A Rare Case of Pyridoxine-dependent Seizures in Infancy

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ABSTRACT

Pyridoxine-dependent seizures is a rare cause of recurrent seizures in neonatal period and resistant to most of the antiepileptic medications, but respond to administration of pyridoxine. We report a male infant who had neonatal seizures which were initially responsive to anticonvulsants and later became unresponsive and presented at 45 days of life with seizures. These seizures were not responding to any anticonvulsant but responded to pyridoxine. After discharge parents inadvertently stopped pyridoxine and the infant presented with seizures once again. These seizures were promptly controlled with readministration of pyridoxine confirming the diagnosis of pyridoxine-dependant seizures.

Key words:
Neonatal seizures, pyridoxine, pyridoxine-dependent seizures, resistant seizures

INTRODUCTION

Refractory neonatal seizure is a major therapeutic challenge. Pyridoxine-dependent seizures present as refractory seizures not responding to any anticonvulsants, but respond dramatically to pyridoxine administration. Only around 100 cases of pyridoxine-dependent seizures have been described worldwide.[1] Especially in infancy, pyridoxine-dependent seizures should be considered early if seizures are resistant to anticonvulsant drugs, to prevent irreversible neurological damage.

CASE REPORT

A 45-day-old male infant was brought to our hospital with complaints of frequent seizures. Birth history revealed that baby delivered by caesarean section and weighed 3.14 kg at birth. He was suspected of having perinatal asphyxia due to APGAR score and the need for ventilation for respiratory difficulty and neonatal seizures he developed. Baby developed respiratory distress and transferred to NICU. Baby required ventilatory support for 3 days. Baby had neonatal seizures which were treated with antiepileptics (levetiracetam and phenobarbitone). After discharge on fifteenth day of life baby developed seizures, readmitted and treated with antiepileptics (phenobarbitone, levetiracetam and phenytoin) and had temporary improvement. Baby was discharged with oral antiepileptics. On 45th day of life baby had seizures again and this time baby was brought to our hospital. Seizures were myoclonic jerks in type and multiple in episodes. Baby was started on antiepileptics after initial investigations. Blood sugar, serum calcium and septic screen were normal. In view of recurrent seizures despite antiepileptic medication we started on pyridoxine and seizures subsided. Ultrasound cranium was normal. Other investigations including MRI brain, Cerebrospinal fluid analysis and blood culture were normal. Baby remained seizure free and was discharged with advice to continue pyridoxine and phenobarbitone. Parents stopped pyridoxine ignoring medical advice. Baby developed seizures at three months of age after two days of stopping pyridoxine and was brought back to our hospital. After reinitiation of pyridoxine, seizures subsided dramatically. Baby was discharged on oral pyridoxine. All antiepileptic drugs were tapered off and stopped. Subsequently the baby remained seizure free on oral pyridoxine. Infant is currently six months old with age appropriate mile stones and neurological examination was normal by Amiel-Tison method. Parents were advised to come for regular follow-up for neurodevelopment assessment. Parents were counselled to continue pyridoxine indefinitely.

DISCUSSION

Pyridoxine-dependent epilepsy (PDE) was first described in 1954. The ALDH7A1 gene mutations resulting in α-aminoadipic semialdehyde dehydrogenase deficiency, as a cause of PDE, was identified only in 2005. Worldwide more

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than 100 cases have been reported. PDE is a rare autosomal recessive disorder causing intractable seizures in neonates and infants. Seizures in these patients are typically resistant to anti-epileptic treatment but respond dramatically to the administration of pyridoxine.

Pyridoxine dependency results from inborn abnormality of enzyme glutamic acid decarboxylase (GAD). This enzyme is responsible for conversion of the excitatory aminoacid neurotransmitter, glutamate to inhibitory neurotransmitter, Gamma amino butyric acid (GABA). Pyridoxal phosphate is the coenzyme for this reaction. Impaired GAD activity causes marked increase in excitatory versus inhibitory neurotransmitter levels. This elevated excitatory state precipitate seizures. High levels of glutamate levels may be lethal to both neurons and oligodendroglia. Although PDE is a rare condition, it is readily treatable. If untreated there can be permanent neurological damage. Intellectual disability is common. The developing nervous system of infant appears susceptible to pyridoxine deficiency. The functional consequences of vitamin B6 deficiency during neuronal development may be through reduced connections among neurons and decreased myelination, which alter the rate and magnitude of transmission of nerve impulses.[2]

