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## MUTATIONS IN THE *ALDH7A1* GENE CAUSE PYRIDOXINE-DEPENDENT SEIZURES

### TO THE EDITOR

Recently, Lin and colleagues have reported a case of pyridoxine-dependent seizures in this journal<sup>1</sup>. The diagnosis was based upon the clinical criteria as formulated by Baxter<sup>2</sup>. In discussing the case the authors state that the underlying pathophysiology of the disorder is unknown and that no biochemical aids are available in establishing the diagnosis.

Indeed, for 50 years pyridoxine dependent epilepsy has been a clinical diagnosis based on the clinical effect of pyridoxine and confirmation of the diagnosis by a trial of pyridoxine withdrawal. However, in 2006 mutations in the *ALDH7A1* gene have been found in patients with pyridoxine-dependent seizures<sup>3</sup>. Since then, mutations within this gene have been shown to be present in the majority of patients with a clinical diagnosis of pyridoxine-dependent seizures<sup>3-6</sup>. These mutations cause a deficiency in  $\alpha$ -amino adipic semialdehyde ( $\alpha$ -AASA) dehydrogenase, indirectly leading to a secondary deficiency in pyridoxal-5-phosphate (P5P), which causes seizures. Administration of pyridoxine restores the P5P pool, thus controlling seizure activity<sup>3</sup>.

Another consequence of  $\alpha$ -AASA dehydrogenase deficiency is an accumulation of  $\alpha$ -AASA within the body, leading to increased plasma and cerebrospinal fluid levels<sup>3</sup>.  $\alpha$ -AASA is excreted in the urine, thus leading to highly increased urinary levels in pyridoxine dependent patients with *ALDH7A1* mutations. We and others have shown that urinary  $\alpha$ -AASA should be used as the biomarker for pyridoxine dependent seizures<sup>3-5,7</sup>.

In conclusion, in contrast to what Lin and co-authors have stated, the underlying pathophysiology and genetic mutations can be determined in the vast majority of patients with pyridoxine-dependent seizures. The diagnosis is no longer merely dependent on clinical criteria, but can be confirmed at the metabolite level by measuring  $\alpha$ -AASA in the urine of suspected patients. Ideally, urinary  $\alpha$ -AASA quantification and, if the biomarker is increased, subsequent DNA analysis should be performed in any child with suspected pyridoxine-dependent seizures. A trial of withdrawal in these patients should be omitted<sup>7</sup>.

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### THE AUTHORS' REPLY

We read with great interest and appreciate the comments made by Dr. Jasper V. Been et al. about our article "pyridoxine-dependent epilepsy initially responsive to phenobarbital"<sup>1</sup>. In his letter, Dr. Jasper called our attention about the mutation in the *ALDH7A1* gene as the cause of pyridoxine-dependent seizures.

In 2006 Mills et al. has conducted the initial studies concerning the mutations in *ALDH7A1*. In his work, the human gene *ALDH7A1* was identified and mapped to locus 5q31 (the locus of pyridoxine dependent epilepsy). This gene encodes antiquitin that has aldehyde dehydrogenase activity and when mutations occur, it abolishes the activity of antiquitin as a D1-piperidine-6-carboxylate (P6C) –  $\alpha$ -amino adipic semialdehyde ( $\alpha$ -AASA) dehydrogenase. The accumulating P6C inactivates pyridoxal 5'-phosphate (PLP) a cofactor essential for normal metabolism of neurotransmitter<sup>2</sup>.

Sequencing of *ALDH7A1* from individuals with pyridoxine dependent seizures (PDS) revealed homozygous and heterozygous mutations that were not detected in control subjects<sup>2</sup>.

In the following years, the pathogenesis of PDS were further detailed, specially in 2007 when Plecko et al. reported the ALDH7A1 mutational analysis in 18 patients with PDS<sup>3</sup> and Kanno et al. revealed point mutation in regions of the ALDH7A1 gene in 4 out of 5 patients with PDS<sup>4</sup>.

Those articles also reported that  $\alpha$ -AASA dehydrogenase deficiency is characterized by increases in  $\alpha$ -AASA in urine, plasma and cerebrospinal fluid<sup>3,4</sup>. Further, Bok et al., measuring  $\alpha$ -AASA in urine and plasma by liquid chromatography-tandem mass spectroscopy in 12 Dutch clinically diagnosed patients with PDS revealed that  $\alpha$ -AASA was elevated in both urine and plasma in 10 patients<sup>5</sup>.

The information provided by those reports culminated in the statement by Dr. Jasper that quantification of the urinary  $\alpha$ -AASA should be used as a biomarker of PDS, that, ideally, DNA analysis should be performed in any child with suspected PDS, and that a pyridoxine trial of withdrawal should be omitted.

The information brought by those articles concerning the pathogenesis of PDS is irrefutable. Unfortunately, the reports of Kanno et al.<sup>4</sup>; Bok et al.<sup>5</sup> and the letter of Struys et al.<sup>6</sup> were published, in their final form, few months after the submission of our article. Also unfortunately, the seminal articles of Mills et al.<sup>2</sup> and Plecko et al.<sup>3</sup> failed to be brought to our knowledge leading to inadvertent and unintentional un-accuracy in our article regarding the pathophysiology of PDS.

The statement that the pyridoxine-withdrawal test for making a definitive diagnosis of PDS should be replaced by DNA analysis and biochemical tests detecting urinary  $\alpha$ -AASA should, however, be considered with care. It must be taken into account that DNA analysis and diagnostic biochemical tests are not available or are not affordable in many countries. It also must be taken into account that PDS leading to neonatal *status epilepticus* is an emergency and when there is a clinical and electroencephalography suspicious of PDS, pyridoxine must be given. Therefore, in places where the ideal situation cannot be achieved, the final diagnosis may only be possible in the traditional and in the readily available way.

This point of view is shared by Kumar et al.<sup>7</sup> that sustain that pyridoxine withdrawal test, wherein pyridoxine is withheld from a suspected PDS patient to observe recurrence of seizures that respond to pyridoxine is considered to be the gold standard for the diagnosis of PDS. He goes further when proposing that in families where the parents are not convinced about the need for life-long pyridoxine therapy, consideration should be given to undertaking an early "pyridoxine withdrawal test". This, according to his opinion, in addition to making a definitive diagnosis of PDS for the physician, also demonstrates the need for continuing pyridoxine therapy to the parents, thereby guarding against the possibility of loss to follow-up<sup>7</sup>.

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