Seizures Due to a *KCNQ2* Mutation: Treatment with Vitamin B₆

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Abstract There is increasing evidence that vitamin B₆, given either as pyridoxine or pyridoxal 5'-phosphate, can sometimes result in improved seizure control in idiopathic epilepsy. Whole-exome sequencing was used to identify a *de novo* mutation (c.629G>A; p.Arg210His) in *KCNQ2* in a 7-year-old patient whose neonatal seizures showed a response to pyridoxine and who had a high plasma to CSF pyridoxal 5'-phosphate ratio, usually indicative of an inborn error of vitamin B₆ metabolism. This mutation has been described in three other patients with neonatal epileptic encephalopathy. A review of the literature was performed to assess the effectiveness of vitamin B₆ treatment in patients with a *KCNQ2* channelopathy. Twenty-three patients have been reported to have been trialled with B₆; in three of which B₆ treatment was used alone or in combination with

other antiepileptic drugs to control seizures. The anticonvulsant effect of B₆ vitamers may be propagated by multiple mechanisms including direct antagonist action on ion channels, antioxidant action on excess reactive oxygen species generated by increased neuronal firing and replenishing the pool of pyridoxal 5'-phosphate needed for the synthesis of some inhibitory neurotransmitters. Vitamin B₆ may be a promising adjunctive treatment for patients with channelopathies and the wider epileptic population. This report also demonstrates that an abnormal plasma to CSF pyridoxal 5'-phosphate ratio may not be exclusive to inborn errors of vitamin B₆ metabolism.

Introduction

Pyridoxine-dependent epilepsy (PDE) (OMIM 266100) was first described by Hunt et al. (1954). Typically patients present with antiepileptic drug-resistant seizures in the neonatal period that respond dramatically to pyridoxine (PN) and remain seizure-free on this treatment. This metabolic defect has been shown to be due to a deficiency of α -aminoacidic semialdehyde (α -AASA) dehydrogenase, an enzyme on the lysine catabolic pathway (Mills et al. 2010). The accumulating upstream metabolite, L- Δ^1 -piperideine-6-carboxylate (P6C), forms an adduct with pyridoxal 5'-phosphate (PLP), the active form of vitamin B₆, rendering it inactive as a cofactor. P6C is in equilibrium with α -AASA, and it is the measurement of these compounds in urine, CSF or plasma that now forms the biochemical basis for diagnosis, alongside molecular genetic analysis of *ALDH7A1*. Patients with pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency (OMIM 610090) are also now being recognised as responding to

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PN, despite early patient cohorts only showing a clinical response to PLP (Mills et al. 2014).

In the majority of patients with PDE, treatment with intravenous PN (50 or 100 mg single dose) followed by a maintenance oral dosing regimen of 5–15 mg/kg/day (maximum 200 mg/day) results in seizure resolution. Whilst the long-term outcome is variable, most children have a degree of developmental delay involving cognitive impairment and speech and language problems. However, a recent review reports 31% of patients having normal developmental outcome (Guerin et al. 2014).

Many reports suggest that a variety of children with epilepsy can respond, either long term or transiently, to vitamin B₆ treatment (Ohtahara et al. 2011). One study suggested that PLP was effective in controlling up to 46% of children with intractable infantile spasms and 11.7% with idiopathic intractable epilepsy, the oldest of which was 15 years old (Wang et al. 2005). Whilst the genetic and biochemical basis for the response of many of these patients has not been investigated, the proportion responding is so high that it is unlikely that they all have antequitin or PNPO deficiency. Whole-exome sequencing is one method that can be used to investigate the genetic aetiologies of cases such as these. We present the case of a girl whose neonatal seizures appeared to respond to a vitamin supplement containing PN and who had a high plasma to CSF PLP ratio indicative of a vitamin B₆ disorder. However, at 7 years of age, she was shown to have a channelopathy caused by a *de novo* mutation in the potassium voltage-gated channel, KQT-like subfamily, member 2 (*KCNQ2*) gene.

Case Report

The patient, a daughter of unrelated parents, was born by spontaneous labour at 38+6 weeks after an uneventful pregnancy. Good foetal movements were reported. The baby had hiccoughs during the last trimester, although similar movements were also reported during the mother's first pregnancy with an unaffected child.

