimize developmental outcomes. We present the rare case of a 9-day-old with seizures refractory to multiple anticonvulsant medications who was diagnosed with pyridoxine-dependent epilepsy. We review differences in the management of neonatal seizures from older patients, the utility of a trial of pyridoxine in refractory neonatal seizures, and the importance of preparing for emergent airway management given pyridoxine's ability to cause apnea and central nervous system depression.

KEYWORDS: neonate, pediatric, seizure, inborn error of metabolism, pyridoxine-dependent epilepsy

INTRODUCTION

One percent of pediatric emergency department visits is due to seizures.[1] Seizures occur in 4 to 10% of children[1] and the highest risk of seizures in children is during the neonatal period.[2] Among neonates with seizures, only a small percentage (13%) have neonatal epilepsy syndromes.[3] The majority of neonatal seizures occur secondary to neonatal encephalopathy or hypoxic-ischemic injury, metabolic disturbances, central nervous system or systemic infections, or structural brain lesions including strokes,[4] and require urgent and specific treatment to avoid further brain injury. Inborn errors of metabolism are an uncommon cause of neonatal seizures that should be considered as part of the workup of seizures in these young patients. Prompt treatment of inborn errors of metabolism is of vital importance to prevent developmental delay and other neurocognitive sequelae.[5,6]

CASE PRESENTATION

A 9-day-old female was transferred from an outside hospital for staring spells and upper extremity spasms. On the day of presentation, she was fussy, refused to feed and had episodes of staring off and 15 second bilateral arm spasms. The mother was breastfeeding and supplementing with formula that was correctly mixed. The patient had no fever, runny nose, cough, vomiting, diarrhea, decreased wet diapers, rash, sick contacts, or recent trauma.

The patient was born via planned cesarean section at 41 weeks. Her mother had routine prenatal care, negative prenatal labs and no medical problems during pregnancy or delivery. She had no home medications, allergies, or significant family history.

At the outside hospital emergency department (ED), vital signs were as shown in **Table 1**. Physical examination revealed eyes that intermittently deviated to the right or left for 15 seconds at a time with no extremity spasms. The eye deviation episodes coincided with cyanosis, bradypnea or apnea, and oxygen desaturation to the low 80s. Between episodes, pupils were equal and reactive bilaterally. The remainder of her examination was normal other than having slowed capillary refill and cool skin peripherally. During the bradypnea/apnea episodes, bulb suctioning the airway and using a nonrebreather mask improved oxygen saturation to 100%. The patient had bloodwork and a lumbar puncture performed (**Tables 2 and 3).** She received 15 mL/kg normal saline, ampicillin and gentamicin, and was transferred to a tertiary children's hospital ED.

Table 1. Vital signs at outside hospital and pediatric emergency department.

Vital Sign	Outside Hospital	Pediatric Emergency Department
Temperature (°C)	34.7 (rectal)	36.1 (rectal)
Heart Rate (Beats Per Minute)	176	188
Blood Pressure (mmHg)	Not recorded	97/59
Respiratory Rate (Breaths Per Minute)	46	96
Oxygen Saturation	91% on room air	97% on room air
Weight		4.4 kg (Birth weight: 4.6 kg)

At the pediatric ED, vital signs were as shown in Table 1. On physical examination, she was pink, active, and crying. She had transient leftward eye deviation and bilateral arm jerking. Her abdomen was distended with grimacing and crying on palpation. She was intubated for airway protection

Table 2. Electrolyte and complete blood count results obtained at outside hospital, pediatric emergency department and pediatric intensive care unit (PICU).

Lab Value	Outside Hospital	Pediatric Emergency Department	Pediatric Intensive Care Unit (PICU)
Electrolytes			
Na (Ref: 131–143 mmol/L)	138	140	142
K (Ref: 3.7–5.9 mmol/L)	5.2	5.8	4.7
Cl (Ref: 99–116 mmol/L)	106	106	110
CO_2 (Ref: 22–32 mEq/L)	<10	7	17
BUN (Ref: 5–27 mg/dL)	13	27	18
Cr (Ref: 0.30–1.00 mg/dL)	0.68	0.71	0.5
Glucose (Ref: 50–80 mg/dL)	351	174	78
Calcium (Ref: 9.0–10.9 mg/dL)	10.7	10.4	9.3
Anion Gap (Ref: 3–13 mEq/L)	22	27	15
Complete Blood Count			
White Blood Count (Ref: 4.4–21.0 x 10^9/L)	29.3		17.6
Hemoglobin (Ref: 14.0–21.0 g/dL)	13.1		12.4
Hematocrit (Ref: 42.0–55.0%)	38.6		36.4
Platelets (Ref: 150–450 x 10^9/L)	625		499
Neutrophils (Ref: 14–77%)	30%		68%
Bands (Ref: 0–6%)	1%		0%
Lymphocytes (Ref: 12–78%)	64%		19%
Monocytes (Ref: 0–12%)	4%		11%
Eosinophils (Ref: 0–6%)	1%		0%
Basophils (Ref: 0–1%)	0%		1%
Metamyelocytes (Ref: 0%)	0%		1%

