Pyridoxine Responsive Seizures: Beyond Aldehyde Dehydrogenase 7A1

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Objective Pyridoxine responsive seizures (PDRs) are characterized by early-onset seizures and epileptic encephalopathy (neonates and infants) which respond to pyridoxine. Any type of seizures can be the first presentation of PDRs in these children. The aim of this 20-year retrospective study was to report the profile of 35 children with PDRs.

Materials and Methods Neonatal and infantile seizures responding to pyridoxine were analyzed retrospectively from 1998 to 2018. Depending on the clinical features, laboratory results, and genetic study, they were divided into following four groups: (A) responders with α-aminoadipic semialdehyde dehydrogenase 7A1 (ALDH7A1) mutation, (B) responders with pyridoxal phosphate homeostasis protein (PLPHP) mutation, (C) responders with none of these two known mutations, (D) and responders in combination with antiepileptic medications.

Results Sixteen of 35 children had genetic mutation, 4 with ALDH7A1 mutation, and 12 with PLPHP mutation recently described. Nineteen of 35 children had no genetic positivity.

Conclusion A large number of children with pyridoxine response do not have known genetic confirmation. Over time, new genes, responsible for pyridoxine dependency, may be identified or an unknown metabolic disorder may be seen in these children.

Abstract

Keywords ▶ aldehyde dehydrogenase 7A1 ▶ pyridoxal phosphate homeostasis protein ▶ pyridoxine ▶ pyridoxine-dependent epilepsy

Introduction

Pyridoxine responsive seizures (PDRs) are characterized by early-onset seizures and epileptic encephalopathy which respond to pyridoxine. Aldehyde dehydrogenase 7A1 (ALDH7A1; antiquitin) mutation is the most common and first known mutation seen in them. Some cases of pyridoxine responsive children have ALDH4A1 mutation related to hyperprolinemia II. Many children with PDRs and ALDH7A1 mutation have intellectual disability even if seizure free on pyridoxine. Differential diagnosis of PDRs includes pyridoxal phosphate (PLP) responsive epileptic encephalopathy due to pyridoxamine phosphate oxidase deficiency, neonatal/infantile hypophosphatasia, familial hyperphosphatasia, and yet undefined conditions. Recently a new gene, PLP homeostasis protein (PLPHP) has been associated with pyridoxine responsiveness. Still, there are children with no known genetic defect who respond to pyridoxine. Future studies may identify new genes in them.

Materials and Methods

All the children with refractory neonatal or infantile seizures who failed to respond to the antiepileptic drugs (single or in combination, including intravenous [IV] medications) but later responded to pyridoxine were retrospectively studied. The data were collected from 1998 to 2018. The children were fully investigated for the underlying cause of seizures.
We learnt this when many of our neonatal-onset seizures were labeled as pyridoxine-dependent epilepsy (PDE), group A. Other groups were PDE with PLPHP (previously pyridoxal phosphate binding protein [PLPB]/pyroline synthetase cotranscribed [PROSC]) mutation (Group B). Group B had 12 children: four were confirmed on genetic testing; eight were their siblings; five siblings were in one family only. PDE with either or unknown mutation, group C. While the children, who responded to pyridoxine but required antiepileptic drugs as well, were labeled as PDRs group D. Stoppage of either drug resulted in frequent seizures.

Results

There were a total of 35 children (19 male and 16 female). Age at presentation was 30 minutes after birth to 2 years and 5 months with a mean age of 3.13 months. Twelve of 35 children presented < 1 week age. Tonic–clonic seizures was the most common in 17 children, followed by myoclonic in seven, infantile spasms in four, focal seizures in four, and mixed among rest. EEG had burst suppression in 12 children, spike wave in four, and rest was normal. Pippecolic acid and AASA were elevated in three and all had ALDH7A1 mutation. Development was normal in 23 children and delayed in 12, seven of them in PR group D. Pyridoxine dose range was 4 to 12 mg/kg/day with a mean of 8.3 mg/kg/day. ALDH7A1 group had 10 mg/kg/day, PLPHP 5.7 mg/kg/day, and PR 7.7 mg/kg/day. Two children were on PLP and one of these two had in addition calcium folinate (Table 1).

