Long-term outcome in pyridoxine-dependent epilepsy


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LEVinus A BOK1 | Feico J Halbertsma1 | Saskia Houterman2 | Ron A Wevers3 | Charlotte VreeSwijk4 | Cornelis Jakobs5 | Eduard Struys5 | Johan H Van der Hoeven6 | Deborah A Sival7 | Michel A Willemsen8

1 Department of Pediatrics, Maxima Medical Center, Veldhoven; 2 MMC Academy, Maxima Medical Center, Veldhoven; 3 830 Laboratory of Genetic Endocrine and Metabolic Diseases, Radboud University Nijmegen Medical Centre, Nijmegen; 4 Department of Developmental Psychology, Tilburg University, Tilburg; 5 Metabolic Unit, Department of Clinical Chemistry, VU University Medical Center, Amsterdam; 6 Department of Neurology, University Medical Center Groningen, University of Groningen, Groningen; 7 Department of Pediatrics, University Medical Center Groningen, University of Groningen, Groningen; 8 Department of Pediatric Neurology, Radboud University Nijmegen, Medical Center, Nijmegen, the Netherlands.

Correspondence to Dr Levinus A Bok, PO Box 7777, 5500MB Veldhoven, the Netherlands. E-mail: l.bok@mmc.nl

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Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive disorder,1 with an incidence of approximately one in 400 000 children in the Netherlands.2 The underlying metabolic defect in the cerebral lysine degradation pathway, alpha-aminoadipic acid semialdehyde (α-AASA) dehydrogenase (antiquitin) deficiency, results in accumulation of several metabolites, mainly α-AASA, Δ1-piperideine-6-carboxylate, and pipecolic acid, and secondary pyridoxine depletion of the central nervous system.3,4 Treatment with pyridoxine is rational and generally sufficient to control the seizure disorder.

Despite the recent elucidation of the molecular basis for PDE,5 and the rapidly increasing number of reported patients since then, detailed data on long-term outcome remain scarce. Overall, outcome in PDE is often considered to be poor.6 To contribute to the understanding of the prognosis of children with PDE, we studied the long-term outcome of a previously described cohort of patients with PDE in the Netherlands by standardized evaluation of present neurocognitive functioning, and systematic review of all available magnetic resonance imaging (MRI) and electroencephalography (EEG) studies. We studied possible relations between the acquired follow-up data and the initial patient characteristics at diagnosis (i.e. the age at diagnosis, age at start of pyridoxine supplementation, and genetic and biochemical data).

METHOD

For this study, we included all patients with PDE (n=14: four males, 10 females, from 11 families; median age at assessment...
6y; range 2y 6mo–16y) diagnosed in our (nationwide reference) laboratory and born in the Netherlands between 1991 and 2008 (Table I). Three families had two affected children; in these families, a diagnosis of PDE in the first-born was made before the birth of the second affected child. In two families, the mother started daily pyridoxine in the first trimester of her second pregnancy, 60mg (patient 1) and 50mg respectively (Bok et al.5). PDE was proven in all patients by demonstration of increased urinary α-AASA concentrations and mutations in the antiquitin gene.3, 7 α-AASA in urine was measured by liquid chromatography–tandem mass spectrometry as previously published.3 The following data were retrieved from the medical records of all patients: sex; age at seizure onset and age at start of pyridoxine therapy; urinary -AASA intake (milligrams per kilogram); developmental milestones such as age at independent walking and school career (regular school or special education); and current medication.

