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Original Article

Long-term outcome in pyridoxine-responsive infantile epilepsy

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ABSTRACT

Background: Dose regimens of pyridoxine (vitamin B6) for treatment of infantile spasms have varied from 200 mg/d to 300 mg/kg/d. Only two long-term outcome studies of the treated patients are available.
Methods: We asked all pediatric neurologists treating pediatric epilepsy in Finland if they had seen patients with pyridoxine-responsive infantile epilepsy. Five children with infantile spasms and hypsarrhythmia and one with focal epilepsy were reported as pyridoxine responders. Data on clinical presentation and outcome were collected from patient charts.
Results: All B6 responders had un-known aetiology. Two patients were studied for pyridoxal 5′-phosphate oxidase (PNPO) deficiency and showed negative results. Ages at seizure onset ranged from 4 to 7 months. The maintenance dose of oral pyridoxine was 150 mg/day. Response occurred within 1-to 14 days (mean 5 days). Two patients were treated with concomitant antiepileptic drugs. Duration of pyridoxine therapy varied from 6 weeks to 4 years (mean 26 months). Four patients had later seizure recurrence: one at 15 months with motor seizures (stopped by valproate), another two in adolescence with focal epilepsy and one at 20 years with unclassified epilepsy. Intelligence was normal in five patients and one had a mild mental deficiency. Follow-up ranged from 8.5 to 24 years.
Conclusions: Rare patients with infantile epilepsy but not pyridoxine dependency may respond to smaller doses of pyridoxine than reported before. Long-term cognitive outcome appears to be good but late seizure recurrence (in adolescence or in adulthood) occur. So far it is unknown if the response was determined by genetic traits or disease-related factors.

1. Introduction

Vitamin B 6 (pyridoxine) – deficiency and vitamin B6 dependency are well-known disorders that cause seizures.[1,2] Although patients with pyridoxine-responsive infantile spasms do not have either vitamin B6 deficiency or dependency, they may respond to high-dose B6 therapy[3–6] and for a long time.[5]

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Blennow and Starck 1986[6] reported three patients with response to very high-dose pyridoxine phosphate treatment 200–400 mg/kg given for 2 weeks. Pietz et al., 1993[6] also used very high doses 300 mg/kg/d for one week. Response was observed in 5/17 patients (30%). One of the five had a relapse at 18 months. The observed adverse effects were gastrointestinal symptoms.

Ohtsuka et al., 1987[4] reported 118 patients who were treated since 1977 with high-dose pyridoxal phosphate 200–400 mg orally as initial treatment for infantile spasms. Pyridoxal phosphate responsive patients were defined in this study as those who were free of seizures for at least 1 month while receiving B6 alone or by addition of B6 to previously ineffective antiepileptic drug therapies. Seizure-freedom was obtained in 15/118 (13%) patients and in five/14 with "idiopathic" (unknown aetiology) (36%). Hypsarrhythmia resolved in 15 patients but some kind of epileptiform discharges remained in six cases. The observed adverse effects were increased levels of liver enzymes gamma-glutamyltranspeptidas (GOT) and glutamic-pyruvic transaminase (GPT). In their later report Ohtsuka et al. (2000)[5] described the long-term follow-up of 25 patients: eight with unknown aetiology and 17 with structural - metabolic aetiology. B6 therapy was discontinued without relapse after a mean of 10 years (1 year 8 months–24 years). All patients with unknown aetiology and seven with structural-metabolic aetiology (41%) had intelligent quotient or developmental quotient scores of 75 or higher.

Our aim was to study short- and long-term outcome in pyridoxine-responsive patients with infantile epilepsy on a nation-wide basis.

2. Patients and methods

We made a retrospective query to all neuropediatric departments centres all university hospitals and the main central hospitals in Finland asking whether B6-responsive patients with infantile epilepsy had been seen during the last 25 years. It was a common practice for infantile spasms during those years to give pyridoxine for 3–4 days before ACTH treatment. Six patients were identified (three from the Helsinki University Hospital, two from the Kuopio University Hospital, and one from Länsi-Pohja Central Hospital). Data on clinical presentation and course, EEG, treatment and outcome was collected from patients.

Our study has the approval of the ethical committees of Helsinki University Hospital and Kuopio University Hospital.

3. Results

All patients had uneventful pre-and perinatal periods and normal development prior to epilepsy onset. All patients were carefully examined for specific etiology and CNS infections. The examination included blood cell counts, vacuolated lymphocytes, plasma/serum glucose, toxoplasmosis, rubella cytomegalo Herpes simplex virus (TORCH) antibodies, C-reactive protein, sodium, potassium, calcium, phosphorus, alkaline phosphatase, urinary amino acids, glycosaminoglycans, and oligosaccharides, and when clinically indicated also organic acids and chromosome analysis. The CSF was studied for cell counts, glucose, protein, and immunoglobulin G (IgG) index. According the protocol all patients at that time were initially treated with pyridoxine to exclude pyridoxine deficiency as aetiology. Magnetic resonance imaging (MRI) and ophthalmologic examinations were performed. MRI and other etiological studies showed no pathological results. Normal alkaline phosphatase excluded alkaline phosphatase deficiency, and amino acids hyperprolinemia. Two patients (Patients 3 and 5, Table 1) were studied for PNPO deficiency which showed negative results.

Family history was positive for epilepsy in patient 1 (Table 1) (mother had focal epilepsy and maternal grandmother epilepsy of unknown type), and for febrile seizures in patient 2 (father). One mother had three spontaneous miscarriages in early pregnancy.

Treatment was started with either 50 mg pyridoxal phosphate intravenously (two patients) or pyridoxine 150 mg/day at onset of the spasms. The maintenance dose was 150 mg administered orally once daily. We did not have any specific treatment protocol. Response (defined as freedom from clinical seizures and normalization of EEG) occurred within 1-to 14 days (mean 5 days). The duration of pyridoxine therapy was six weeks to four years.

Four patients had received no antiepileptic drugs before or after pyridoxine (Table 1). Patient 4 was started simultaneously on B6 and nitrazepam, responded within 14 days, relapsed after B6 was stopped and remitted again when pyridoxine was restarted. Patient 5 was treated with vigabatrin 120 mg/kg with no effect for one week before B6 onset and was taken off vigabatrin one month later with no relapse.

Four patients had seizures recurrences. One patient (Patient 5 in the Table) had unclassified motor seizures at 1 year 3 months while still on pyridoxine; these stopped with valproate. Two patients started to have motor focal seizures at age 11 years (Patient 2) or 19 years (Patient 3). One patient (Patient 4) relapsed with unclassified epilepsy at age 20 years.

Neurocognitive investigation using age-appropriate psychological tests (Bayley, WPPSI and/or WICS) confirmed normal intelligence in three patients (Patients 1, 2, 4) and mild mental deficiency in one (Patient 3). Patients 5 and 6 were not tested but they attend mainstream school with good performance. No patients had any motor impairment.

4. Discussion

Our patients in this study were pyridoxine-responsive but not pyridoxine-dependent (as defined below). The results of our study revealed that B6 therapy given in smaller doses than in previous studies could be discontinued in the patients without recurrence of seizures or hypsarrhythmia after relatively short treatment periods compared to the literature.[4,5]

Pyridoxine-dependent epilepsy (PDE) seems to be different from pyridoxine-responsive epilepsy. PDE presents with neonatal or early infantile seizures or epileptic encephalopathy. Four clinical criteria are traditionally required for the diagnosis of PDE: 1) seizures refractory to common anticonvulsants but 2) good response to pyridoxine, 3) complete