Table 3. Metabolism, toxicology, blood gas, urinalysis, cerebrospinal fluid (CSF), respiratory viral panel and culture results obtained at outside hospital, pediatric emergency department and pediatric intensive care unit (PICU).

Lab Value	Outside Hospital	Pediatric Emergency Department	Pediatric Intensive Care Unit (PICU)
Metabolism Labs			
Lactate (Ref: 0.2–1.9 mEq/L)		>17.1	
Lactate Dehydrogenase (LDH) (Ref: 100–220 IU/L)			375
Ammonia (Ref: 2–50 µmol/L)			70
Uric Acid (Ref: 1.9–5.4 mg/dL)			7.6
Creatine Kinase (CK) (Ref: 34–204 IU/L)			555
β–Hydroxybutyrate (Ref: 0.02–0.27 mmol/L)			2.96
Toxicology Labs			
Serum Acetaminophen Level			Undetectable
Serum Salicylate Level			Undetectable
Urine Drug Screen			Positive for barbiturates, benzodiazepines, fentanyl
Blood Gas	**Arterial**	**Venous**	**Arterial**
pH	7.01	6.995	7.382
pCO_2 (mmHg)	30	46	30
pO_2 (mmHg)	250	47	150
HCO_3– (mmol/L)	7.6	13	19
Base Excess	–22.5	–20	–7
Urinalysis			Normal other than 1+ ketones
CSF			
White Cell Count (Ref: 0–8 cells/mm^3)	2		
Red Cell Count (Ref: <1 cell/mm^3)	27		
Glucose (Ref: 40–80 mg/dL)	128		
Total Protein (Ref: 15–45 mg/dL)	106.7		
CSF HSV PCR	Negative		
Respiratory Viral Panel		Negative	
Cultures (blood, urine, CSF)	No growth at 5 days		

with fentanyl and midazolam. An orogastric tube was placed for stomach decompression. Pediatric surgery was consulted. Acyclovir was given.

Repeat bloodwork and a respiratory viral panel were performed (Tables 2 and 3). Chest radiograph (**Figure 1**) showed diffuse hazy opacities bilaterally. Abdomen radiographs (**Figures 2 and 3**) showed non-specific diffuse air-filled loops of small and large bowel to the level of the rectum without complete obstruction and no free air. CT pan-scan was normal.

Figure 1.

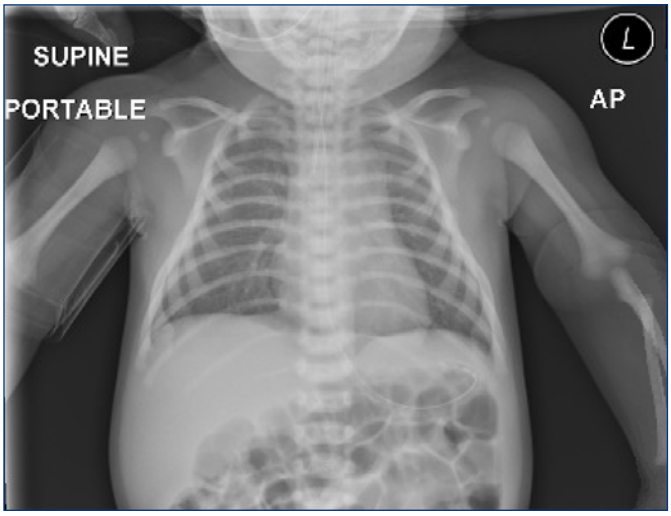


Figure 2.