She was born in good condition and discharged on day three of life. Prior to this, she suffered two episodes of facial reddening, stiffening and then becoming pale; these were associated with feeding and thus assumed to be reflux. One day post-discharge, she had episodes of choking and cyanosis, associated with stiffening after which she became floppy. Further seizures on day 4 were documented at her local hospital; these were accompanied by 'cycling' movements of her arms with oxygen saturations dropping to 68%, lasting less than 1 min. A full septic screen including a lumbar puncture was negative and she was given a loading dose of phenobarbitone. Seizures continued follow-

ing this requiring control with phenobarbitone, phenytoin and lorazepam.

At 9 days of age, she had a normal cranial ultrasound and CT scan but an electroencephalogram (EEG) demonstrated some asymmetry with larger amplitude responses on the right and abnormal paroxysmal components. A brain MRI on day 28 demonstrated normal brain structures with appropriate maturation but some increased signal intensity in the subthalamic nuclei around the lateral geniculate nuclei bilaterally.

A series of biochemical investigations (7 days–1 month) demonstrated mild, but likely insignificant, abnormalities of plasma amino acids (Data S2). Urine analysis showed widespread mild elevation of multiple amino acids and organic acid analysis revealed mildly elevated 2-oxoglutarate and pyruvate interpreted as a possible renal tubule leak or immaturity. Other analytes found to be high were gamma-glutamyl transferase 256 U/L (ref: 12–43 U/L) and alkaline phosphatase 342 U/L (ref: 129–291 U/L), a common finding in children on anticonvulsants.

By 6 weeks of age, seizures continued to occur sporadically, beginning with both eyes staring towards the corner of the room, mouth pouting, clonic movements of both limbs and respiratory grunting sounds. A repeat EEG at this time demonstrated abnormal delta activities and intermittently occurring angular or sharp waves, mainly anteriorly whilst at rest. Conversely, when she cried or had been alerted, the recording was of lower voltage without sharp waves but the content was abnormal. An electrocardiogram showed a normal corrected QT interval. At 2 months of age, she was commenced on 0.3 mL of DaliVit multivitamin oral drops per day, a dose which contained 0.25 mg of PN. Seizures were reported to have ceased 6 days after this, at a time when she was also receiving 6.7 mg/kg/day of phenytoin and 11 mg/kg/day of carbamazepine. Further biochemical testing (3 months) revealed a plasma PLP level of 670 nmol/L (ref: 15–73 nmol/L) but a CSF PLP level of 12 nmol/L (ref: 14–92 nmol/L). This high plasma to CSF PLP gradient suggested an abnormality of vitamin B₆ metabolism; thus, she was commenced on 5 mg/kg/day of PN. Urinary α -AASA was not elevated and no mutations were detected in *ALDH7A1* or *PNPO*.

Throughout the following 2 years, she continued to have seizures, mainly during intercurrent illness, requiring 15 mg/kg/day of carbamazepine for control, in addition to PN supplementation. An MRI and EEG were unremarkable; therefore, weaning of carbamazepine was carried out over a period of 2 months. Three days after weaning, she had two generalised seizures lasting between 3 and 4 min, consisting of tongue biting, stiffening, going pale, grunting, frothing at the mouth and becoming floppy afterwards. The carbamazepine was recommenced at her original dose but

she became very ataxic (a side effect of this medication); therefore, the dose was halved (7.3 mg/kg/day). Neurotransmitter analysis (4 years) revealed a slightly low level of methyltetrahydrofolate of 41 nmol/L (ref: 52–178 nmol/L); thus she was started on calcium folinate (7.5 mg/day).

Since commencing PN treatment (at four months), her dose had been increased to 15.6 mg/kg/day in addition to 7.3 mg/kg/day of carbamazepine, in line with weight gain. She is developmentally delayed (7 years old) with minimal expressive language and attends a special school but remains healthy except for seizures in the context of intercurrent illness. A recent EEG has shown a change to a left temporal lobe focus. Since genetic diagnosis, weaning of PN has commenced and her dose has been halved with no increase in seizures.

Methods

This study was approved by the ethics committee of Great Ormond Street Hospital for Children and National Research Ethics Committee London (Bloomsbury). Whole-exome sequencing (WES) was carried out for the proband and parents (BGI Genomics, Hong Kong). Further details of sequencing and data analysis techniques can be found in Data S3.

