EDITORIAL

Pyridoxine Dependent Epilepsy: Enduring Mystery and Continuing Challenges

Can J Neurol Sci. 2012; 39: 411-412

Since the initial description of seizures that were responsive to vitamin B6 (pyridoxine) supplements in 1954 (Hunt 1954), the disorder and its biochemical pathogenesis remained a mystery for nearly half a century[1]. In the intervening five decades, the published medical literature is replete with case reports providing detailed clinical descriptions and much speculation regarding potential mechanisms underlying this intriguing disorder[2-6].

The paper by Alfadhel et al in this issue of the Journal is a timely reminder to neurologists and paediatricians alike of the current state of our understanding of pyridoxine dependent epilepsy (PDE) and the continuing challenges to the effective management of this disorder[7]. The authors describe the variable presentation in two siblings sharing the same mutations, and treated with pyridoxine since early infancy. Despite excellent control of their epileptic seizures the two differed in their cognition and intellectual outcomes significantly.

Pyridoxine dependent epilepsy merits greater interest from the academic community as well as clinicians to further understand the wider implications of this condition.

Firstly, it is useful to examine what is known about the condition. The clinical presentation of this disorder is highly variable and the symptoms are not necessarily restricted to the nervous system. Seizures may begin within the first month of life (early onset classical PDE), or in atypical forms as late as two years. Recognition in the neonatal period can be, easier if seizures are the primary presentation but particularly challenging if there are multisystem features that may often be mistaken for sepsis[8,9]. Until the end of the last century, the diagnosis could only be made if the disorder was considered by the treating clinician, and empirical treatment was initiated. This was more likely if the presentation was in the neonatal period with seizures when a pyridoxine trial was initiated as part of a standard protocol followed in most neonatal units.

In the last decade, rapid progress has been made with the recognition of the biochemical markers pipecolic acid (plasma and CSF) and L-α-aminoadipic semialdehyde (AASA) (plasma, CSF and urine). The assay for urinary AASA has been considered until now to be a reliable marker for PDE, and it is valuable to know that its excretion continues to be elevated whether or not the patient is on treatment with pyridoxine supplements. Thus, treatment need not be deferred or withdrawn for the fear of interference with the assay[10].

Confirmation of the diagnosis of PDE can now be established with certainty by the identification of pathogenic mutations in *ATQ* coding for α-aminoadipic-semialdehyde hydrogenase (ALDH7A or antiquitin)[11-13]. Recent data suggests that urinary AASA may also be elevated in molybdenum co-factor and sulfite oxidase deficiency, suggesting that both the urinary AASA assay and molecular confirmation of a pathogenic mutation in the antiquitin gene are necessary for a confirmed diagnosis of PDE[14]. Further, the condition of "folinic acid dependent epilepsy" is now established to be an allelic condition to PDE, as patients diagnosed with the former condition have also been shown to carry mutations in *ATQ*[15]. A cautionary footnote is the overlap of PDE related to ALDH7A deficiency and pyridoxine-5'-phosphate oxidase (PNPO) deficiency based on plasma amino acid and amine profiles in the CSF[16]. This diagnostic confusion may arise, as several of the symptoms reported may be due to secondary deficiencies in pathways dependent on pyridoxal phosphate. Thus, urinary AASA measurement needs to be carried out to differentiate between ALDHA7 and PNPO deficiencies.

So why do neurologists need to be aware of these disorders? It is possible that the PDE may not have been in the diagnostic considerations in adults with refractory epilepsy. This would now be important, particularly if the patient history indicates that the epilepsy had an early onset and/or the patient never had a pyridoxine trial. Many cases in adults are attributed to a static encephalopathy if there is a structural lesion on imaging, and we are learning that this should not preclude a diagnosis of PDE[8]. The diagnosis once established would no doubt lead to improved seizure control with initiation of treatment with pyridoxine.

The report highlights a particular area of concern, that the intellectual outcome may remain compromised despite early institution of therapy. Contrary to this notion is the evidence in published literature of patients in whom documented treatment delay was associated with normal cognition. This raises additional questions about the relationship between institution of pyridoxine treatment and cognitive/neurological outcomes. It is not clear whether the effects of pyridoxine deficiency are prenatal, perinatal or postnatal in timing. Furthermore it is not known whether the secondary deficiencies in neurotransmitter metabolism as demonstrated on CSF amine profiles also merit treatment and whether dietary modifications such as lysine restriction will provide added benefit. The patients described in the published report are compound heterozygotes for two known pathogenic mutations (c. 1195G>C (p.107 Glu399Gln) and c.1429G>C(p. Gly477 Arg).The genotype-phenotype correlations in PDE are still not clearly established and likely to be complex. Genetic counseling needs to be provided to the families of affected patients.

