Publisher
MEDRESEARCH
www.medresearch.in

Pediatric Review - International Journal of Pediatric Research

2023 Volume 10 Number 6 November-December

E-ISSN:2349-3267
P-ISSN:2349-5499

Case Report

Pyrodoxine

An Atypical Presentation of Pyridoxine Dependent Epilepsy

Susarla B[1*], Chintapally S[2], Gundapuneni R[3], Gattu H[4]

DOI: https://doi.org/10.17511/ijpr.2023.i06.02

[1*] Balaji Venkata Rama Susarla, Consultant, Department Of Neonatology, Ankura Hospital For Women And Children, Boduppal, Hyderabad, Telangana, India.

[2] Suman Kumar Chintapally, Consultant, Department Of Neonatology, Ankura Hospital for Women and Children, Boduppal, Hyderabad, Telangana, India.

[3] Ravali Gundapuneni, Consultant, Department Of Neonatology, Ankura Hospital for Women and Children, Boduppal, Hyderabad, Telangana, India.

[4] Harshita Gattu, Consultant, Department Of Neonatology, Ankura Hospital for Women and Children, Boduppal, Hyderabad, Telangana, India.

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive disorder and is considered a prototypical form of metabolic epilepsy. It is characterised by recurrent seizures in the prenatal, neonatal and/or postnatal periods that are resistant to conventional antiepileptic drugs, but responsive to pharmacological doses of pyridoxine. The point prevalence of PDE may vary from 1:20,000 to 1:600,000, based on the degree of systemic ascertainment via therapeutic trial with pyridoxine. Often, pyridoxine-dependent epilepsy can cause diagnostic dilemmas, due to a lack of awareness of this clinical condition, the wide spectrum of clinical manifestations and phenotype genotype variances. Accumulation of the toxic metabolites will lead to developmental delay and mental retardation in the long term, which can be prevented by pyridoxine supplementation and restriction of lysine from diet. Hence, early detection of this condition is very important. Novel instrumental screening methods need to be developed for early detection of this condition to achieve better seizure control and prevent long-term brain damage in this group of patients. Here, we report a case of a newborn who presented with atypical features of neonatal epileptic encephalopathy along with abdominal distension and a mixed seizure pattern and was diagnosed as pyridoxine-dependent epilepsy on whole exome sequencing.

Keywords: Pyrodoxine, deficiency, Epilepsy, Epilepsy

Corresponding Author

Balaji Venkata Rama Susarla, Consultant, Department Of Neonatology, Ankura Hospital For Women And Children, Boduppal, Hyderabad, Telangana, India.
Email: susbalaji3@gmail.com

How to Cite this Article

Susarla B, Chintapally S, Gundapuneni R, Gattu H, An Atypical Presentation of Pyridoxine Dependent Epilepsy. Pediatric Rev Int J Pediatr Res. 2023;10(6):101-104.
Available From https://pediatrics.medresearch.in/index.php/ijpr/article/view/760

To Browse

Manuscript Received	Review Round 1	Review Round 2	Review Round 3	Accepted
2023-11-18	2023-11-21	2023-11-28	2023-12-05	2023-12-12

Conflict of Interest	Funding	Ethical Approval	Plagiarism X-checker	Note
Nil	Nil	Yes	18%	

Introduction

Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive disorder and is considered a protypical form of metabolic epilepsy [1]. It is characterised by recurrent seizures in the prenatal, neonatal and/or postnatal periods that are resistant to conventional antiepileptic drugs, but responsive to pharmacological doses of pyridoxine [2]. Hunt et. al. first described PDE in 1954 in a newborn with pharmaco-resistant seizures that were controlled immediately after parenteral administration of a multivitamin cocktail containing vitamin B6 [3]. The point prevalence of PDE may vary from 1:20,000 to 1:600,000, based on the degree of systemic ascertainment via a therapeutic trial with pyridoxine [4-6]. Here, we report a case of a newborn who presented with features of neonatal epileptic encephalopathy along with abdominal distension and a mixed seizure pattern and was diagnosed as pyridoxine-dependent epilepsy on whole exome sequencing.

