Case Report

Pyridoxine-dependent epilepsy owing to antiquitin deficiency — mutation in the *ALDH7A1* gene

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Pyridoxine-dependent epilepsy (PDE) is an inborn error of metabolism resulting from antiquitin deficiency. There is marked elevation of α-amino adipic semi-aldehyde (αAASA), piperidine-6-carboxylate (P6C) and pipecolic acid. The diagnosis can be confirmed by identifying the mutation in the *ALDH7A1* gene in chromosome 5q3l. An 8-year-old Indian girl presented with severe developmental delay and seizures and was found to have pyridoxine-dependent epilepsy owing to an antiquitin mutation. Genetic evaluation of the parents allowed antenatal diagnosis to be made during the next pregnancy.

Keywords: Antiquitin, Pyridoxine-dependent epilepsy

Introduction

Pyridoxine-dependent epilepsy (PDE) is an autosomal recessive disorder which presents with intractable seizures in the neonatal period and early-onset epileptic encephalopathy. Recent advances in molecular biology and biochemistry have demonstrated that this is an inborn error in the metabolism of lysine owing to deficiency of the enzyme antiquitin.[1] With the advent of reliable screening tests and DNA mutation analysis, molecular confirmation of this entity is possible. An 8-year-old girl presented with PDE, which led to a prenatal diagnosis in a subsequent pregnancy.

Case Report

An 8-year-old girl with developmental delay and seizures was brought to the Department of Clinical Genetics, Mediscan Systems for evaluation by her parents. Mediscan Systems is a private tertiary care research centre for Fetal Medicine, Genetics and Perinatal Pathology in Chennai. The parents were third-degree consanguineous (Figure 1). Their first child, a girl, was born at term. The pregnancy and delivery were uncomplicated but the infant had intractable neonatal seizures and severe global developmental delay and died at 2 years of age.

The second child (index child) was well until day 7 when she developed intractable seizures which could not be controlled with phenytoin and phenobarbitone but responded to the addition of pyridoxine. Blood glucos, sodium, calcium and cerebrospinal fluid were normal. Septic work-up was negative. Urine screening for inborn errors of metabolism was reported negative as there was no specific increase in urinary organic acids. Ultrasound of the cranium and ophthalmological evaluation were normal. Subsequently, the child was seizure-free but she had a breakthrough seizure when an attempt was made to wean her off the anticonvulsants at 9 months of age. All anti-epileptics in addition to pyridoxine were withdrawn as the child was clinically seizure-free and hence EEG was not done.

The seizures were refractory to conventional anti-epileptics and could only be controlled by the addition of pyridoxine. Following this breakthrough seizure, the child lost all previously acquired milestones and subsequently made a slow recovery. At 5 years, she could walk only with support, and at 8 years she had only a few simple words. Her cognition was poor. At the time of evaluation at 8 years of age there was severe developmental delay and cognitive impairment. MRI of the brain showed diffuse cerebral and cerebellar atrophy. As the clinical picture was strongly suggestive of pyridoxine-dependent epilepsy, urine was tested for alpha amino-adipic semi-aldehyde (αAASA). The urinary αAASA concentration was >12 mmol/mol creatinine (0.0–1.0), suggestive of αAASA dehydrogenase (antiquitin)

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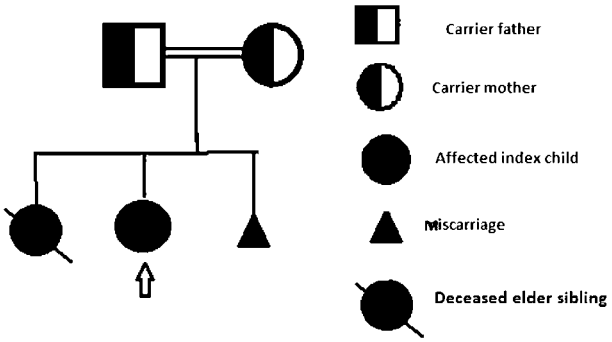
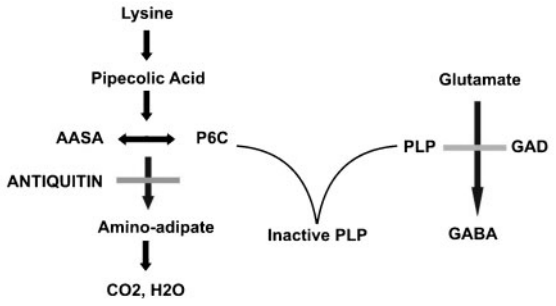