Results

WES data was analysed initially assuming that this disorder had been inherited in an autosomal recessive manner. No plausible variants were identified that fitted a homozygous or compound heterozygous inheritance pattern. Since there was no family history of the disorder, data was reanalysed to look for *de novo* variants. Stringent filtering identified 7 variants (7 genes). The best candidate was a known pathogenic *de novo* missense change (c.629G>A; p.Arg210His) in exon 1 of *KCNQ2* (Fig. 1). WES data was also scrutinised for potentially pathogenic variants in genes known to cause inborn errors of B₆ metabolism, a high plasma to CSF PLP ratio or hyperphosphatasia, namely, *PNPO*, *ALDH7A1*, *ALPL* and genes involved in glycosylphosphatidylinositol (GPI) anchor synthesis. None were identified.

A comprehensive literature review of reports indexed in PubMed describing patients with *KCNQ2* mutations who have had a trial of vitamin B₆ was performed using the terms *KCNQ2* and epilepsy. Ten reports detailing 23 patients with mutations in *KCNQ2* having been trialled on vitamin B₆, either transiently or on a long-term basis (Data S1) were found. Three of these were reported to have had a clinical response to varying degrees. The first, a patient with a 1.5-Mb terminal deletion of the long arm of

chromosome 20 which included deletion of *KCNQ2*, masqueraded as pyridoxine-dependent epilepsy with a 95% reduction in seizure activity seen within 1 min of administration of intravenous PN (Mefford et al. 2012). The others included a child with benign familial neonatal seizures (BFNS) reported to have been treated acutely with PLP (Allen et al. 2014) and a child with neonatal epileptic encephalopathy (NEE) in which a combination of topiramate, vigabatrin and PN controlled seizures (Weckhuysen et al. 2012). 6/23 additional patients were treated with vitamin B₆ during the first month of life; however, responses to each antiepileptic drug (AED) were not stated. Whilst in the majority of patients no clinical improvement was noted, this may be related to the length of trial they received and other AEDs that were being taken concurrently. None of the patients were documented as having CSF PLP measured.

Discussion

The patient described here had an apparent improvement in seizure control on PN treatment and had an abnormally high plasma to CSF PLP ratio prior to PN supplementation. Antiquitin and PNPO deficiency were both ruled out biochemically and/or genetically. The high plasma PLP level whilst on only 0.25 mg/day (0.07 mg/kg/day) PN was noteworthy, being much higher than levels reported in healthy individuals and similar to levels in adults taking 40 mg/day (0.63 mg/kg/day) PN (Midttun et al. 2005) and in fact more comparable to children taking 200 mg/day (8 mg/kg/day) for treatment of PDE (Footitt et al. 2013). Moreover, the plasma to CSF PLP ratio of 55.8 was very striking, being much higher than the upper limit of 4.4 in paediatric patients with neurological disease (Footitt et al. 2011). The only other genetically defined disorder in which a high plasma to CSF PLP ratio has been documented is hypophosphatasia due to mutations in alkaline phosphatase (*ALPL*). Defects in GPI anchor biosynthesis can also cause B₆-responsive epilepsy (Kuki et al. 2013) due to a decrease of the membrane-associated tissue non-specific alkaline phosphatase required to allow PLP to enter the brain. No potentially pathogenic variants were found in these genes. This report confirms the utility of WES for the diagnosis of childhood epilepsy and reveals that this patient's neonatal epilepsy and developmental disorder were caused by a *de novo* dominant mutation in *KCNQ2*. With the benefit of hindsight, this patient may have been diagnosed using a targeted epilepsy gene panel. Targeted gene panel sequencing has advantages over WES, including increased depth of gene coverage, more robust coverage of regions of interest and reduced incidental findings. WES was employed in this case due to the atypical presentation and biochemical

Fig. 1 *KCNQ2* sequence analysis of affected family. The affected individual shows a heterozygous missense change from G to A at position 629 of the cDNA (c.629G>A) causing a change of amino acid 210 from arginine to histidine (p.Arg210His)

findings; however, diagnostic panels remain a timely and cost-effective alternative for the diagnostic workup of children with neonatal/infantile epilepsies.

