

Chapter 2

Pyridoxine-Dependent Epilepsy

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Case Presentation

A 2-day-old male neonate became increasingly irritable and developed repetitive twitching in the eyelids, face, and limbs around 24 h of life. He was the full-term product of non-consanguineous parents following a normal pregnancy and uneventful spontaneous vaginal delivery. Investigations for infectious etiologies including blood and urine cultures as well as cerebrospinal fluid analysis were unrevealing. An MRI of the brain was normal. Prolonged video EEG demonstrated voltage suppression of the background activity. Irritability and recurrent irregular lightening-like jerks became noted several hours after birth that were associated with electrographic bursts of high-voltage epileptiform discharges on the EEG suggesting myoclonic seizures (Fig. 2.1). Myoclonic seizures remained refractory to conventional antiseizure drugs (ASDs). Pyridoxine 100 mg IV resulted in almost immediate cessation of his myoclonic seizures. In addition, gradual return of continuous EEG background activity was noted. Extensive investigations to find metabolism inborn error or genetic etiologies later revealed an elevated plasma pipercolic acid level and an elevated urinary α -aminoadipic semialdehyde level that supported a diagnosis of pyridoxine-dependent epilepsy.

Clinical Questions

1. What are the differential diagnoses for neonatal seizures?
2. What is the significance of the EEG suppression-burst pattern in a neonate?
3. What should be expected from pyridoxine challenge?

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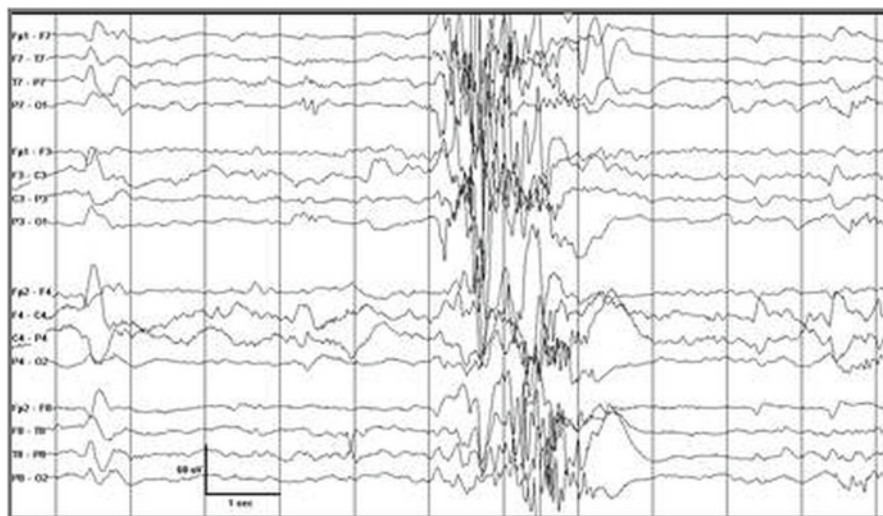


Fig. 2.1 Scalp ictal EEG showed background suppression (note scale legend) with paroxysmal bursts of high-voltage spikes, polyspikes, and sharp waves associated with myoclonic jerks

4. What causes pyridoxine-dependent epilepsy?
5. What causes pyridoxine-deficient seizures?

Diagnostic Discussion

1. Neonatal seizures occur in three per 1,000 live births and commonly imply a serious neurological disease. The most common cause is hypoxic-ischemic encephalopathy, though other causes include stroke, metabolic derangements (hypoglycemia, hypocalcaemia), prenatal and neonatal infections, malformation of cortical development, inborn errors of metabolism, and benign epilepsy syndromes. Neonatal seizures are usually subtle clinically and are characterized by bicycling movements, sucking, smacking, tonic eye deviation, and autonomic phenomena such as apneic episodes. Clonic seizures and myoclonic seizures comprise nearly 50 % of neonatal seizures; however, generalized tonic-clonic seizures rarely occur due to immature myelination. The diagnosis of seizures in the newborn can be challenging because many suspected clinical seizures have no electrographic correlate and many electrographic seizures have no clinical correlate (electroclinical dissociation). Polygraphic video-EEG is the standard for neonatal monitoring and includes monitoring of respirations, electrocardiogram, eye movement, and chin myogram to help differentiate epileptic seizures from benign neonatal movements such as jitteriness, posturing, and sleep myoclonus.