All patients underwent a standardized neurocognitive test battery for this study (n=6) or test results were retrieved from the records (n=8). The Bayley Scales of Infant Development (2nd edition, Dutch manual) was used for children below 3 years of age,8 the Snijders-Oomen Non-Verbal Intelligence Test (Revised) for children between 2 years and 7 years of age,9 and the Wechsler Intelligence Test (Revised) for children between 2 years and 17 years of age.10 The Wechsler Intelligence Scale for Children and Snijders-Oomen Non-Verbal Intelligence Test are also provided separate outcomes for Performance and Verbal IQ. These tests have been judged as sufficient (Bayley Scales of Infant Development) or good (Snijders-Oomen Non-Verbal Intelligence Test and WISC-III); test results can be compared with one another.9 Developmental outcome was defined as normal with total developmental outcome scores between 70 and 84 (group 2), moderately delayed with total developmental outcome scores between 55 and 69 (group 3), and severely delayed with total developmental outcome scores under 55 (group 4). This definition was used for this study and is based (groups 1–3) on the Bayley Scales of Infant Development with a subdivision of group 4 with severely delayed development.8 SD was set at 15 IQ points. The median age at assessment was 6 years (range 2.5y–16y).

We collected all available MRI and EEG recordings of the 14 children with PDE. As MRIs and EEGs were collected over a period of 15 years from eight different Dutch centres, different machines and protocols had been used for MRI and EEG recordings. Although most of the MRIs were retrospectively collected and not done for this study, most MRI studies were extensive. Minimally studied MRI sequences included axial T1 and T2 and sagittal T1 images. All MRIs had been evaluated by a neuroradiologist in the original centre and were reviewed and scored separately by two investigators (LAB and MAW). A structured method was used by the investigators to study all MRIs.11 A mega cisterna magna was defined as a distance of more than 10mm, and an enlarged cisterna magna as a distance of 5 to 10mm, between cerebellum and skull. All EEGs were qualitatively assessed by two investigators (DAS and JHvdH). We applied the term ‘epileptiform’ activity for interictal sharp waves (i.e. peaked configurations at paper speed 70 to 200ms, observable in theta and/or delta frequency bands). We reserved the term ‘discrete’ epileptiform activity to denote sporadic, isolated sharp waves at a frequency of fewer than 10 per 30 minutes. We reserved the term ‘more pronounced’ epileptiform activity to denote isolated or small clusters of sharp waves exceeding a frequency of 10 per 30 minutes.

The study was approved by the institutional review board of Máxima Medical Centre, Veldhoven, the Netherlands. Signed,

Table I: Characteristics of patients with pyridoxine-dependent epilepsy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Male/female</th>
<th>Seizure onset</th>
<th>Start B6</th>
<th>α-AASA urine (mmol/mol creatinine)</th>
<th>DNA mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>M</td>
<td>Not</td>
<td>Antenatal</td>
<td>20</td>
<td>c.[1195 G&gt;C] [1195 G&gt;C]</td>
</tr>
<tr>
<td>2b</td>
<td>M</td>
<td>Not</td>
<td>Antenatal</td>
<td>75</td>
<td>c.[1195 G&gt;C] [1195 G&gt;C]</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>1d</td>
<td>16d</td>
<td>32</td>
<td>c.[1195 G&gt;C] [1195 G&gt;C]</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>5d</td>
<td>6mo</td>
<td>5</td>
<td>c.[750 G&gt;A] [1348 T&gt;A]</td>
</tr>
<tr>
<td>5a</td>
<td>F</td>
<td>1d</td>
<td>2.5mo</td>
<td>29</td>
<td>c.[1195 G&gt;C] [1195 G&gt;C]</td>
</tr>
<tr>
<td>6c</td>
<td>F</td>
<td>2d</td>
<td>10d</td>
<td>16</td>
<td>c.[1195 G&gt;C] [1195 G&gt;C]</td>
</tr>
<tr>
<td>7b</td>
<td>F</td>
<td>Intrauterine</td>
<td>5d</td>
<td>39</td>
<td>c.[1195 G&gt;C] [1195 G&gt;C]</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>3d</td>
<td>2.5mo</td>
<td>4</td>
<td>c.[750 G&gt;A] [750 G&gt;A]</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>2d</td>
<td>5d</td>
<td>99</td>
<td>c.[1195 G&gt;C] [1195 G&gt;C]</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>2d</td>
<td>13d</td>
<td>60</td>
<td>c.[1195 G&gt;C] [1195 G&gt;C]</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>0d</td>
<td>3d</td>
<td>71</td>
<td>c.[1195 G&gt;C] [1195 G&gt;C]</td>
</tr>
<tr>
<td>12c</td>
<td>F</td>
<td>2d</td>
<td>3d</td>
<td>24</td>
<td>c.[1195 G&gt;C] [1195 G&gt;C]</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>1d</td>
<td>8mo</td>
<td>10</td>
<td>c.[1195 G&gt;C] [1195 G&gt;C]</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>1d</td>
<td>3d</td>
<td>12</td>
<td>c.[1195 G&gt;C] [244 C&gt;T]</td>
</tr>
</tbody>
</table>