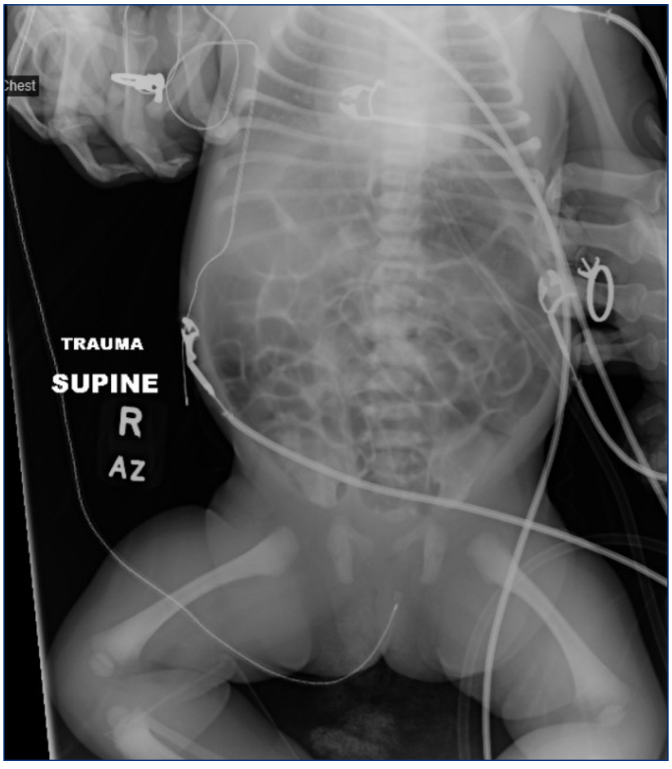
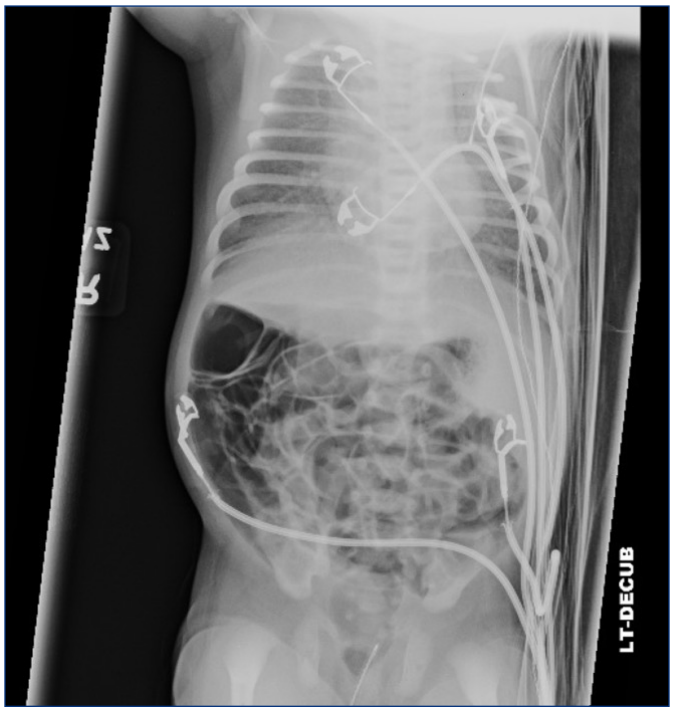


Figure 3.



She was admitted to the pediatric intensive care unit (PICU) where she continued to have intermittent leftward eye deviation with arm jerking. She was given a phenobarbital bolus and Neurology was consulted. The patient was placed on continuous electroencephalogram (EEG) and started on maintenance phenobarbital. Additional lab work was performed (Tables 2 and 3) several hours after admission.

The patient was extubated given her improved labs. Shortly after extubation, she developed episodes of eye deviation, head turning to the right, and flexion of all extremities. She was given phenobarbital and levetiracetam without improvement, corresponding with refractory status epilepticus on EEG. Pyridoxine was then given with seizure resolution clinically and on EEG. The Genetics/Metabolism team was consulted, and the workup revealed an ALDH7A1 gene mutation consistent with pyridoxine-dependent epilepsy. She was discharged with oral pyridoxine.

DISCUSSION

The differential for pediatric seizures includes infectious, neurologic (including hypoxic-ischemic encephalopathy), metabolic (including inborn errors of metabolism in neonates), traumatic, vascular, toxicologic, and oncologic etiologies. The evaluation of a neonatal seizure should focus on the preceding events and description of the seizure, including precipitating factors such as trauma, ingestion, immunizations, fever, or systemic illness. In formula-fed infants, families should be asked about the formula preparation process to assess for electrolyte derangements such as

hyponatremia from formula over-dilution. Maternal history to elicit includes group B streptococcus status, antibiotic treatment during delivery, and the presence of herpes simplex virus (HSV) lesions or risk factors. A thorough physical examination should be performed with a focus on the neurologic exam and assessment for microcephaly/macrocephaly, dysmorphism, signs of trauma, and bulging fontanelles.[7]