KCNQ2 encodes a voltage-gated potassium channel expressed in the brain (Biervert et al. 1998) and plays a critical role in determining response to synaptic inputs and subthreshold electroexcitability of neurons. Dominant mutations in *KCNQ2* result in a range of epileptic disorders including Ohtahara syndrome, NEE and 60–70% of BFNS (Weckhuysen et al. 2013). The evidence that the mutation found in our patient causes epileptic encephalopathy is strong. Three patients have been reported previously to have the same *de novo* p.Arg210His mutation (Weckhuysen et al. 2013; Numis et al. 2014). All had NEE presenting with seizures on the first day of life and, similarly to our patient, two became seizure-free on administration of carbamazepine after failure of other AEDs. Carbamazepine acts to stabilise the inactive state of voltage-gated sodium channels which co-localise with KCNQ potassium channels in neuronal membranes (Pan et al. 2006). Thus modulation of one channel may affect the function of the channel complex. The other patient showed no improvement on carbamazepine treatment and died shortly afterwards due to respiratory failure in the context of infection (Numis et al. 2014). None of these three patients were trialled on vitamin B₆.

Whilst *KCNQ2*-related epilepsy is very variable phenotypically, seizures, characterised by cyanosis or apnoea as seen in the case described, are a common presentation (Allen et al. 2014). The tonic stiffening and choking seen initially, associated with asynchronous discontinuity of EEG activities, have some parallels with the much more severe electro-clinical phenotype described in *KCNQ2*

encephalopathy. However, in this case, the EEG abnormalities remained mild, with resolution of any discontinuity within 2 weeks and normal findings during initial treatment with vitamin B₆. All EEG changes were non-specific and no distinctive electro-clinical pattern was discernible.

One of the most striking features seen in our patient, which directed further metabolic investigations, was her abnormally high plasma to CSF PLP ratio. The role of oxidative stress resulting from excessive free-radical production in epilepsy initiation and propagation is becoming a well-accepted paradigm and may explain this biochemical finding in our patient. Many studies have demonstrated that repeated seizure activity results in increased oxidation of cellular macromolecules such as proteins, lipids and nucleotides, which in turn can lead to neuronal death. It has been hypothesised that a cascade of events including excessive neuronal firing, increased glutamate release, N-methyl-D-aspartate receptor activation, influx of calcium into the cytosol and mitochondria and increased ATP consumption leads to abundant production of reactive oxygen species (ROS) (Shin et al. 2011). The brain is rich in mitochondria due to its high metabolic demand and it is plausible that this ROS production may overwhelm the normal mitochondrial antioxidant defences leading to mitochondrial dysfunction and greater superoxide production through a damaged respiratory chain, thus producing a self-perpetuating vicious cycle of oxidative stress. B₆ vitamers can also be attacked by oxygen-derived free radicals (Footitt et al. 2011) thereby depleting PLP in the CSF, as seen in our patient. Indeed ROS can also react with and deplete folates (Footitt et al. 2011) which would explain the low 5-methyltetrahydrofolate seen in our patient.

There is increasing evidence that vitamin B₆, given either as PN or PLP, can result in improved seizure control in idiopathic epilepsy (Ohtahara et al. 2011). However, the mechanisms underlying this response are unknown. Our patient showed an apparent improvement in seizure control upon starting multivitamin drops containing 0.25 mg of PN. If excessive ROS production due to unregulated neuronal firing results in the CSF PLP deficiency seen in our patient, it is intuitive that PN supplementation should correct this abnormality. In addition to this, a number of studies have demonstrated the antioxidant properties of the B₆ vitamers by preventing oxygen radical generation and lipid peroxidation (Chumnantana et al. 2005). Treatment with PN/PLP may therefore prevent secondary seizures due to oxidative stress-induced PLP depletion caused by unregulated neuronal firing, as well as curtailing the cycle of mitochondrial and neuronal dysfunction.

PLP has recently been shown to inhibit P2X receptors in vitro (Thériault et al. 2014). These receptors are cation-permeable ligand-gated ion channels that are activated by ATP and gate fast depolarising sodium and calcium entry. Effects of their activation include neuromodulation under conditions of excessive firing and indirect effects on excitability by control of neuroinflammation and gliosis (Henshall et al. 2013). Certain P2X receptors, particularly P2X7R, have been shown to be activated during pathologic brain activity including neuronal necrosis due to excitotoxicity and prolonged or repeated brief seizures. This activation modulates neurotransmitter release, promotes activation and release of interleukin 1 β (a proconvulsant) from microglia and acts on oligodendrocytes and astrocytes to trigger cell death (Henshall et al. 2013). P2X7R antagonists have been reported to have potent anticonvulsant effects (Jimenez-Pacheco et al. 2013); thus, it is possible that PLP is having anticonvulsant effects by acting as a P2X7R antagonist. It is also possible that the action of PLP is not only limited to P2X receptors. Perhaps PLP is also a ligand of the KCNQ family of potassium channels; the clinical improvement seen in our patient upon PN supplementation may then be due to PLP modulation of excessive firing due to the lack of inhibitory potassium current due to *KCNQ2* mutations.

