**Epidemiology of pyridoxine dependent seizures in the Netherlands**

J V Been, L A Bok, P Andriessen, W O Renier

**Background:** Pyridoxine dependent epilepsy is a rare cause of seizures in childhood. The diagnosis is made on clinical criteria, that in many cases are never met. Therefore, epidemiological data on pyridoxine dependency are scarce.

**Aims:** To study the epidemiology of pyridoxine dependent epilepsy in the Netherlands, and to determine whether the diagnosis is based on the appropriate criteria.

**Methods:** Nationwide all departments of paediatrics (n = 113) and of paediatric or neonatal neurology (n = 17) were asked to report cases of pyridoxine dependent seizures. Birth incidences were calculated using national data on live births from 1991 to 2003.

**Results:** Response was received from 67% of paediatric departments, including all university hospitals and 94% of child neurology departments. Thirteen patients were reported. Four definite (31%), three probable (23%), and four possible cases (31%) were identified. Two cases (15%) did not meet criteria for either of these groups. The birth incidence was 1:396,000 for definite and probable cases and 1:252,000 when possible cases are included.

**Conclusions:** Thus far, epidemiological data on pyridoxine dependent seizures were only available from the UK and Ireland. A higher incidence was found in the Netherlands, in accordance with earlier suggestions of a regional difference. The study shows that the diagnosis is often made without performance of a formal trial of withdrawal. The importance of confirming the diagnosis, concerning the consequences as for individual prognosis, the potential side effects of prolonged pyridoxine substitution, and the possibility of treating the mother in case of future pregnancies are emphasised.

**Methods**

A questionnaire by letter was send to all heads of paediatric departments in the Netherlands, who were asked to report any case of pyridoxine dependent seizures born between 1980 and 2003. Likewise, all paediatric neurologists and neonatologists of the neonatal neurology working group were individually approached to report cases. Respondents were asked to fill out a questionnaire. The referred data were reported and stored anonymously, for which no ethical approval is necessary in the Netherlands. The criteria of definite, probable, and possible cases of pyridoxine dependent seizures were applied as published by Baxter in 1999. Birth incidences were calculated over the period January 1991 to December 2003, using the total number of live births in the Netherlands during this period as adapted from http://statline.cbs.nl.

**Results**

Response was obtained from 76 of 113 paediatric departments (67%), including all university hospitals (n = 8), and from 16 of 17 departments of paediatric and/or neonatal neurology (94%). Eighteen notifications of known pyridoxine dependent cases were received, including five duplicate reports. Each patient was at least reported by one academic specialist or child neurologist. In addition, one patient from our personal experience was included (patient 10 in table 1).

Of all patients reported, only one was born before 1991. This was one of two patients for whom only sparse clinical data were retrieved. Many respondents mentioned difficulty reporting patients or retrieving clinical data from several
### Table 1

| Characteristics of definite, probable, and possible pyridoxine dependent patients |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Birth year | Probable | Definite | Possible | Probable | Definite | Possible |
| 1991 | X | 1 | 1 | 2 | 3 | 1 |
| 1992 | X | 2 | 2 | 3 | 3 | 2 |
| 1993 | X | 4 | 4 | 4 | 5 | 4 |
| 1994 | X | 6 | 6 | 6 | 7 | 6 |
| 1995 | X | 8 | 8 | 8 | 9 | 8 |
| 1996 | X | 10 | 10 | 10 | 11 | 10 |

*Patient number of sibling in parentheses.

<table>
<thead>
<tr>
<th>Birth year</th>
<th>Initial dose (mg)</th>
<th>Pyridoxine dependency</th>
<th>Pyridoxine dependency</th>
<th>Pyridoxine dependency</th>
<th>Pyridoxine dependency</th>
<th>Pyridoxine dependency</th>
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<tbody>
<tr>
<td>1991</td>
<td>120</td>
<td>Delayed initially but currently normal</td>
<td>Delayed initially but currently normal</td>
<td>Delayed initially but currently normal</td>
<td>Delayed initially but currently normal</td>
<td>Delayed initially but currently normal</td>
</tr>
<tr>
<td>1992</td>
<td>100</td>
<td>Delayed; attends special school</td>
<td>Delayed; attends special school</td>
<td>Delayed; attends special school</td>
<td>Delayed; attends special school</td>
<td>Delayed; attends special school</td>
</tr>
<tr>
<td>1993</td>
<td>80</td>
<td>Pyridoxine-dependent poor long-term skills</td>
<td>Pyridoxine-dependent poor long-term skills</td>
<td>Pyridoxine-dependent poor long-term skills</td>
<td>Pyridoxine-dependent poor long-term skills</td>
<td>Pyridoxine-dependent poor long-term skills</td>
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<tr>
<td>1994</td>
<td>60</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>1995</td>
<td>40</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>1996</td>
<td>20</td>
<td>Normal</td>
<td>Normal</td>
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### DISCUSSION

