CASE REPORT

# Long-Term Follow-up of a Successfully Treated Case of Congenital Pyridoxine-Dependent Epilepsy

**Malcolm Proudfoot • Philip Jardine • Agne Straukiene •
Rupert Noad • Andrew Parrish • Sian Ellard •
Stuart Weatherby**

**Abstract** Autosomal recessive disorders affecting pyridoxine (vitamin B6) metabolism are a rare but well-recognized cause of neonatal seizures. Antiquitin deficiency, caused by mutations in *ALDH7A1*, is a disorder of the lysine degradation pathway causing accumulation of an intermediate that complexes with pyridoxal phosphate. Reports of long-term follow-up of neonatal pyridoxine-dependent seizures (PDS) remain scarce and prognostic information is varied. We report a case of PDS in a 47-year-old lady who originally presented shortly after birth in 1964. Pyridoxine replacement was successful and diagnostic confirmation was obtained later in life, initially by biochemical analysis of serum pipecolic acid. Subsequently we organized genetic analysis of *ALDH7A1*, which revealed compound heterozygous mutations. To our knowledge, this represents the longest duration of follow-up published to date.

M. Proudfoot (✉)
Dept of Neurology, Derriford Hospital, Plymouth, UK
e-mail: m.proudfoot@nhs.net

P. Jardine
Dept of Neurology, Bristol Royal Hospital for Children, Bristol, UK

A. Straukiene
Dept of Neurology, Derriford Hospital, Plymouth, UK

R. Noad
Dept of Clinical Neuropsychology, Derriford Hospital, Plymouth, UK

A. Parrish
Dept of Molecular Genetics, Royal Devon & Exeter NHS Foundation Trust, Exeter, UK

S. Ellard
Dept of Molecular Genetics, Royal Devon & Exeter NHS Foundation Trust, Exeter, UK

S. Weatherby
Dept of Neurology, Derriford Hospital, Plymouth, UK

## Case

### Clinical History

Our patient was born full term weighing 3.6 kg; hours after delivery, generalized convulsions began. No cause was immediately apparent for the continuous seizures. Her sibling had died shortly after birth with uncontrollable seizures of unknown aetiology. After 24 h of unsuccessful treatment with anti-convulsants and sedatives, pyridoxine was prescribed. Convulsions ceased 5 min after administration of 75 mg IV. Maintenance therapy with oral pyridoxine, 20 mg 8 hourly, was commenced. EEG demonstrated excess generalized theta.

Confirmatory testing of PDS was performed aged 8 months. After 48 h of pyridoxine withdrawal, there were frank convulsions and recurrence of encephalopathy. Recovery after reinstitution of pyridoxine was prompt. Oral replacement therapy was continued long term.

Developmental assessment aged 6 years revealed mild developmental delay despite freedom from seizures. At 11 years, a further EEG was performed. An excess of theta and relative paucity of rhythmic alpha activity was noted. She attended a school for children with learning difficulties and has relatively poor literacy.

Aged 20 years, she was reviewed in the adult neurology clinic, querying the necessity of continued pyridoxine therapy. Pyridoxine, then 50 mg three times daily, was withdrawn for 2 weeks. Seizure recurred and pyridoxine recommenced. A subsequent EEG revealed minimal epileptiform activity.

### Current Status

She returned for review at 42 years. She lives independently, works as a pre-school assistant and has one healthy

daughter. She enjoys ongoing seizure freedom but is troubled by migraine with aura. Examination was normal and nerve conduction studies excluded peripheral neuropathy. MRI brain revealed mild ventriculomegaly, prominent cisterna magna and no evidence of parenchymal abnormalities. No change was noted on 2-year interval scanning.

Neuropsychological assessments have been undertaken, after initial interview in November 2010. She declined cognitive testing in March 2011 but consented in August 2012.

She was assessed on the Wechsler Adult Intelligence Scale – Version IV. Her full scale IQ was calculated as 75, which equates to the 5th percentile. In terms of profile of abilities, there was a significant discrepancy between her verbal and non-verbal abilities ($p < 0.05$). Her verbal intellectual abilities were an area of relative weakness (2nd percentile). Her non-verbal intellectual abilities were a relative strength (34th percentile), and she performed particularly well on block design (high average range). She scored at the 13th percentile on tests of working memory and 4th percentile for processing speed.

In summary, her overall intellectual ability would be categorized in the 'borderline' range with relative strengths in non-verbal as opposed to verbal abilities.

Investigations

Metabolic confirmation of PDS was provided by raised serum pipecolic acid (PPA) at 7.4 μmol/l (<2.6 μmol/l) and a significant mass spectrometry peak of α-amino adipic semialdehyde (AASA) in urine (Bok et al. 2007). Sequence analysis of the *ALDH7A1* gene (RefSeq NM_001182.3) revealed compound heterozygosity for a missense mutation c.1279G>C (p.E427Q) in exon 14 and a cryptic splicing mutation c.834G>A (p.V250V) in exon 9. Both mutations have been reported previously (Salomons et al. 2007). Further detail is provided in a supplementary footnote.