Moving forward, what are the next steps in seeking to further understanding and clarification around these questions? It is necessary that the assays for urinary AASA and molecular testing for mutations in the antiquitin gene be available for clinicians to access for their patients with suspected diagnosis of PDE. Developing such assays in reference laboratories across the country is a priority. A nationwide registry needs to developed

and implemented where data regarding suspected and confirmed clinical cases are collected. A registry requires time and resources to be maintained but is one way forward in evaluating the critical questions that remain to be answered; what is the relationship between genotype and phenotype in patients with PDE, is there a temporal relationship between timing of treatment and intellectual outcome, what is the correct dose of pyridoxine supplementation, and how long should it be continued safely? A registry would provide estimates of the prevalence of this disorder and permit patients to participate in multicenter clinical trials using standardized protocols. We need to know if AASA has sufficient stability, sensitivity and specificity for PDE to propose incorporation into newborn screening programs so that diagnosis and intervention may be achieved in the presymptomatic stage, as is the case with other disorders such as phenylketonuria where early interventions have a very significant impact on outcomes.

Acknowledgements

The authors thank Dr. Tony Rupar, PhD, FCCMG Director of Biochemical Laboratory, Child Parent Resource Institute, London, Ontario for his insightful comments.

Asuri N. Prasad, Chitra Prasad
Western University, London, Ontario, Canada

References

1. Hunt AD, Jr., Stokes J, Jr., Mc CW, Stroud HH. Pyridoxine dependency: report of a case of intractable convulsions in an infant controlled by pyridoxine. Pediatrics. 1954;13:140-5.
2. Goto T, Matsuo N, Takahashi T. CSF glutamate/GABA concentrations in pyridoxine-dependent seizures: etiology of pyridoxine-dependent seizures and the mechanisms of pyridoxine action in seizure control. Brain Dev. 2001;23:24-9.
3. Baxter P. Epidemiology of pyridoxine dependent and pyridoxine responsive seizures in the UK. Arch Dis Child. 1999;81:431-3.
4. 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;38:998-1006.
5. Gospe SM, Jr., Olin KL, Keen CL. Reduced GABA synthesis in pyridoxine-dependent seizures. Lancet. 1994;343:1133-4.
6. Bankier A, Turner M, Hopkins IJ. Pyridoxine dependent seizures--a wider clinical spectrum. Arch Dis Child. 1983;58:415-18.
7. Alfadhel M, Sirrs S, Waters PJ, et al. Variability of phenotype in two sisters with pyridoxine dependent epilepsy. Can J Neurol Sci. 2012;39(4):516-19.
8. Mills PB, Footitt EJ, Mills KA, et al. Genotypic and phenotypic spectrum of pyridoxine-dependent epilepsy (ALDH7A1 deficiency). Brain. 2010;133:2148-59.
9. Schmitt B, Baumgartner M, Mills PB, et al. Seizures and paroxysmal events: symptoms pointing to the diagnosis of pyridoxine-dependent epilepsy and pyridoxine phosphate oxidase deficiency. Dev Med Child Neurol. 2010;52:e133-42.
10. 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;104:48-60.
11. Mills PB, Struys E, Jakobs C, et al. Mutations in antiquitin in individuals with pyridoxine-dependent seizures. Nat Med. 2006; 12:307-9.
12. Plecko B, Hikel C, Korenke GC, et al. Pipecolic acid as a diagnostic marker of pyridoxine-dependent epilepsy. Neuropediatrics. 2005;36:200-5.
13. Plecko B, Stockler-Ipsiroglu S, Paschke E, Erwa W, Struys EA, Jakobs C. Pipecolic acid elevation in plasma and cerebrospinal fluid of two patients with pyridoxine-dependent epilepsy. Ann Neurol. 2000;48:121-5.
14. Mills PB, Footitt EJ, Ceyhan S, et al. Urinary AASA excretion is elevated in patients with molybdenum cofactor deficiency and isolated sulphite oxidase deficiency. J Inherit Metab Dis. 2012 - [in press].
15. Gallagher RC, Van Hove JL, Scharer G, et al. Folinic acid-responsive seizures are identical to pyridoxine-dependent epilepsy. Ann Neurol. 2009;65:550-6.
16. Hoffmann GF, Schmitt B, Windfuhr M, et al. Pyridoxal 5'-phosphate may be curative in early-onset epileptic encephalopathy. J Inherit Metab Dis. 2007;30:96-9.