The workup for neonatal seizures includes a rapid glucose test, serum electrolytes, calcium, magnesium, ammonia and lactate to screen for inborn errors of metabolism, and complete blood counts. A sepsis workup including blood cultures, urinalysis, urine culture and cerebrospinal fluid studies should be obtained. Empiric antibiotic and anti-HSV coverage should be given. A head CT should be considered depending on the provider's clinical suspicion for structural brain lesions such as intracranial hemorrhage or stroke. EEG may be needed following stabilization in patients with refractory seizures.[7]

The management of neonatal status epilepticus involves stabilization of the airway, breathing and circulation.[7] Reversible causes such as glucose, sodium, magnesium, and calcium abnormalities should be corrected.[8] Phenobarbital is the most commonly used first-line therapy for neonatal seizures. Fosphenytoin is the second most commonly used. Phenobarbital and phenytoin are both equally but incompletely effective as neonatal anticonvulsants, with cessation of seizure activity in less than half of neonates with either medication.[9] Phenobarbital is much more effective at achieving complete seizure freedom for 24 hours in neonates compared with levetiracetam.[10] IV phenobarbital (20 mg/kg) should therefore be used as first-line medication for neonatal seizures, as is recommended in most neonatal seizure algorithms.[11,12] If timely IV access cannot be obtained, a short-acting benzodiazepine can be used in the interim. Second-line medications differ between neonatal seizure algorithms and include benzodiazepines, phenytoin, lidocaine,[11] fosphenytoin or levetiracetam.[12] Second-line neonatal seizure medications should therefore ideally be individualized for patients and selected with input from a pediatric neurologist. For seizures that are unresponsive to one or more second-line anticonvulsants, a trial of pyridoxine may be warranted ideally with EEG monitoring.[13,14] In neonates, pyridoxine can be given as 100 mg IV. Oral pyridoxine can be considered in older children (15-30 mg/kg/day divided three times daily). IV or oral pyridoxine can lead to central nervous system depression and apnea,[13] so clinicians should be prepared for emergent airway management.

Pyridoxine-dependent epilepsy is an autosomal recessive epileptic encephalopathy caused by antiquitin deficiency. Antiquitin is an enzyme involved in lysine catabolism in the brain and liver. When there is a deficiency in antiquitin, there is a buildup of intermediate products in the catabolism pathway proximal to antiquitin, and a decrease in breakdown products distal to antiquitin. These factors collectively lead to increased seizure activity and developmental delay.[15]

The classic presentation of pyridoxine-dependent epilepsy is neonatal seizures not responsive to traditional anticonvulsants and at least partially responsive to pyridoxine.[16] Diagnosis is based on seizure recurrence when pyridoxine is withheld and seizure resolution with pyridoxine supplementation,[11,13] biochemical evaluation including elevated urine alpha-aminoadipic semialdehyde and/or plasma pipecolic acid,[15,17,18] and mutation analysis of the ALDH7A1 gene.[17,18] There is a wide spectrum of clinical presentations in terms of prodromal symptoms, associated seizure types, and biochemical derangements in pyridoxine-dependent epilepsy.[16]

Clinicians should have a low threshold to suspect pyridoxine-dependent epilepsy in refractory neonatal seizures. Pyridoxine-dependent epilepsy is a treatable cause of seizures and intellectual disability. Early treatment with lysine-lowering strategies and pyridoxine supplementation will optimize seizure control and childhood development.[13,16]

While seizures are a common reason for emergency department visits, neonatal seizures are unique in the early use of phenobarbital in the treatment of status epilepticus. Astute clinical suspicion, early diagnosis, and treatment of inborn errors of metabolism will facilitate acute stabilization of these children, optimize developmental outcomes,[19] and ensure that genetic counseling can be initiated if indicated.[5]

CONCLUSION

Physicians should be aware of the unique early use of phenobarbital in the treatment of neonatal status epilepticus, which is different from older children or adults. There is a broad differential for neonatal seizures that includes inborn errors of metabolism such as pyridoxine-dependent epilepsy. Prompt suspicion, workup and treatment of metabolic disorders is imperative to prevent developmental delay and other complications. A trial of pyridoxine can be used in the management of refractory neonatal seizures but can lead to central nervous system depression and apnea. Physicians should be prepared for emergent airway management such as intubation when administering pyridoxine.

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Disclosures

None

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