**a,b:** pair of siblings (1 and 5; 2 and 7; 6 and 12); reference ranges for urinary α-AASA: ≤6mo, <2mmol/mol creatinine; >6mo to 1y, ≤1mmol/mol creatinine; >1y, ≤0.5mmol/mol creatinine; α-AASA, alpha-aminoacidic acid semialdehyde.

**What this paper adds**

- Age at start of treatment and corpus callosum abnormalities significantly correlated with outcome in children with PDE.
- Normal follow-up imaging did not predict good outcome.
informed parental consent was obtained to collect the studied data.

Statistical analysis
A Mann–Whitney U-test and Fisher’s exact test were used to analyse non-parametric divided numeric and categorical data respectively. Significance was defined as p<0.05. Spearman’s correlation coefficients were estimated.

RESULTS
Neurodevelopmental outcome
Test results are summarized in Table II. All 14 children had learned to walk independently (mean age 26mo); however, only five children could walk independently before the age of 2 years. No child was physically disabled and all of the children were in level I of the Gross Motor Function Classification System. Six children attended regular school; three of these children needed extra support at school. Eight children attended a school for special education. One child had been treated for hydrocephalus by third ventriculostomy.

Normal cognitive development (IQ or developmental index >85) was seen in four children, mildly delayed development (IQ or developmental index 70–84) in four children, moderately delayed development (IQ or developmental index 55–69) in three children, and severely retarded development (IQ or developmental index <55) also in three children. Mean IQ was 72 (SD 19; median IQ 72). Performance versus Verbal IQ was tested in five children. In four of these children, Verbal IQ was higher than Performance IQ. In only one patient did this difference reach significance of more than one SD. In six children between 3 years and 7 years of age a pretest assumption of poorly developed Verbal skills was made by the psychologist, and subsequently a developmental test, the Snijders-Oomen Non-Verbal Intelligence Test, was chosen. This implied that comparison between Verbal and Performance IQ could not be studied in these children. Although in most reports the psychologist made some remarks about the behaviour of the studied child, we did not perform a structured systematic behavioural study in the children with PDE. The remarks on behaviour were (1) normal behaviour (n=9); (2) good concentration (n=10); (3) not well concentrated (n=2); (4) dyspraxia (n=3); (5) timid (n=2); (6) dysphasia (n=1); and (7) unknown (n=2).

Neuroimaging
Neonatal MRI
Neonatal T1- and T2-weighted MRIs were available for analysis for eight children; in four children additional diffusion-weighted images were available, and in one child we assessed neonatal computed tomography images. Corpus callosum was normal in five children, dysplastic in two (splenium), and hypoplastic in one child. Neonatal intracranial, subdural haemorrhage near the falx and tentorium cerebri was observed in three children. On T1 and T2, no distinctive white matter abnormalities (WMA) were seen, except in one patient. However, diffusion-weighted images revealed abnormal signals in all four studies. Lesions with an increased apparent diffusion coefficient were predominantly located in the frontal and parietal regions. In two neonates, small focal lesions with decreased apparent diffusion coefficient, next to extensive regions with increased apparent diffusion coefficient, were seen.