Infants with the classic neonatal presentation have seizures soon after birth. Atypical cases have been reported, such as late-onset PDE starting after nineteen months of life, seizures that initially respond to antiepileptic medications and later become intractable.[3] Seizures that initially respond to very small doses of pyridoxine but later require larger doses, seizures during early life that do not respond to pyridoxine but controlled with pyridoxine several months later and prolonged seizure-free intervals that occur after pyridoxine discontinuation. The seizures are typically generalized tonic-clonic, although myoclonic seizures or infantile spasms have been described. Yoshii *et al.* reported PDE presenting as a case of focal status epilepticus.[4] Unusual foetal movements, suggesting intrauterine seizures, have been described. PDE should be considered in any infant with intractable epilepsy regardless of previous type of seizure and response to conventional treatment. Baxter *et al.* observed that almost a third of neonatal cases of pyridoxine dependency present with apparent birth asphyxia and/or suspected hypoxic-ischemic encephalopathy.[5] A neonate with seizures, even with documented birth asphyxia, should be given 100 mg of intravenous pyridoxine.[6] Even early treatment may result in mild mental retardation.[7] A case of profound neonatal hypoglycemia and lactic acidosis caused by PDE is reported by Mercimek-Mahmutoglu *et al.*[8]

Due to its rarity and in the absence of specific biochemical tests the diagnosis of PDE is not always easy. This entity is an obligatory differential diagnosis in any child less than three years of age with early onset intractable seizures or status epilepticus, since there is a possibility of treatment, which may affect its outcome.[3] Magnetic resonance spectroscopy could be a useful tool in the neuroimaging evaluation for assessment of parenchymal changes despite a normal-appearing brain magnetic resonance image in patients with pyridoxine dependent seizures.[9]

Nabbout *et al.* reported that EEG recordings prior to administration of pyridoxine produce a suggestive pattern: Continuous diffuse high voltage rhythmic delta slow waves, with myoclonic jerks are typical.[10] Interictal EEG after pyridoxine administration shows slow background and slow rhythm, occasional sharp waves in the posterior quadrant, very poorly developed slow and low voltage background, often, but not always resulting in normality. Naasan *et al.* noted the presence of burst suppression patterns for up to 5 days following pyridoxine treatment, and a long period between initiation of pyridoxine treatment and normalization of the EEG.[11] Bok, *et al.* in their study of ten cases of therapy resistant seizures identified 6 cases of genetically confirmed PDE by ALDH7A1 mutation analysis and 4 cases of non-PDE. Digital EEG tracings were analyzed before and after administration of pyridoxine in both groups. It was concluded that EEG response to pyridoxine neither confirms nor refutes the diagnosis of PDE.[12]

The assessment of urinary α-aminoadipic semialdehyde (α-AASA) has become the diagnostic laboratory test for pyridoxine dependent seizures. α-AASA is in spontaneous equilibrium with its cyclic form Δ (1)-piperideine-6-carboxylate (P6C). The diagnostic strength of urinary P6C and α-AASA assessments is comparable, implying that both markers can be applied in a diagnostic setting. Early testing of biomarkers including pipecolic acid and α-aminoadipic semialdehyde may prevent delays in diagnosing PDE. Segal *et al.* recommended that all patients presenting with cryptogenic seizures before age 18 months should undergo this evaluation.[13]

All children younger than 3 years with early onset intractable seizures or status epilepticus should receive a trial of pyridoxine whatever the suspected cause.[5] Epileptic seizure discharges subside within few minutes after the intravenous injection of pyridoxine. Once the diagnosis is confirmed, maintenance therapy should be continued indefinitely and all antiepileptic medications can be withdrawn. Dosage of pyridoxine should be doubled during illness. It should also be increased as the age and weight of child increases. The maintenance dose of pyridoxine to control seizures is unclear and a wide range of daily dosing has been recommended by various authors.[14] A daily dose of 15-300 mg/kg has been recommended for lifelong treatment in these patients. Experience of Roshan Koul showed that a dose of

5 mg/kg-20 mg/kg/day was enough.[15] Bok *et al.* suggested that antenatal pyridoxine supplementation may be effective in preventing intrauterine seizures, decreasing the risk of complicated birth and improving neurodevelopmental outcome in PDE.[16]

Pyridoxal phosphate dependent neonatal epilepsy should be considered in neonates not responding to pyridoxine. Pyridoxamine-5-phosphate oxidase converts pyridoxine phosphate and pyridoxamine phosphate to pyridoxal phosphate. Mutation in the pyridoxamine phosphate oxidase gene presents with neonatal seizures unresponsive to anticonvulsant and pyridoxine anticonvulsant treatment but responds to pyridoxal phosphate. Wang *et al.* suggested that pyridoxal phosphate is better and more effective than pyridoxine in some children with idiopathic intractable epilepsy, more so in children with infantile spasms.[17]

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