Epilepsy and Hydrocephalus: Should Pyridoxine-Dependent Epilepsy Cross Our Minds?

Sir,

Pyridoxine-dependent epilepsy (PDE) is an inborn error of lysine metabolism characterized by neonatal-onset refractory seizures that are responsive to pharmacologic doses of pyridoxine. Majority of cases are associated with variations in the antiquitin gene *ALDH7A1*, which encodes for alpha-amino-adipic semialdehyde dehydrogenase enzyme. The deficiency of this enzyme results in accumulation of metabolites such as alpha-aminoadipic semialdehyde and piperidine-6-carboxylate, which inactivate pyridoxal phosphate (the active form of pyridoxine) and cause pyridoxine dependency.[1] The disorder has a prevalence of 1 in 100,000–700,000 individuals.[2,3]

PDE has been associated with several structural brain abnormalities, although none of these is pathognomonic for the disorder.[4,5] In a review of brain malformations associated with PDE, agenesia/hypoplasia of corpus callosum (33%), nonspecific white matter abnormalities (32%), mega cisterna magna (17%), ventriculomegaly (17%), hemorrhages (15%), cerebellar hypoplasia/dysplasia (12%), cortical atrophy (8%), hydrocephalus (8%), dysplasia of corpus callosum (7%), and cysts (5%) have been noted.[6] We discuss here a young boy with PDE who developed acute hydrocephalus during an episode of breakthrough status epilepticus. Our case highlights the need to recognize the association of PDE with hydrocephalus to guide appropriate management. Additionally, the presence of hydrocephalus in children with refractory epilepsy should guide investigations to exclude an underlying PDE, especially in cases with early-onset treatment refractory epilepsies.

A 13-month-old infant with epilepsy and language delay presented with unprovoked, focal-onset left-sided motor seizures for 1 day, followed by a generalized status epilepticus. There was no preceding history of fever, alteration in sensorium, missed or changed dosing schedule, trauma, or intercurrent illness. The infant was fourth in birth order; the parents were nonconsanguineously married and there was no family history of epilepsy. He had been delivered by uncomplicated vaginal delivery but developed drug-refractory, multifocal clonic and tonic seizures on day 3 of life. The seizures had responded promptly to the pharmacological doses of oral pyridoxine (25 mg/kg/day). A provisional diagnosis of PDE was assigned. Electroencephalogram showed epileptic encephalopathy and normalized after pyridoxine supplementation. Magnetic resonance imaging (MRI) of the brain showed markedly thinned-out corpus callosum with colpocephaly [Figure 1]. He was discharged by the end of the first week of life and remained seizure-free on oral pyridoxine supplementation. The other anticonvulsants were gradually tapered and stopped on follow-up. Next generation sequencing of the *ALDH7A1* gene showed a homozygous pathogenic variant (c. 1115delT) in exon 13 resulting in a frameshift and premature truncation of the protein, which was predicted to be damaging by *in-silico* prediction models. Sanger sequencing confirmed the variant, but parental testing was denied by the family. In follow-up, he had speech delay without other autistic features, with age-appropriate motor and cognitive milestones.

On examination during his deterioration at 13 months of age, he had normal head circumference (45.5 cm; 0 to −3 *Z*-core), encephalopathy with generalized hypotonia, normal muscle stretch reflexes, and bilateral Babinski's sign. Rest of the systemic examination was unremarkable. A computed tomography scan of the head showed diffuse cerebral edema. He required mechanical ventilation, osmotherapy (3% hypertonic saline) for raised intracranial pressure, anticonvulsants for control of status epilepticus (including folinic acid, phenytoin, levetiracetam, lacosamide) and intravenous antimicrobials. He developed hepatitis, hemolysis, rhabdomyolysis, renal dysfunction, and myocardial dysfunction attributed to prolonged status epilepticus. After control of seizures, he developed generalized, severe dystonia and was continued on supportive measures. He was discharged after 3 weeks of hospital stay in a vegetative state with tracheostomy-tube *in-situ*, nasogastric feeding, anticonvulsant (levetiracetam 40 mg/kg/day, phenytoin 6 mg/kg/day, lacosamide 10 mg/kg/day), and antidystonia and antispasticity drugs (baclofen 30 mg/day, trihexyphenidyl 12 mg/day, diazepam 2 mg/kg/day, clonidine 0.5 mcg/kg/day), in addition to 500 mg/day oral pyridoxine and 3 mg/kg/day folinic acid. MRI of the brain after discharge showed arrested hydrocephalus [Figure 2]. Currently, at 1 year of follow-up, he is in a chronic vegetative state, with a head circumference of 47 cm (−1 to −2 *Z*-score) with control of further seizures.