Follow-up MRI
In 13 children, MRI could be studied after the neonatal period (range 3mo–16y of age; Table II). Structural anomalies were still present on follow-up MRIs in all patients with neonatal MRI anomalies. One patient had a mega cisterna magna on follow-up that was not observed at the
time of neonatal imaging; this was the patient who required shunting. Taking all radiological data together, the corpus callosum was normal in seven children, four had a hypoplastic posterior area (isthmus) and three had an abnormal dysplastic posterior area (splenium) of the corpus callosum. Ventriculomegaly was observed in six children. Four had a normal ventricular size on their neonatal MRI. In the other two children, neonatal MRI was unavailable. In three children with ventriculomegaly, MRI suggested the presence of a narrow aqueduct.

In five children, WMA were present on T2-weighted imaging as discrete, multifocal lesions (predominantly) in the periventricular and/or central zone. WMA were located at frontal (n=3), parietal (n=1), or occipital zones (n=1) (see Figure 1). On follow-up, diffusion-weighted images and apparent diffusion coefficient were normal in all children. A mega cisterna magna was seen in one child. An enlarged cisterna magna was seen in three children.

**Focal signal abnormalities**
An abnormal focal MRI signal was seen in the globus pallidus (hypointense on T1) in one child, in a cerebellar peduncle (hyperintense on T2) in two children, and in the frontal subcortical white matter in one child (hyperintense on T2). In this last child there was a slight increase in size in time. A unilateral periventricular cyst (4mm) just above the frontal horn was seen in one child, and a bone cyst was observed in the orbital bone of another.

**EEG characteristics**
Neonatal EEG characteristics have been described previously. At follow-up, EEG background activity had normalized in 12 of the 14 children (Table III). Only in one patient did we observe polymorphic spike wave-like activity (child 3). In five children epileptiform activity was absent, in five it was only discrete, and in four it appeared more pronounced. EPILEPTIFORM ACTIVITY was located at frontal (in five children), frono-central (in three), temporal (in one), or central (in one) regions.

**Patient characteristics in relation to developmental outcome**

**Start of treatment**
Children treated antenatally had a higher IQ than their siblings and had the highest IQ scores in group 1. Outcome of antenatal treatment versus postnatal treatment was significant in this group. Of the eight children who were treated in the first month of life, five revealed a developmental outcome in group 1 or 2, and three in group 3 or 4. Of the five children who were treated after 2.5 months of age, two showed a developmental outcome in group 1 or 2, and three in group 3 or 4. One patient who was only treated after 6 months of age had severely delayed development. Although there was no significant correlation between long-term neurodevelopmental outcome and age at which treatment was initiated, we observed a suggestive trend in favour of early treatment initiation. No pyridoxine daily doses were changed after 1 year of age.

**Genotype outcome**
Three children had a different mutation than the common Dutch one (Table I): two had a developmental outcome in groups 1 or 2, the other in group 4 (not significant).