Case Report

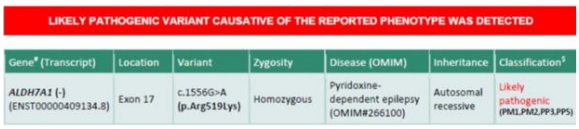
A 12 hours old male newborn, born to 3rd-degree consanguineous parents at term gestation with a birth weight of 2.540 kgs was brought with an episode of vomiting and sudden onset abdominal distension. He was exclusively breastfed. Mother had an uneventful antenatal period. He did not have any history of perinatal insult. At admission, he had severe acidosis which was managed as per protocol. His sepsis screen, serum electrolytes and other relevant investigations sent were within normal limits. However, on day 3 of life his abdominal distension increased with a deranged capillary filling time, hence he was electively intubated and ventilated for a brief duration of 48 hours. He had 2 episodes of seizure activity predominantly as paroxysmal facial grimacing and abnormal eye movements, hence he was loaded with Inj. Phenobarbitone. He was seizure-free for a brief period of 48 hours. Once, he was stable he was weaned off from the ventilator. His serum ammonia levels were within normal limits. Blood lactate levels were elevated.

Over the next 2 days, a rebound increase in seizure activity was noted with excessive irritability and abnormal eye and facial movements; hence a second anticonvulsant was added.

Each episode of seizure activity was different from the other in onset, involvement, duration and amplitude (mixed seizure pattern). His EEG showed diffuse cerebral dysfunction with electrographic seizures arising from the left occipital region. Repeat blood lactate levels showed an increasing trend. A pediatric neurologist's opinion was taken who advised an MRI brain with MR spectroscopy which was normal.CSF analysis along with CSF lactate, paired plasma and CSF glycine were sent, all of which were within normal limits. Urine GCMS showed increased excretion of lactic acid. Congenital lactic acidosis vs. Medium chain acyl co-A dehydrogenase deficiency, hence he was started on all cofactor supplementation His TMS (Tandem mass spectrometry) report was normal.

On day 7 of admission, he had an increase in abdominal distension with hyperalertness, irritability and emesis with abnormal eye movements, hence with the suspicion of pyridoxine-dependent epilepsy, whole exome sequencing was sent and a dose of pyridoxine administered. Whole exome sequencing and mitochondrial genome sequencing report showed a homozygous missense variant in exon 17 of the ALDH7A1 gene that results in the amino acid substitution of Lysine for Arginine at codon 519. This observed variant has been previously reported in patients affected with pyridoxine-dependent epilepsy and it lies in the aldehyde dehydrogenase family domain of the ALDH7A1 protein. He was discharged with a long-term neurodevelopmental follow-up on pyridoxine supplementation, lysine-restricted diet and Arginine fortification.

Results



LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene[4] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification[5]
ALDH7A1 (-) (ENST00000409134.8)	Exon 17	c.1556G>A (p.Arg519Lys)	Homozygous	Pyridoxine-dependent epilepsy (OMIM#266100)	Autosomal recessive	Likely pathogenic (PM1,PM2,PP3,PP5)

Figure 1: Whole exome sequencing report of the baby.

Discussion

The point prevalence of PDE may vary from 1; 20,000 TO 1:6,00,00 based on the degree of systemic ascertainment via a therapeutic trial with pyridoxine[4-6]. The underlying genetic defect was identified in 2006 as mutations in ALDH7A1 resulting in the deficiency of α-aminoadipic

Semialdehyde dehydrogenase (antiquitin) which is involved in cerebral lysine catabolism[7]. Antiquitin deficiency results in the accumulation of intermediate substrates arising from lysine degradation proximal to the deficient enzyme activity, including α-aminoadipic semialdehyde(AASA), Δ-1-piperidine -6-carboxylate (P6C) and pipecolic acid (Figure 1). Inactivation of pyridoxal 5' phosphate (PLP) via a chemical reaction with P6C is the pathophysiological mechanism of pyridoxine dependency[8].