Our case illustrates the unusual association of acute hydrocephalus with PDE. Additionally, our cases also highlights the natural course of PDE in infants and children who may remain seizure-free for several years and may show worsening of epilepsy with acute neurological deterioration and poor neurodevelopmental outcomes, despite timely diagnosis and regular pyridoxine supplementation.

Neuroimaging findings in patients with PDE range from a structurally normal brain to the presence of complex malformations, as mentioned previously. Expression of antiquitin in the neuroglia may play a role in the pathogenesis of abnormalities of neuronal migration.[7] Among the structural abnormalities seen in this disorder, the development of acute hydrocephalous in PDE remains the most enigmatic. Navarro-Abia *et al.* observed seven cases of hydrocephalus

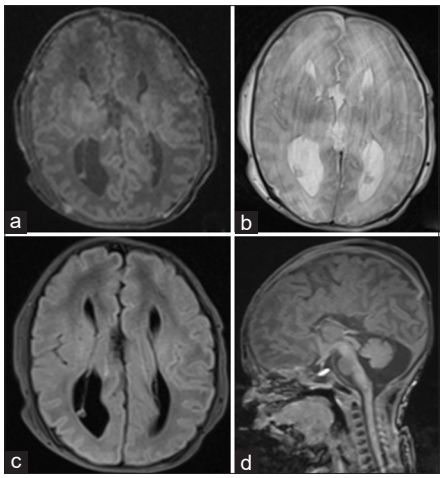

Figure 1: (a-d): Magnetic resonance imaging brain - (a) T1, (b) T2, (c) FLAIR axial sections, and (d) T1 sagittal section done on day 3 of life showing markedly thinned out corpus callosum with parallel orientation and dilated bilateral ventricles (right > left; occipital horns dilated > frontal horns). Third ventricle is located higher up than expected. Brain parenchyma shows normal bulk

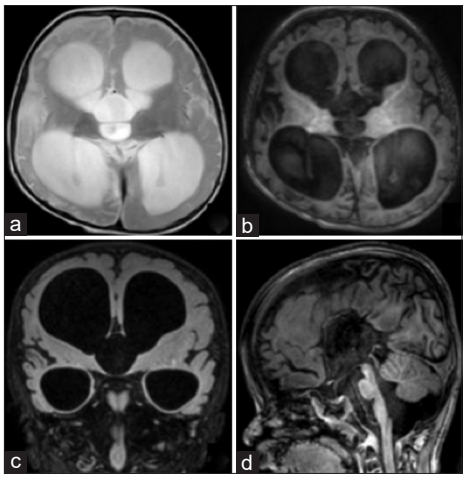

Figure 2:(a-d): Follow-up magnetic resonance imaging brain at one and a half years of age - (a) T2, (b) T1 axial (c) FLAIR coronal, and (d) T1 sagittal section showing gross hydrocephalus with markedly dilated bilateral lateral ventricles, including marked dilatation of both temporal horns and third ventricles. Fourth ventricle (not shown here) was also dilated. White matter is diffusely reduced in bulk, however has normal signal intensity. Extra-axial spaces including sulci were normal. Corpus callosum is nearly nonperceptible

in their series of patients, of which the majority developed hydrocephalus as a later complication and only a few infants were diagnosed with antenatal ventriculomegaly.[8] In one of our previous patients with neonatal-onset PDE, obstructive hydrocephalus was noted in follow-up. Various hypotheses have been formulated to explain this phenomenon. It has been postulated that recurrent neonatal intracerebral micro-hemorrhages, which occur in patients with PDE (unclear mechanism) could lead to gliotic changes causing aqueductal stenosis and subsequent hydrocephalus.[9] Also, the expression of antiquitin in the choroid plexus and ependymal cells, in addition to neuroglia, is thought to be involved in alteration of the CSF circulation, causing ventriculomegaly and/or symptomatic hydrocephalus.[7] An additional contribution of severe hypoxia, secondary to prolonged status epilepticus, to gliosis in the cerebrospinal fluid pathways and subsequent hydrocephalus in our patient remains conjectural.

Although therapeutic doses of pyridoxine initiated and maintained in the early infantile period, result in excellent control of seizures, nearly two-thirds of patients may have intermittent breakthrough seizures and persistent neurocognitive abnormalities. The cause of breakthrough seizures remains unclear. The accumulation of substrates from lysine degradation, which is not reversed by pyridoxine therapy, and intercurrent febrile illnesses, which may increase the requirement of pyridoxine may be contributory. Short-term increase in the doses of pyridoxine and addition of folinic acid have been recommended to treat breakthrough seizures in these patients.[10] The long-term effects of the accumulating compounds including alpha-aminoadipic semialdehyde and piperidine-6-carboxylate, which is not corrected by pyridoxine alone, has also been postulated as the mechanism underlying the high rate of cognitive impairment. Hence, lysine-restriction and arginine supplementation as means of substrate reduction may be attempted to improve cognitive outcomes.[10]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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