**Seizure onset, persistence of epilepsy or EEG abnormalities, use of antiepileptic drugs**
Because all PDE seizures had started during the first few days of life, we did not observe a relation between seizure onset and developmental outcome (Table III). The persistence of seizures, the use of antiepileptic drugs (other than pyridoxine), the EEG background activity, and presence of epileptiform activity appeared to be unassociated with outcome.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>B6</th>
<th>AED</th>
<th>Background activity for age</th>
<th>Epileptiform activity</th>
<th>Seizure type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12y</td>
<td>1.2</td>
<td>None</td>
<td>Normal</td>
<td>Absent</td>
<td>I, II</td>
</tr>
<tr>
<td>2</td>
<td>2y</td>
<td>12</td>
<td>CBZ</td>
<td>Normal</td>
<td>Absent</td>
<td>I, II</td>
</tr>
<tr>
<td>3</td>
<td>1.5mo</td>
<td>6</td>
<td>VPA</td>
<td>Normal</td>
<td>Δ (F-C)</td>
<td>I</td>
</tr>
<tr>
<td>4</td>
<td>15y</td>
<td>1.8</td>
<td>None</td>
<td>Normal</td>
<td>Δ (F-C)</td>
<td>I</td>
</tr>
<tr>
<td>5</td>
<td>15y</td>
<td>1</td>
<td>None</td>
<td>Normal</td>
<td>Δ (F-C)</td>
<td>I, II</td>
</tr>
<tr>
<td>6</td>
<td>14y</td>
<td>1</td>
<td>None</td>
<td>Normal</td>
<td>Δ (F-C)</td>
<td>I</td>
</tr>
<tr>
<td>7</td>
<td>4y</td>
<td>9</td>
<td>None</td>
<td>Normal</td>
<td>Δ (F-C)</td>
<td>I</td>
</tr>
<tr>
<td>8</td>
<td>15y</td>
<td>1.3</td>
<td>None</td>
<td>Normal</td>
<td>Δ (F-C)</td>
<td>I, III</td>
</tr>
<tr>
<td>9</td>
<td>2y</td>
<td>7.5</td>
<td>PHB</td>
<td>Normal</td>
<td>Δ (F-C)</td>
<td>I</td>
</tr>
<tr>
<td>10</td>
<td>1mo</td>
<td>15</td>
<td>None</td>
<td>Normal</td>
<td>Δ (F-C)</td>
<td>I</td>
</tr>
<tr>
<td>11</td>
<td>3y</td>
<td>4.8</td>
<td>VPA</td>
<td>Normal</td>
<td>Δ (F-C)</td>
<td>I</td>
</tr>
<tr>
<td>12</td>
<td>14y</td>
<td>1</td>
<td>None</td>
<td>Intermittently slowed</td>
<td>Absent</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>5y</td>
<td>3</td>
<td>None</td>
<td>Normal</td>
<td>Absent</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>3y</td>
<td>9</td>
<td>None</td>
<td>Normal</td>
<td>Absent</td>
<td>–</td>
</tr>
</tbody>
</table>

All electroencephalograms (EEGs) revealed continuous and reactive brain activity; „abc“pair of siblings (1 and 5; 2 and 7; 6 and 12); seizure types: I, febrile seizures; II, partial seizures; III, generalized seizures; B6, daily vitamin B6 dose in mg/kg body weight; AED, antiepileptic drug; CBZ, carbamazepine; VPA, valproic acid; PHB, phenobarbital; Δ, epileptiform activity in theta spectrum; Δ, epileptiform activity in delta spectrum; (C), at central region; (T), at temporal region; (F), at frontal region; (F-C), at fronto-central region.
A relatively high prevalence of structural anomalies and WMA was seen on neonatal MRI, including one antenatal treated patient, which raises the question whether structural MRI abnormalities should be explained as an intrinsic part of the phenotype or as phenomena that are secondary to metabolic disturbances or treatment failure. Although corpus callosum abnormalities appeared associated with unfavourable neurodevelopmental outcome, a normal MRI at follow-up did not warrant good outcome.

So far, cerebral MRI characteristics have been described in 50 patients. In these patients, structural anomalies like corpus callosum hypoplasia, mega cisterna magna, as well as non-specific multifocal T2 WMA, cerebral atrophy, and hydrocephalus, are common findings. However, a normal MRI does not exclude PDE. In accordance with the literature, we also observed frequent MRI anomalies, involving structural corpus callosum abnormalities in half of the studied children. Although corpus callosum abnormalities have been described before (especially a thin posterior area), the dysplastic shortening of the corpus callosum is a new finding.

Although the presence of ventriculomegaly in PDE has been reported incidentally, no data exist on its prevalence. In this cohort it was seen at follow-up in six of the studied children. Interestingly, ventriculomegaly was present in a neonate who had received prenatal treatment, and in some children ventriculomegaly developed after the neonatal period. In three of the six patients, ventriculomegaly coincided with an apparently narrow aqueduct, even necessitating shunting of the cerebrospinal fluid in one patient. Although these numbers are small, it appears advisory to monitor children with PDE for development of raised intracranial pressure.

In four out of nine neonates with PDE, we observed WMA (indicated by abnormal diffusion-weighted images with increased apparent diffusion-coefficient signal intensity). Interestingly, these transient diffusion-weighted images/WMA, which are not uncommon in vasogenic edema, were mainly frontally located, whereas moderate to mild epileptiform activity was also frontally located. It remains speculative whether these morphological and functional abnormalities of frontal (white and grey) matter are associated and whether they should be regarded as common features of the underlying metabolic and epileptic encephalopathy.