Discussion

PDRs must have been here since early humankind. PDR was first time recognized in 1954. Responsible gene ALDH7A1 was described later. Over the years, search for new mutations of the known gene as well as a new gene was going on till PLPB/PROSC was found, now named or labeled PLPHP. It goes beyond saying that pyridoxine should be tried in all seizures in infancy, particularly if there is a family history of epilepsy, and the seizures are drug resistant. It is a practice at our institute to start oral pyridoxine in all children with infantile spasms, epileptic encephalopathy, and neonatal seizure for initial 2 to 7 days till the baseline workup for seizures is going on. We learnt this when many of our neonatal-onset resistant seizures and status epilepticus failed to respond to conventional antiepileptic drug therapy and finally responded to pyridoxine. However, if the child presents with status epilepticus, IV anticonvulsants are given first. In case, the status becomes refractory, pyridoxine is tried (ideal would have been trial of IV pyridoxine in each child below 3 years age, presenting first time with status epilepticus). ALDH7A1 is the most common gene with mutations known in PDRs. Only 4 out of 35 (11.4%) children had this mutation. These children also have associated intellectual disability. This was noted in three out of four children in our series. Intellectual disability is also reported in children with PLPBP/PROSC, now PLPHP mutation. However, only one of four children in our series had intellectual disability. Only limitation in this study is that no proper intelligence quotient (IQ) assessment was performed in them. This child with intellectual disability did not respond well to pyridoxine on follow-up and required calcium folinate to control seizures. On day 1 after birth, this child had onset of tonic–clonic status epilepticus requiring IV phenytoin sodium, levetiracetam, oral topiramate, and midazolam infusion to control seizures. The child was given 20 mg pyridoxine orally (IV was not available). This resulted in complete control of seizures, excessive sedation, and generalized hypotonia necessitating dose reduction of pyridoxine. The dose of pyridoxine was lowered to 5 mg/day (1 mg/kg/day) and titrated weekly increments of 5 mg/day till 20 mg twice a day was reached (8 mg/kg/day). Antiepileptic drugs tapering was started after the first 24 hour of pyridoxine response. Such excessive sedation on initial administration of pyridoxine has not been reported before. Overall, there were 12 children with PLPHP mutation in our series as four index cases in the four families had eight siblings and five of them in one tribe. These eight siblings responded to pyridoxine. PR is another group of children in our series. All of them had intellectual and motor disability. They responded to combination of pyridoxine and antiepileptic drugs. Stopping either of the drugs resulted in frequent breakthrough seizures. A detailed research in them in the future may reveal some different gene or totally different metabolic disease. We have still many children who responded typically to pyridoxine but did not have any known genetic association (Group C). Whole exome study revealed two siblings in this group with possible benign infantile seizures and they had proline-rich transmembrane protein 2 (PRRT2) mutation. PRRT2 gene mutations have been found to cause other neurological conditions, including benign familial infantile seizures (BFIS), infantile convulsions, and choreoathetosis, and familial paroxysmal kinesigenic dyskinesia. BFIS is characterized by recurrent seizures that begin in infancy and usually disappear by 2 years of age. Both the siblings had discontinued pyridoxine and were fit free. Seizures onset was late in PR group D as compared with other three groups, indicating that pyridoxine-dependent seizures appear early in life. We also observed in utero onset in PLPHP and non-A and -B groups (group C). Most common seizure type was tonic–clonic alone or associated with myoclonic or focal onset in nearly all cases, except four cases with infantile spasms. This is another important feature of the pyridoxine-dependent seizures that tonic–clonic seizures may be the presentation in neonatal age. Such seizures are uncommon at this age. Whenever there are
tonic–clonic seizures in neonatal age, one must consider a possible metabolic disorder, particularly PDE. Developmental delay was seen in all children in PDR group D, suggestive of an associated underlying brain involvement. EEG was abnormal in 26 (74.3%) and epileptic encephalopathy in 13 (37.1%) children. MRI was abnormal in 4 of 24 (16.6%) and three of these four children were from PDR group D. No imaging was performed in 11.

Initial good response to pyridoxine does not indicate long-term response, as was seen in our one PLPHP child. This child had excessive sedation and hypotonia when the first dose of oral 20 mg of pyridoxine was given. We also observed that if a child is pyridoxine responsive, there will be response within 24 hour of starting the oral treatment. Excessive sedation was the first indication of pyridoxine response in a child with refractory seizures. Tonic–clonic seizures and tonic–clonic status epilepticus are uncommon in neonatal age. In case, if a neonate presents with tonic–clonic seizures and tonic–clonic status epilepticus, one should always consider PDE and pyridoxine trial is indicated.