2. The suppression-burst pattern is characterized by low-amplitude background activity that is less than 10–15 mV and that alternates with bursts of asynchronous, high-voltage activity (Fig. 2.1). Suppression-burst pattern does not suggest a specific etiology, but is associated with severe encephalopathy. In the absence of a clinical course suggesting hypoxic-ischemic encephalopathy, severe metabolic derangement, medication effects, and hypothermia, the suppression-burst pattern in a term neonate suggests an early-onset epileptic encephalopathy. Ohtahara syndrome (early infantile epileptic encephalopathy with suppression-burst pattern) and early myoclonic encephalopathy can be differentiated based upon different seizure manifestations and their EEG patterns. Ohtahara syndrome is characterized by frequent tonic seizures that are often associated with a structural etiology. Most of these infants develop West's syndrome and have epileptic spasms, developmental delay, and hypsarrhythmia. The presence of myoclonic seizures and suppression-burst pattern in the case scenario describes a neonate with early myoclonic encephalopathy. Early myoclonic epilepsy is linked to the inborn errors of metabolism. Suppression-burst pattern occurs in both wakefulness and sleep in Ohtahara syndrome, in contrast to early myoclonic epileptic encephalopathy where the suppression-burst pattern is almost limited to sleep.
3. Vitamin B6 includes pyridoxine, pyridoxamine, pyridoxal, and their related 5'-phosphate esters. Pyridoxine is available from nutritional sources. Pyridoxal-5-phosphate is the biologically active form of vitamin B6 and is an essential cofactor for several neurotransmitter synthesis and amino acid metabolism. Pyridoxine challenge is recommended for neonates and young children with epilepsy that is refractory to ASDs. A single dose of pyridoxine 100 mg intravenously is given to see if the typical, dramatic cessation of seizures occurs. Apnea and respiratory depression have been reported after intravenous pyridoxine, especially when higher doses are utilized. Therefore, cardiorespiratory monitoring and the need for respiratory support should be anticipated. An absence of an EEG abnormality that fails to normalize or the lack of seizure control does not rule out pyridoxine-dependent epilepsy. A trial of oral pyridoxine 30 mg/kg/day (200 mg/day in neonates and 500 mg/day in adults) may be continued until pyridoxine-dependent epilepsy can be excluded by biochemical or mutation analysis. A diagnostic withdrawal of pyridoxine resulting in seizure recurrence or seizure resolution after resumption of the vitamin B6 supports the diagnosis of pyridoxine-responsive epilepsy.
4. Pyridoxine-dependent epilepsy is characterized by myoclonic, clonic, and focal or generalized tonic-clonic seizures that are resistant to conventional ASDs, yet respond to vitamin B6. Pyridoxine-dependent epilepsy is an autosomal recessive disorder due to mutations in the *ALDH7A1* gene. The enzyme that is deficient is α -aminoadipic semialdehyde dehydrogenase (antiquitin). A deficiency results in the accumulation of α -aminoadipic semialdehyde, piperidine-6-carboxylate, and pipercolic acid with a secondary deficiency in pyridoxal-5-phosphate (active form of vitamin B6). Elevation of plasma pipercolic acid and urinary and CSF α -aminoadipic semialdehyde act as diagnostic markers. Pyridoxal-5-phosphate is

an essential cofactor in neurotransmitter synthesis (especially GABA) and amino acid metabolism. The treatment for pyridoxine-dependent epilepsy is lifelong supplementation with pyridoxine. Some patients with *ALDH7A1* gene mutation do not have a clear response to pyridoxine, but show a response to folinic acid. Folinic acid 3–5 mg/kg/day may be considered in those neonates who have an incomplete pyridoxine response. Infants who do not respond to pyridoxine should have a trial of pyridoxal-5-phosphate. Other pyridoxine- or pyridoxal-5-phosphate-responsive epilepsies include neonatal/infantile hypophosphatasia, familial hyperphosphatasia, and nutritional vitamin B6 deficiency.

5. An acquired deficiency in pyridoxine can also cause seizures, but unlike pyridoxine-dependency where continuous replacement is needed with pyridoxine deficiency, a single dose of vitamin B6 is sufficient. Reduced pyridoxine intake from malnutrition or a diet limited to grains increases the risk for pyridoxine deficiency. In infants, pyridoxine deficiency can cause growth delay, weight loss, irritability, anemia, and seizures. Adults may have other manifestations such as seborrheic dermatitis and cheilosis. Medications such as isoniazid or intestinal malabsorption and hepatic or renal disease can cause increased excretion of pyridoxine. Sensory polyneuropathy from pyridoxine deficiency typically affects the feet and legs and is characterized by paresthesias and burning dysesthesias. The finding that some children with epileptic spasms responded to pyridoxal-5-phosphate prompted a separate group of patients with pyridoxine-responsive epilepsy. The active form was found to have greater activity for more pediatric patients with inborn errors of vitamin B6 metabolism.

Clinical Pearls

1. Clinical features of pyridoxine-*dependent* epilepsy in the neonatal period include irritability, status epilepticus, and medically refractory epilepsy. Neonatal seizures associated with pyridoxine-dependent epilepsy may mimic hypoxic-ischemic encephalopathy, infectious etiologies, and inborn errors of metabolism, but unlike pyridoxine *deficiency*, it requires lifelong supplementation with vitamin B6.
2. A suppression-burst pattern on the EEG in a neonate in the absence of medication effect, metabolic derangements, and hypothermia is associated with epileptic encephalopathy and implies a poor prognosis.
3. The lack of an immediate clinical or EEG improvement to pyridoxine IV challenge does not exclude pyridoxine-dependent epilepsy. Therapeutic trial of pyridoxine and diagnostic pyridoxine withdrawal along with biochemical or mutation confirmation and pyridoxine withdrawal can support the diagnosis of pyridoxine-dependent epilepsy.
4. Antiquitin deficiency is the main cause of pyridoxine-dependent epilepsy, which results in accumulation of neurotoxic organic acids and secondary deficiency of pyridoxal-5-phosphate.

5. Mental retardation and neurological deterioration in newborns may occur if pyridoxine administration is delayed. Respiratory precautions are warranted during initial and higher dose pyridoxine use.

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