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Case Report

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Pyridoxine-responsive seizures in pyridoxamine phosphate oxidase deficiency: case report and review of the literature

Abstract

Pyridoxamine 5-phosphate oxidase (PNPO) deficiency results in a block in the final step of producing pyridoxal 5'- phosphate. This is expected to result in neuronal cell dysfunction that leads to the early neonatal encephalopathy and intractable seizures that are theorized to be resistant to pyridoxine and responsive to pyridoxal 5'-phosphate. As a matter of fact, the lack of response of the intractable seizures to high dose supplementation with pyridoxine is one of the main clinical clues for suspecting PNPO deficiency, although partial response can be observed. This is a case report of genetically confirmed PNPO deficiency that had complete response to high dose Intravenous and then oral pyridoxine after failure to control his seizures with of conventional anti-epileptic drugs. This case further supports the increasingly recognized phenotypic heterogeneity of PNPO deficiency and the potential pitfall of diagnosing pyridoxine responsive seizures proper related to ALDH7A1 (Aldehyde Dehydrogenase 7 family, member A1) pathogenic mutations solely on the bases of clinical response to pyridoxine

Keywords: pyridoxamine phosphate, aldehyde dehydrogenase, vitamin B6, amino acids

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Abbreviations: PRS, pyridoxine responsive seizures; PLP, pyridoxal 5'- phosphate; PNPO, pyridoxamine 5-phosphate oxidase; ALDH7A1, aldehyde dehydrogenase 7 family, member A1

Introduction

Pyridoxamine 5-phosphate oxidase (PNPO) deficiency (OMIM 6032870) is an extremely rare autosomal recessive disorder that deprives then brain from the only active cofactor of the vitamin B6 precursors pyridoxine and pyridoxamine, namely pyridoxal 5'-phosphate. Neonates present with neonatal encephalopathy and intractable seizures that are classically pyridoxine-resistant due to the fact that PNPO is required for converting pyridoxine and pyridoxamine into pyridoxal 5'- phosphate (PLP). Only supplementation with PLP is expected to correct the deficiency and result in full symptom control. Recently, however, there has been an expansion in the recognized clinical spectrum of PNPO deficiency including the variable response to pyridoxine and surprisingly the worsening of some cases when therapy was switched from pyridoxine to PLP. This expanding spectrum of clinical phenotype of PNPO deficiency warrants heightened awareness of this readily treatable disorder and raises certain therapeutic consideration that are illustrated in the discussion.

Case presentation

This 35 weeks premature male was the product of spontaneous vaginal delivery after an uneventful pregnancy. He was normal at birth but soon developed seizures at 12 hours of age. He progressed to having repeated seizures with encephalopathy on day 1. Seizures were refractory to conventional anti-epileptic drug (AED) treatment with phenobarbital, phenytoin as well as parenteral midazolam infusion. Full seizure control was only achieved with the empiric addition of high dose (100 mg daily) of parentral pyridoxine.

His EEG showed independent temporal spikes and multifocal epileptiform discharges. Brain MRI was normal.

The family history was significant for a female sibling death at 21 months of age with similar history of seizures and encephalopathy, so the suspicion was high for an inborn error of metabolism. The neonatal metabolic screen, urine organic acid, plasma amino acid, CSF Glycine, very long chain fatty acid were all normal. Further testing showed mild elevation of urine pipecolic acid supporting the suspicion of a pyridoxine responsive seizure, however, DNA sequencing for ALDH 7A1 gene was normal. Further genetic testing revealed pyridoxamine phosphate oxidase deficiency secondary to homozygous disease (mutation of PNPO gene c.674G>T;R225L) and pyridoxal 5'-phosphate (PPL) was added to pyridoxine therapy.

Developmentally (at 3 months of age) he was smiling, had visual fixation and was supporting his head. He was thriving well on breast feeding. His physical exam showed an alert, normocephalic infant with no dysmorphism. His heart, chest and abdomen exam was normal. On neurologic examination he was fixing and following in the horizontal plane, had normal muscle power, and preserved deep tendon reflexes throughout with good tone. Sensory exam is grossly intact. Moro reflex was symmetric. He was seizure free on phenobarbital, levetiracetam, pyridoxine and pyridoxal 5'-phosphate. Follow up at age 6 month showed continued normal development he is able to sit unsupported, laugh, and has good interaction with the examiner.

Discussion

The rare disorder of pyridoxamine phosphate oxidase deficiency results in blocking of the conversion of pyridoxine and pyridoxamine phosphate into the only active cofactor pyridoxal 5' phosphate; the resulting encephalopathy and intractable seizures are expected to respond only to replacement with pyridoxal 5'-phosphate, since supplementation with high dose pyridoxine does not overcome the PNPO deficiency. As a matter of fact, the very lack of response to pyridoxine is one of the diagnostic clues for suspecting PNPO deficiency. A previous case of partial responsiveness to pyridoxine

in PNPO deficiency was reported by Pearl et al, but the response was not sustained beyond 6 weeks, while our case had full control as well as an age appropriate neurodevelopmental exam at 3 and 6 months of age. They speculate that their patients mutation (c.325G>A p.G118 R) may retain some oxidation activity of pyridoxine activity.[1] In a large series by Mills et al, 8 of 13 cases of PNPO deficiency presenting with seizures before 3 months of age had a dramatic response to pyridoxine.[2] Expression studies on different genotypes in their series appear to support the notion that certain PNPO mutations may retain some oxidation activity as speculated by Pearl et al.[1] Plecko et al. reported 9 cases of PNPO deficiency with partial or full responsiveness to pyridoxine. Plecko et al. have previously described PNPO patients as typically resistant to pyridoxine, a notion that is now evidently challenged.[3]

Our case is another example supporting the observation of pyridoxine responsiveness in PNPO deficiency and argues in favor of keeping pyridoxine empiric therapy on the frontline of therapeutic interventions in neonates and infants below 3 months of age with intractable seizures and encephalopathy as opposed to the proposition of exclusive challenge with pyridoxal 5'-phosphate as an only first line treatment in intractable neonatal seizures.[4] This is particularly important when considering that some patients were observed to have worsening of their seizures when switched from pyridoxine to pyridoxal 5'-phosphate in the series by Mills et al.[2] We hence suggest that pyridoxine should remain the first line treatment in intractable neonatal/infantile seizures with addition of pyridoxal 5'-phosphate in the case of no or incomplete response. Moreover, PNPO mutation testing should be pursued despite responsiveness to pyridoxine when ALDH7A1 genetic studies are not supportive of pyridoxine responsive seizures. Finally, the normal neurodevelopmental outcome of our case compared to the deceased sibling (presumed to have been a missed case of PNPO deficiency) emphasizes the importance of early empiric therapy in cases of intractable neonatal seizures and encephalopathy.

Conclusion

Early recognition and treatment of cofactor intractable neonatal seizures should include empiric treatment with pyridoxine as a first line with add on pyridoxal 5 phosphate for incomplete or absent seizure control. Genetic confirmation should pursue both entities to enable informed long term treatment decision and genetic counseling.

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Conflicts of interest

The authors declare there is no conflict of interests.

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