Thus far, epidemiological data on pyridoxine dependent seizures were only available from the UK and Ireland. As reported in this paper, a higher incidence of possible, probable, and definite pyridoxine dependent cases was found in the Netherlands. This is in accordance with previous reports of a regional difference in the prevalence of pyridoxine dependent seizures. The relative proportion of definite, probable, and possible cases in our study was 36%, 27%, and 36%, respectively. These percentages are very similar to those reported by Baxter: 39%, 25%, and 36%, respectively. Therefore, regional differences in diagnostic skills are unlikely to account for the different incidences between the two studies. A genetic factor is likely to play an
important role, since there were three sibling cases in our small study.

Moreover, our study confirms that the diagnosis is often made without application of the appropriate clinical criteria. Of all 13 patients reported, eight (62%) had been diagnosed with pyridoxine dependent seizures without the formal trial of withdrawal having been carried out. Parents may be reluctant to agree to a trial of pyridoxine withdrawal, because they fear it will cause harm to the child. On the other hand, we believe that in many cases physicians may never consider a trial of withdrawal due to insufficient knowledge of this rare disorder.

A standardised therapeutic approach to neonatal seizures has previously been suggested to heighten the awareness and improve the recognition of classical pyridoxine dependent seizures. In the Netherlands, a treatment protocol including a pyridoxine trial is increasingly used to address neonatal seizures in a standardised manner. We believe that this will indeed increase the recognition of pyridoxine dependent seizures and support an appropriate establishment of the diagnosis.

Such an approach should recommend administration of parenteral pyridoxine 50–100 mg as a test dose in neonates with seizures intractable to conventional antiepileptics. Clinicians should be aware of possible cardiorespiratory depressive effects of a first pyridoxine administration. Recently, there have been promising reports of pipecolic acid being a possible diagnostic marker of pyridoxine dependent seizures. It has even been suggested that measurement of pipecolic acid may be sufficiently sensitive to replace a trial of withdrawal. Therefore, we think measurement of pipecolic acid in plasma and/or CSF should be included in such a protocol as well. Additional data on this issue need to be collected in order to clearly establish the value of pipecolic acid in the diagnosis of pyridoxine dependency. Unfortunately, no data are available on pipecolic acid measurements in the patients reported here.

Confirmation of the diagnosis is reassuring for the patient and his or her family and is of great importance. It may have consequences for genetic counselling and facilitates a more precise prognosis. Furthermore, confirmation of the diagnosis in a young child may warrant pyridoxine administration to the mother in case of a future pregnancy, which in turn may prevent developmental delay in a subsequent pyridoxine dependent child. On the other hand, a trial of withdrawal may identify patients who have wrongfully been diagnosed with pyridoxine dependency. Previous data have shown that a large minority of patients treated as having pyridoxine dependent seizures in fact remain permanently seizure-free after pyridoxine withdrawal. This is important since needless maintenance treatment with high doses of pyridoxine may cause a serious, although largely reversible, dorsal root gangliopathy. No hard data are available as to what would be the proper timing for a trial of withdrawal. Probably it is better not to perform a trial shortly after the initiation of pyridoxine supplementation. Baxter has suggested that the trial should be carried out before school entry—that is, around the age of 4 years.