Figure 1 Pedigree chart



AASA, alpha amino-adipic semi-aldehyde
P6C, piperidine-6-carboxylate
PLP, pyridoxal phosphate
GABA, gamma amino butyric acid
GAD, glutamate decarboxylase

Figure 2 Pathway involved in lysine catabolism

deficiency. DNA sequencing demonstrated homozygous mutation in the *ALDH7A1* gene in chromosome 5q31. The mutation detected was c.1472G>A:p (Arg491Lys). Following this confirmation, all anti-convulsants were withheld and the child has been on pyridoxine monotherapy at a dose of 5 mg/kg/day in two divided doses and has been seizure-free for more than a year of follow-up.

The parents were also evaluated and found to be heterozygous for the same mutation. With the next pregnancy the couple opted to undergo prenatal diagnosis. Chorionic villus sampling was undertaken and the fetal DNA showed the same homozygous mutation. The couple were counselled and the mother was commenced on pyridoxine supplementation. However, after much deliberation, the couple decided to terminate the pregnancy in view of the family history.

Discussion

Pyridoxine-dependent epilepsy (PDE) was first described by Hunt *et al.* in 1954.[1] However, only in 2005 did Mills *et al.* demonstrate that this condition is owing to a deficiency of antiquitin (α-AASA dehydrogenase) encoded by the gene *ALDH7A1* on chromosome 5q31.[1–3] It is a rare disorder with an incidence of 1:687,000 in the UK and Ireland.[4] PDE is an autosomal recessive inborn error of metabolism of lysine. It is characterized by intractable seizures which are not controlled by conventional anti-epileptics but respond clinically and electrographically to large daily supplements of pyridoxine (vitamin B_6), as was seen in our patient.[5] Children with antiquitin deficiency accumulate L-pipecolic acid, piperidine-6-carboxylate (P6C) and αAASA. This is thought to be the minor pathway for L-lysine catabolism in most tissues, but it is the major pathway in the brain (Figure 2).[5] P6C, which accumulates in the brain, inactivates the active form of pyridoxine (pyridoxal phosphate) by the formation of a Knoevenagel condensation product.[6] This reduction in the concentration of pyridoxal phosphate in the brain causes disruption in the conversion of glutamate to γ-aminobutyric acid (GABA). This excess glutamate, an excitatory neurotransmitter, is responsible for the refractory seizures in PDE. There are two types of PDE.[1]

Classic PDE (CPDE)

Seizures in CPDE are observed in the first month of life, often within hours of birth, as in this patient. They are resistant to anti-convulsants but are controlled within an hour by 50–100 mg of pyridoxine, usually given intravenously. The epilepsy remains controlled by 5–10 mg/kg/day of pyridoxine; seizures may recur within days if pyridoxine is stopped but are rapidly controlled again when treatment is restarted.[6] Other clinical features include abnormal fetal movements, features suggestive of birth asphyxia, irritability, abnormal cry, exaggerated startle response, dystonic movements, respiratory distress, abdominal distension, bilious vomiting, hepatomegaly, hypothermia, shock and metabolic acidosis.[3]

Atypical/late-onset PDE (APDE)

In APDE, seizures usually start later (up to 2 years). Freedom from seizures may then continue for up to 5 years after withdrawal of pyridoxine.

Seizures in PDE may be of any type but generalized tonic-clonic seizures predominate. The EEG is usually abnormal and the patterns include burst suppression, hypsarrhythmia and multiple spike-wave discharges. Imaging may be normal or may demonstrate cerebral and cerebellar dysplasia, as in this patient, or hemispheric hypoplasia or atrophy, neuronal dysplasia, periventricular hyperintensity or intracerebral haemorrhage. Elevated urinary αAASA excretion is a good marker for screening infants with a clinical picture suggestive of PDE, and mutations in the *ALDH7A1* gene confirm the diagnosis. Treatment involves lifelong supplementation of pyridoxine at a dose of 5–10 mg/kg/day; the dosage should not exceed 500 mg/day. Affected individuals may have exacerbation of clinical seizures and or encephalopathy during an acute illness, such as gastro-enteritis or a febrile respiratory infection. To prevent such exacerbation in these circumstances, the daily dose of pyridoxine may be doubled

for several days until the acute illness resolves.[1,7,8] Early diagnosis and treatment of PDE will significantly improve outcome; untreated children have severe intellectual and psychomotor disability. Identifying the mutations in the *ALDH7A1* gene confirms the diagnosis and will help the family in prenatal diagnosis of subsequent pregnancies.

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