Finally, one effect of the lack of inhibitory current and thus excessive neuronal firing is a depletion of inhibitory neurotransmitters, for example, γ -aminobutyric acid (GABA). GABA is synthesised from glutamate by the enzyme L-glutamic acid decarboxylase for which PLP is a cofactor. Supplementation with either PN or PLP may favour conversion of glutamate to GABA, leading to anticonvulsant effects.

Unfortunately, there are no prospective studies observing CSF PLP levels in seizure patients on various AEDs to determine whether low PLP is a general finding in all

patients independent of underlying genetic defect. In addition, there are no studies of CSF PLP levels in healthy newborns or infants. All reference ranges are generated from neurologically abnormal children undergoing CSF metabolite measurement for diagnostic workup. Thus there are limitations in establishing a true reference range and these vary throughout the literature, making interpretation of low values such as those seen in our patient difficult.

Despite the potential benefits of vitamin B₆ as an anticonvulsant, there are well-documented adverse effects that can occur in patients taking high doses, namely, peripheral neuropathy for PN and liver toxicity for PLP (Mills et al. 2014). We recommend that patients with intractable epilepsy, including those with channelopathies, should be trialled on B₆ and in those showing a response liver function and nerve conduction should be tested periodically. In addition, a trial of discontinuation should be carried out to confirm that there is a real necessity for PN/PLP supplementation.

Conclusions

We present the case of a girl whose neonatal seizures showed an apparent improvement on PN treatment and had an abnormally high plasma to CSF PLP ratio, who at 7 years of age was shown to have a channelopathy disorder caused by a *de novo* mutation in *KCNQ2*. In previous reports, the anticonvulsant effect of vitamin B₆ was assumed to be coincidental or not discussed further, perhaps due to the lack of dramatic response. We hypothesise that the anticonvulsant effect of B₆ vitamers may be more universal than previously thought and may be propagated by multiple mechanisms: (1) direct antagonist action on ion channels, (2) antioxidant action on excess ROS generated by increased neuronal firing and (3) replenishing the pool of PLP needed for the synthesis of some inhibitory neurotransmitters. Further work is required to understand these proposed mechanisms and its utility as an adjunctive treatment for patients with *KCNQ2* mutations and the wider epileptic population.

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Take-Home Message

This paper presents a case of KCNQ2 channelopathy showing an apparent response to pyridoxine treatment and indicates that a high plasma to CSF pyridoxal 5'-phosphate ratio is not specific for disorders directly affecting vitamin B₆ metabolism.

Compliance with Ethics Guidelines

Conflict of Interest

Emma S. Reid, Hywel Williams, Polona Le Quesne Stabej, Chela James, Louise Ocaka, Chiara Bacchelli, Emma J. Footitt, Stewart Boyd, Maureen A. Cleary, Philippa B. Mills and Peter T. Clayton declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

All authors have read the manuscript and agreed to it being submitted for publication. All individuals listed as authors meet the appropriate authorship criteria, nobody who qualifies for authorship has been omitted from the list, contributors and their funding sources have been properly acknowledged, and all authors and contributors have approved the acknowledgement of their contributions. Emma Reid contributed to data analysis and wrote and submitted the manuscript. Hywel Williams, Polona Le Quesne Stabej, Chela James and Louise Ocaka together prepared the DNA samples for whole-exome sequencing, analysed the data and confirmed the pathogenic mutation. Emma Footitt submitted the initial application for whole-exome sequencing to be carried out. Chiara Bacchelli considered and accepted the application for sequencing. Peter Clayton, Maureen Cleary, Emma Footitt and Emma Reid consulted with the patient and her family regarding the research and the results of the study. Stewart Boyd reviewed all EEGs from the patient. Philippa Mills and Peter Clayton made large contributions to the critical revision of the manuscript. All authors had access to the study data that support this publication.

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