All patients reported in this study had relatively early onset of seizures, while the initial presentation of pyridoxine dependent seizures may occur up to the age of 9 months. This may be due to both under-reporting and under-recognition of late onset pyridoxine dependency. Early onset seizures in pyridoxine dependency are known to be associated with a poorer outcome, especially when treatment initiation is delayed. In our study however, only half of all patients were reported to have a substantial degree of developmental delay. Also there was no clear correlation between the age of treatment and outcome. Earlier reports on this issue have been conflicting. Baxter and Aicardi have suggested that earlier pyridoxine treatment is beneficial, and this has been confirmed by Plecko et al whereas Haenggeli et al found no correlation between the time of treatment and outcome. Conclusions are to be drawn with caution however, since the number of patients is relatively small, and comparative performance tests have not been performed.

The data presented in this study are based on the cooperation of the clinicians addressed. A methodological limitation of the study is related to the retrospective character of the study. Therefore, cases of pyridoxine dependent patients may be missed due to lack of response, leading to an underestimation of the actual incidence. Overall the response was limited, yet virtually all university hospitals and neurological departments replied. Since each patient was reported by at least one of the latter, we believe an incomplete report of patients is not very likely. Unfortunately, our study period had to be narrowed due to the inability of many respondents to retrieve clinical data from several years back. Theoretically this may have caused a reduced report of patients as well, although the relatively even birth year distribution of the reported patients over time does not support this. On the other hand, the high number of sibling cases may have led to an overestimation of the incidence of pyridoxine dependent epilepsy.

In conclusion, we think our data are indicative of a reliable number of patients born between 1991 and 2003 who are believed to be pyridoxine dependent in the Netherlands. Pyridoxine dependency seems to be more prevalent in the Netherlands than in the UK and Ireland, supporting earlier suggestions of a regional variation in the demographics of pyridoxine dependency. However, our results confirm that the diagnosis is still regularly made without application of the appropriate clinical criteria. On the other hand, many patients may never have been recognised and may continue to be unsuccessfully treated with conventional antiepileptics. A better knowledge of the disease entity and the clinical criteria needed for establishment of the diagnosis will contribute to heightened awareness and more adequate management of potentially pyridoxine dependent seizures. A standardised treatment protocol for neonatal seizures including a pyridoxine trial may be of additional value, at least as long as pyridoxine dependent epilepsy remains a clinical diagnosis.
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REFERENCES


ARCHIVIST

Using soap prevents diarrhoea, pneumonia, and impetigo

Diarrhoea and acute lower respiratory tract infections kill more than 3.5 million children under 5 years old each year. Most of the children are in poor communities in developing countries. Regular handwashing with soap reduces the incidence of diarrhoea but little is known about its effect on respiratory infections in these communities.

Now a study in Karachi, Pakistan (Stephen P Luby and colleagues. Lancet 2005;366:223–33; see also comment, ibid: 185–7) has confirmed that regular handwashing and bathing with soap is effective in preventing both diarrhoea and pneumonia.

In two side-by-side multiethnic squatter settlements in central Karachi 25 neighbourhoods were randomised to handwashing promotion and 11 to a control group. Three hundred households were assigned to promotion of handwashing with antibacterial soap containing 1.2% triclocarban and 300 to handwashing with plain soap. Three hundred and six households acted as controls. Each household contained at least two children under 5 years, at least one of them under 5 years. Fieldworkers visited intervention and control households weekly for a year to record symptoms, and to encourage regular handwashing and daily bathing, and to supply soap, in the intervention households. (In these communities thorough handwashing with soap is not universal practice although soap is sold in neighbourhood shops.)

In the intervention households the incidences of respiratory symptoms in children under 15 years, pneumonia in children under 5 years, and diarrhoea in children under 15 years were all halved. The results were similar in antibacterial and plain soap households. The incidence of pneumonia in under-5s was 4.4 episodes per 100 person-weeks in control households, 2.4 per 100 person-weeks in antibacterial soap households, and 2.2 per 100 person-weeks in plain soap households. The incidences of diarrhoea in children under 15 years were 4.1, 2.0, and 1.9 episodes per 100 person-weeks respectively. The incidence of impetigo in children under 15 years was reduced by one third in intervention households (0.94, 0.61, and 0.62 episodes per 100 person-weeks).

Promotion of handwashing and bathing with soap halved the incidence of both diarrhoea and pneumonia in children and reduced the incidence of impetigo by one third.
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