In contrast to others, we were unable to demonstrate a relation between epileptiform activity, persisting seizures (including antiepileptic drugs), and neurodevelopmental outcome. This can be explained by the strong normalizing trend of follow-up EEGs, which have been described before. The finding that early (postnatal) initiation of pyridoxine treatment does not sufficiently save the patient from long-term neurocognitive deficits, and the occurrence of different MRI abnormalities at different ages (i.e. at fetal [structural], neonatal [transient], and older age), may reflect the complexity of the underlying pathophysiological mechanisms of PDE.

The wide range of developmental outcome in this PDE cohort is in accordance with the literature. We have reviewed developmental outcome data of 93 patients with PDE that we found in the literature. In those studies (five) that

**DISCUSSION**

In the Dutch PDE cohort, we aimed to elucidate the underlying relationship between clinical, radiological, electrophysiological, and biochemical parameters in developmental perspective. In this present cohort, all children had the classic phenotype of PDE with seizure onset shortly after birth, and most patients shared the same genotype. None of these children suffered from severe motor disturbances and all had learned to walk independently. The individual courses of intellectual development showed a wide range and most patients suffered from a delayed development, which is in accordance with the literature. In 10 of the 14 children, seizures were well controlled with monotherapy pyridoxine, and four of the 14 patients received long-term treatment with additional antiepileptic drugs, also reported by others. Outcome was significantly correlated with corpus callosum abnormalities and antenatal start of pyridoxine treatment.

**Other parameters and developmental outcome**

There was also no statistical relation between outcome and urinary z-AASA levels at presentation, outcome and daily pyridoxine dose, or outcome and head circumference. Intellectual outcome was related to age at independent walking.

**MRI and developmental outcome**

Of the seven children with an abnormal corpus callosum, five had a development outcome in group 3 or 4, whereas of the seven children with a normal corpus callosum only one child had a development outcome in group 3 (abnormal or normal corpus callosum versus IQ or developmental index < or >70; significant). No data were available to determine an association between corpus callosum abnormalities and Verbal or Performance IQ.

**Figure 1:** Axial fluid-attenuated inversion recovery image of patient 2 showing bifrontal subcortical hyperintense signal abnormalities.
presented quantitative data on IQ15,21,23,25,26 (a total of 24 patients), mean IQ was 68, comparable to our data. Using less detailed developmental scores for categorizing patients in whom exact data were lacking (i.e. normal vs mild, moderate, or severe delay) revealed similar results: normal development was seen in 25% (n=24), mildly delayed in 27% (n=25), moderately delayed in 24% (n=22), and severely delayed development in 24% (n=22).

Interesting results were found for the outcome of Verbal versus Performance IQ. In the normal population, Performance IQ equals Verbal IQ. In the literature, 17 of 24 patients with PDE in whom Verbal and Performance IQ data were studied, Performance IQ was significantly higher than the Verbal IQ. In the normal population, Performance IQ exceeds Verbal IQ. In the present study, Verbal IQ exceeded Performance IQ in the tested children. These test results do not support the findings of others who found a poor development of expressive language skills. These discrepancies with PDE indicate that ongoing testing during development in each PDE patient is important.

Owing to the low prevalence of PDE, the studied cohort was small. This makes statistical analysis difficult and less sensible, and conclusions limited (low power). In addition, the retrospective character of this study, at least in the acquisition of most clinical, radiological, and EEG data, as well as disease course during the neonatal period and early development, precludes firm conclusions. Enlarging the number of patients, for example by combining cohort databases, and structured prospective follow-up will provide better insight in the clinical course of PDE, and its correlation with different clinical, metabolic, and radiological parameters. Only when we learn more about the long-term course of the disease will we be able to optimize already available treatment options (pyridoxine supplementation) and to develop novel (e.g. dietary) interventions.

REFERENCES