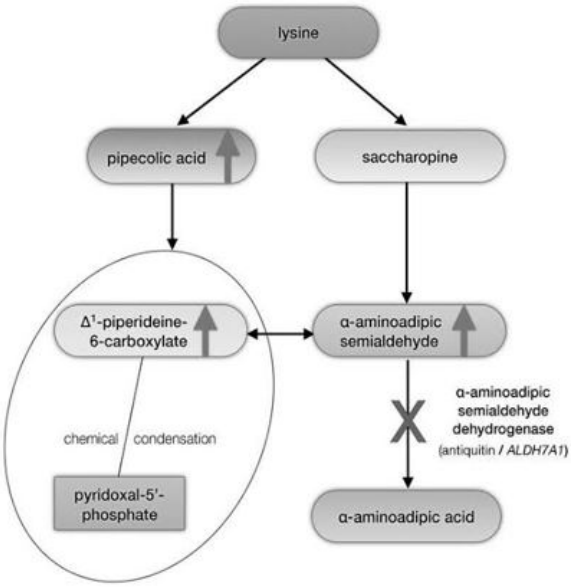


Figure 2: Pathophysiology of pyridoxine dependent epilepsy showing the accumulation of toxic metabolites.Pyridoxine supplementation compensates for the chemical pyridoxal 5 phosphate inactivation, but the accumulation of substrates from lysine degradation is not sufficiently reduced.

PDE patients have a heterogeneous clinical phenotype. The neonatal epileptic encephalopathy presentation may include gastrointestinal symptoms such as emesis and abdominal distension, sleeplessness, hyperalertness, irritability, paroxysmal facial grimacing and abnormal eye movements. These striking findings are associated with recurrent partial motor seizures, generalised tonic seizures or myoclonus. Depending upon the phenotype, response (if any) to Antiepileptic drugs and timing of the initiation of pyridoxine supplementation, complex partial seizures, infantile spasms, other myoclonic seizures and a mixed seizure pattern may develop[6,9, 10-13].

Treatment involves Pyridoxine supplementation lifelong in pharmacological doses. In most patients with PDE, therapeutic pyridoxine dosages may vary from 15-30 mg/kg/day in infants or up to 200 mg/day in neonates and 500 mg/day in adults [14-15]. Lysine restricted diet is needed as pyridoxine compensates for the chemical inactivation, but the accumulation of substrates from lysine degradation is not sufficiently reduced. The presence of these neurotoxic compounds could explain the partial efficacy of pyridoxine, as 75-80% of patients suffer from developmental delay or intellectual disability, despite excellent seizure control [16]. Cerebral lysine influx and oxidation can be modulated by Arginine, which competes with lysine for transport at the blood-brain barrier and the inner mitochondrial membrane. It is hypothesized that Arginine supplementation will compete with lysine, thereby reducing the excess lysine influx into the brain, which leads to the accumulation of the neurotoxic substrates caused by Antiquitin deficiency [17].

Conclusion

PDE, being a rare disease, poses some inherent challenges to research, which include under-diagnosis due to sufficient awareness, clinical heterogeneity, incomplete insight into the clinical spectrum and genotype-phenotype correlation. Novel approaches for early detection will be instrumental in effectively determining the frequency of this condition, providing an opportunity to initiate treatment at the earliest and control seizures, ultimately also limiting brain damage in affected individuals.

References

1. Mills PB, Footitt EJ, Mills KA, et al. Genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy (ALDH7A1 deficiency). Brain. 2010;133(Pt 7):2148-2159. *doi:10.1093/brain/awq143 [Crossref][PubMed][Google Scholar]*

2. Pérez B, Gutiérrez-Solana LG, Verdú A, et al. Clinical, biochemical, and molecular studies in pyridoxine-dependent epilepsy. Antisense therapy as possible new therapeutic option. Epilepsia. *2013;54(2):239-248. doi:10.1111/epi.12083 [Crossref][PubMed][Google Scholar]*

3. Hunt Ad Jr, Stokes J Jr, Mccrory Ww, Stroud

Hh. Pyridoxine dependency: report of a case of intractable convulsions in an infant controlled by pyridoxine. Pediatrics. 1954;13(2):140-145. *[Crossref][PubMed][Google Scholar]*

4. Ebinger M, Schultze C, König S. Demographics and diagnosis of pyridoxine-dependent seizures. J Pediatr. 1999;134(6):795-796. *doi:10.1016/s0022-3476(99)70307-0 [Crossref][PubMed][Google Scholar]*