Comment

PDS, although rare as a cause of neonatal seizures, may have a higher incidence than early estimates of 1 in 730,000 (Baxter 1999; Been et al. 2005). Classically seizures occur within a few days of birth and may perhaps be detected as abnormal intra-uterine movements (Bejsovec et al. 1967). Antenatal treatment may improve cognitive outcomes (Bok et al. 2012). The seizures may be accompanied by EEG changes and both focal and diffuse inter-ictal dysfunction is recognized, but paroxysmal movements may be unaccompanied by EEG discharges (Schmitt et al. 2010).

Our case was typical in having complete freedom from seizures on pyridoxine monotherapy, plus withdrawal of pyridoxine led to a recurrence of seizures. Relative normalization of the EEG following therapy provides supportive evidence. Atypical cases described include those with an initially favourable response to anti-epileptic drugs, those with a later age of onset (Goutières and Aicardi 1985) and those in whom later withdrawal of pyridoxine is tolerated. Some such cases do not have currently identifiable genetic mutations (Bennett et al. 2009).

Diagnosis of Pyridoxine-Dependent Seizure

Confirmatory testing of suspected PDS cases has evolved in line with improved molecular and genetic analysis techniques (Mills et al. 2006; Stockler et al. 2011).

Neurochemical abnormalities in PDS include reduced CSF GABA and elevated glutamic acid. More specifically, significant elevation of pipecolic acid occurs in both plasma and CSF, and may increase further during pyridoxine withdrawal (Plecko et al. 2000). Various mutations in *ALDH7A1*, situated on chromosome 5q31, are now recognized as a major cause of PDS (Mills et al. 2006). This gene encodes an enzyme in the cerebral lysine degradation pathway, AASA dehydrogenase (antiquitin). Diagnosis can thus be made both antenatally and after initiation of pyridoxine (Segal et al. 2011) without risking potentially harmful withdrawal of therapy (Plecko et al. 2007).

Treatment, Prognosis and Risks of Therapy

Pyridoxine toxicity in high doses, typically beyond 200 mg/day, is well established and peripheral neuropathy is reported to be dose dependent in severity (Berger et al. 1992). Nonetheless, reports of iatrogenic neuropathy in PDS are rare (McLachlan and Brown 1995) and reassuringly, nerve conduction studies performed on our patient at 44 years of age, returned normal motor and sensory responses.

MRI studies of PDS patients have revealed varying degrees of abnormality; typically atrophy (Gospe and Hecht 1998) and in keeping with this, our patient demonstrated mild ventriculomegaly with prominent cisterna magna only. Dysplasia of the corpus callosum has been noted in some series (Mills et al. 2010) as have white matter abnormalities, but these findings are aetiologically non-specific and correlate poorly with functional outcomes.

Other long-term case reports of treated PDS have remarked upon discrepancy between verbal and performance IQ scores in the context of mild developmental delay (Baynes et al. 2003), but cognitive profiles may be globally blunted (Rankin et al. 2007). A broad range of cognitive outcomes are described in the literature, with a trend to higher function in those treated earlier in life (Bok et al. 2012). Our adult subject demonstrates psychometric function slightly above previously averaged IQ values of children with PDS, in keeping with her early and continued therapy. It seems likely that preservation of intellect is

dependent upon adequate pyridoxine replacement (Baxter et al. 1996), but may vary with differing genotypes (Striano et al. 2009; Scharer et al. 2010) or unknown environmental influences (Alfadhel et al. 2012). Further restoration of higher functions may prove possible with additional dietary modification such as lysine restriction (van Karnebeek et al. 2012), emphasizing the complex pathogenesis of antiquitin defects beyond that of central pyridoxine deficiency.

## Conclusion

At the time of our patient's birth, only 12 cases of PDS had been described worldwide. To our knowledge, the duration of follow-up in this case is the longest yet reported and descriptions of cognitive outcomes in treated adults remain scarce. Our patient achieved complete seizure freedom on long-term pyridoxine replacement without any apparent significant side effects. We hope that this case will provide encouragement to patients and their families, and remind clinicians of the sustained beneficial impact from early PDS diagnosis.

## Synopsis

This report demonstrates an instance of long-term successful treatment of pyridoxine-dependent seizures, which was achieved without serious adverse effects.

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## Supplementary Information

*Mutation numbering has been updated to reflect the mitochondrial leader sequence. The missense mutation p.E427Q (RefSeq NM_001182.3) is the same mutation previously reported as E399Q* (NM_001182.2) *and the cryptic splicing mutation c.834G>A (NM_001182.3) was previously reported as c.750G>A (NM_001182.2). We initially failed to identify this as pathogenic in part due to this nomenclature change and also since only one of the four splicing prediction tools within Alamut (www.interactive-biosoftware.com) predicted an effect.*