### Conclusion

PDRs have to be considered in all new-onset seizures in neonatal age group, infancy, and early childhood. Initial trial of pyridoxine in all such children till workup for underlying

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**Table 1** Features of pyridoxine responsive seizures

| Features                | PDRs 35 children | ALDH7A1 4 children group A | PLPBP (PROSC), now PLPHP (4) + 8 = 12 group B | Non-A, non-B 12 children group C | PR-7 children group D |
|-------------------------|------------------|-----------------------------|-----------------------------------------------|---------------------------------|----------------------|
| Onset of seizures       |                  |                             |                                               |                                 |                      |
|                         | 30 min–1 d       | 1 h–10 d in utero-2         | 4 h–2 y, 5 mo (5.2 mo)                        | 7 d–7 mo                        |
| Type of seizures        |                  |                             |                                               |                                 |                      |
| Tonic clonic            | 2                | 3                           | 4                                             | 1                               |
| Tonic clonic + myoclonic| 0                | 1                           | 2                                             | 4                               |
| Tonic clonic + focal    | 0                | 0                           | 4                                             | 0                               |
| Tonic–clonic SE         | 2                | 0                           | 0                                             | 0                               |
| Infantile spasms        | 0                | 0                           | 2                                             | 2                               |
| Development             |                  |                             |                                               |                                 |                      |
| Normal                  | 1                | 10                          | 12                                            | 0                               |
| Delayed                 | 3                | 2                           | 0                                             | 7                               |
| Family history          | +                | +                           | +                                             | +                               |
| Pipiecolic acid and AASA|                  |                             |                                               |                                 |                      |
| Elevated                | 3                |                             |                                               |                                 |                      |
| Normal                  | 1                | 4                           | 12                                            | 7                               |
| EEG                     |                  |                             |                                               |                                 |                      |
| Epileptic encephalopathy| 1                | 2                           | 5                                             | 5                               |
| Spikes                  | 0                | 0                           | 2                                             | 2                               |
| Slowing                 | 1                | 0                           | 0                                             | 0                               |
| Normal                  | 2                | 2                           | 5                                             | 0                               |
| MRI                     |                  |                             |                                               |                                 |                      |
| Normal                  | 1                | 2                           | 5 (CT-1)                                      | 1                               |
| Leukopathy              | 0                | 1                           | 0                                             | 3                               |
| PVL                     | 0                | 0                           | 0                                             | 1                               |
| Not done                | 3                | 1                           | 4                                             | 2                               |
| No record               | 1                |                             |                                               |                                 |                      |
| PN mg/kg                | 10               | 5.7                         | 6.2                                           | 7.7                             |
| Control                 | All              | All except 2                | All                                           | Poor all                        |

Abbreviations: AASA, alpha aminoadipic semialdehyde; CT, computerized tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; PDRs, pyridoxine responsive seizures; PLPBP, pyridoxal-phosphate binding protein; PN, pyridoxine; PROSC, proline synthetase cotranscribed; PR, pyridoxine responsive; PVL, periventricular leukomalacia; SE, status epilepticus; +, positive.
cause is identified. Other conditions need to be differentiated from typical PDRs, such as benign infantile seizures, hypophosphatasia, and hyperprolinemia.

Conflict of Interest
None declared.

References
1 Mills PB, Struys E, Jakobs C, et al. Mutations in antiquitin in individuals with pyridoxine-dependent seizures. Nat Med 2006;12(3):307–309
2 Mitsubuchi H, Nakamura K, Matsumoto S, Endo F. Biochemical and clinical features of hereditary hyperprolinemia. Pediatr Int 2014;56(4):492–496
3 Baynes K, Farias ST, Gospe SM, Jr. Pyridoxine-dependent seizures and cognition in adulthood. Dev Med Child Neurol 2003;45(11):782–785
4 Gospe SM, Jr. Pyridoxine-dependent epilepsy. In: Adam MP, Ardinger HH, Pagon RA, eds. Gene Reviews. Seattle, WA: University of Washington, Seattle: 1993–2018
5 Darin N, Reid E, Prunetti L, et al. Mutations in PROSC disrupt cellular pyridoxal phosphate homeostasis and cause Vitamin-B6-dependent epilepsy. Am. J Hum Genet 2016;99(6):1325–1337
6 Plecko B, Zweier M, Begemann A, et al. Confirmation of mutations in PROSC, as a novel cause of vitamin B6 -dependent epilepsy. J Med Genet 2017;54(12):809–814
7 Johnstone DL, Al-Shekaili HH, Tarailo-Graovac M, et al; Care4Rare Canada Consortium. PLPHP deficiency: clinical, genetic, biochemical, and mechanistic insights. Brain 2019;142(3):542–559
8 Hunt AD Jr., Stokes J Jr., McCORRY WW, Stroud HH. Pyridoxine dependency: report of a case of intractable convulsions in an infant controlled by pyridoxine. Pediatrics 1954;13(2):140–145
9 Koul R. Pyridoxine-dependent seizures: 10-year follow-up of eight cases. Neurol India 2009;57(4):460–463
10 Ono S, Yoshiura K, Kinoshita A, et al. Mutations in PRRT2 responsible for paroxysmal kinesigenic dyskinesias also cause benign familial infantile convulsions. J Hum Genet 2012;57(5):338–341
11 Mills PB, Footitt EJ, Mills KA, et al. Genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy (ALDH7A1 deficiency) Brain 2010;133(Pr 7):2148–2159