5. Been JV, Bok LA, Andriessen P, Renier WO. Epidemiology of pyridoxine dependent seizures in the Netherlands. Arch Dis Child. 2005;90(12):1293-1296. *doi:10.1136/adc.2005.075069 [Crossref] [PubMed][Google Scholar]*

6. Baxter P. Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. Arch Dis Child. 1999;81(5):431-433. *doi:10.1136/adc.81.5.431 [Crossref][PubMed] [Google Scholar]*

7. Mills PB, Struys E, Jakobs C, et al. Mutations in antiquitin in individuals with pyridoxine-dependent seizures. Nat Med. 2006;12(3):307-309. *doi:10.1038/nm1366 [Crossref][PubMed][Google Scholar]*

8. Stockler S, Plecko B, Gospe SM Jr, et al. Pyridoxine dependent epilepsy and antiquitin deficiency: clinical and molecular characteristics and recommendations for diagnosis, treatment and follow-up. Mol Genet Metab. 2011;104(1-2):48-60. *doi:10.1016/j.ymgme.2011.05.014 [Crossref] [PubMed][Google Scholar]*

9. Gospe Jr SM. Pyridoxine-dependent seizures: findings from recent studies pose new questions. Pediatr Neurol. 2002;26:181–5. *[Crossref][PubMed] [Google Scholar]*

10. Basura GJ, Hagland SP, Wiltse AM, Gospe SM Jr. Clinical features and the management of pyridoxine-dependent and pyridoxine-responsive seizures: review of 63 North American cases submitted to a patient registry. Eur J Pediatr. 2009;168(6):697-704. *doi:10.1007/s00431-008-0823-x [Crossref] [PubMed][Google Scholar]*

11. Baxter P, Griffiths P, Kelly T, Gardner-Medwin D. Pyridoxine-dependent seizures: demographic, clinical, MRI and psychometric features, and effect of dose on intelligence quotient. Dev Med Child Neurol. 1996;38(11):998-1006. *Doi:10.1111/j.1469-8749.1996.tb15060.x [Crossref][PubMed][Google Scholar]*

12. Kluger G, Blank R, Paul K, et al. Pyridoxine-dependent epilepsy: normal outcome in a patient with late diagnosis after prolonged status epilepticus causing cortical blindness. Neuropediatrics. 2008;39(5):276-279. *doi:10.1055/s-0029-1202833 [Crossref][PubMed][Google Scholar]*

13. Ohtsuka Y, Hattori J, Ishida T, Ogino T, Oka E. Long-term follow-up of an individual with vitamin B6-dependent seizures. Dev Med Child Neurol. 1999;41(3):203-206. *doi:10.1017/s0012162299000390 [Crossref] [PubMed][Google Scholar]*

14. McLachlan RS, Brown WF. Pyridoxine dependent epilepsy with iatrogenic sensory neuronopathy. Can J Neurol Sci. 1995;22(1):50-51. *doi:10.1017/s0317167100040506 [Crossref] [PubMed][Google Scholar]*

15. Rankin PM, Harrison S, Chong WK, Boyd S, Aylett SE. Pyridoxine-dependent seizures: a family phenotype that leads to severe cognitive deficits, regardless of treatment regime. Dev Med Child Neurol. 2007;49(4):300-305. *doi:10.1111/j.1469-8749.2007.00300.x [Crossref][PubMed][Google Scholar]*

16. Bok LA, Halbertsma FJ, Houterman S, et al. Long-term outcome in pyridoxine-dependent epilepsy. Dev Med Child Neurol. 2012;54(9):849-854. *doi:10.1111/j.1469-8749.2012.04347.x [Crossref][PubMed][Google Scholar]*

17. Z Schmidt, G. Murthy, M. Ennis, S Stockler-Ipsiroglu, and R. Elango, "Impact of enteral Arginine suplementationon lysine metabolism in humans; a proof-of-concept for lysine related inborn errors of metabolism",Journal of Inherited Metabolic Disease, vol. *43, no. 5, pp.952-959, 2020 [Crossref] [PubMed][Google Scholar]*