

# Electroencephalographic changes in pyridoxine-dependant epilepsy: new observations

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**ABSTRACT – Objective.** Pyridoxine-dependent epilepsy (PDE) is a rare disease, of which the EEG manifestations are only partially characterised. We report our observations of EEG recordings in four patients with PDE. **Materials and methods.** EEG tracings from four patients fulfilling the clinical criteria for PDE were reviewed. Relative to the time of treatment with pyridoxine, EEG recordings were available before treatment in two patients (at ages four and 10 months), immediately after treatment in two patients and during long-term follow-up with treatment in all four patients. **Results.** Pre-pyridoxine interictal EEG findings included: diffuse slowing, bilateral independent multifocal epileptiform discharges, generalized bursts of polyspike slow waves and focal or generalized sharp waves. In addition, the EEG was often asymmetrical and included: generalized semi-rhythmic sharp and slow waves, a burst suppression pattern and continuous generalized spike and slow waves. In one patient, who was followed subsequently, a decrease in multifocal spikes and sharp waves and permanent cessation of clinical seizures, within 10 minutes of concurrent reduction of spikes in the pre-existing generalized spike slow wave pattern, was observed immediately after pyridoxine treatment. However, despite the clinical response in this patient we observed persistent generalized burst suppression for four days, and fluctuation of the EEG with diffuse slowing on day four and transient exacerbation of discharges with continuous spike slow waves on day 22. This was followed by intermittent sharp waves at eight and 20 months, mild slowing at 31 months and normal EEG at 43 months. Long-term EEG findings in the other three patients receiving pyridoxine ranged between normal and intermittent multifocal sharp waves. **Conclusion.** Our data confirm previous observations and provide the following new findings: (1) the presence of burst suppression pattern after cessation of seizures can occur for up to five days after initiation of pyridoxine and should not exclude the diagnosis of PDE, (2) possible fluctuation and even transient worsening of electrographic discharges were observed for up to three weeks after initiation of pyridoxine and (3) the abnormal EEG can persist for up to 43 months before normalizing (range 1–43 months) and in other cases in which it continues to be abnormal it may still improve after increasing the dose of pyridoxine.

**Key words:** pyridoxine dependent epilepsy, status epilepticus, child, electroencephalography, antiepileptic

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Pyridoxine-dependant epilepsy (PDE) was first described by Hunt *et al.* in 1954. It is a rare disorder, encountered most commonly in the first few days of life. Birth prevalence has been studied previously in the UK and the Netherlands and found to be roughly 1:783,000 and 1:396,000, respectively (Baxter, 1999; Been *et al.*, 2005). A study in South India determined that 7.4% of children with intractable childhood epilepsy were conclusively diagnosed with PDE, defined as intractable recurrent seizures that respond to pyridoxine administration; seizures recur when vitamin supplementation is discontinued and cease when pyridoxine therapy is reinstated (RamachandranNair and Parameswaran, 2005).

Recent studies have demonstrated the efficiency of diagnostic tests such as measurements of urinary alpha-aminoadipic semialdehyde (AASA) and pipercolic acid, as well as gene testing for mutations in the antiquitin gene encoding for the AASA dehydrogenase enzyme (Bok *et al.*, 2007; Plecko *et al.*, 2007). Recognition of PDE is crucial for a proper diagnostic approach and appropriate management. Due to the rarity of the condition, the electroencephalographic (EEG) patterns of PDE, whether ictal or interictal, are not fully defined and few descriptions exist in the literature, of which most are rare case reports and case series. Thus, additional observations are expected to increase our knowledge of this disorder and especially our index of suspicion, for the prompt recognition of the disease. Here, we report our observations in four previously unreported PDE cases. The objective of the study was to characterize, in particular, the EEG manifestations rather than the clinical manifestations or seizure types of PDE.

## Materials and methods

The medical records and EEG recordings of four patients diagnosed with pyridoxine-dependant epilepsy in our institution, the American University of Beirut Medical Center in Lebanon, were reviewed. The patients were diagnosed based on Baxter's criteria (Baxter, 1999):

- seizures were resistant to antiepileptic drugs and ceased after administration of pyridoxine;
- seizures were completely controlled by monotherapy with pyridoxine;
- recurrence of seizures was observed upon cessation of pyridoxine therapy and controlled again after reinstatement of the therapy.

For all patients, pyridoxine was withdrawn at follow-up, usually 6-12 months following initiation of therapy depending on the progress of each case, and seizures usually subsequently recurred one to four weeks later. Recent urinary AASA and genetic testing currently preclude the use of pyridoxine withdrawal as a required diagnostic criteria, however, at the time, such tests were not available for patients, hence the use of the above diagnostic criteria.

EEG recordings were available for two patients prior to pyridoxine therapy (however, these were recorded at four and 10 months of age and not in the neonatal period), two patients immediately after pyridoxine treatment and in all four patients during long-term follow-up receiving pyridoxine.

## Results

### Patient characteristics

The characteristics of the patients are summarized in *table 1*. All the patients were initially consulted and treated elsewhere, thus the details concerning the type or evolution of seizures were based only on the history given at the time and further details were not available to us. None of the patients gave a history of intrauterine movements, encephalopathy or abdominal symptoms. Onset of seizures occurred in the first few days of life (two to five days old). Three patients had generalized tonic clonic seizures and one had a focal left-sided tonic clonic seizure. These were the only types of seizures recorded as the patients were not initially diagnosed or treated at our centre during their neonatal period. Pyridoxine treatment was initiated very early for two patients and delayed to four months and 10 months of age in the other two patients, due to a delay in seeking specialized medical care. Pyridoxine was administered orally, except for patient 1 who initially received treatment intravenously and presented a mild immediate reaction consisting of mild hypotonia. The patient was also monitored for respiratory distress and apnoea, although none was recorded. All the patients who received pyridoxine from the onset of treatment to their last medical check-up were clinically seizure-free (except those whose treatment was tapered). Two patients with a delay in treatment presented moderate mental retardation. All other concomitant antiepileptics were tapered off and then stopped after starting pyridoxine therapy.

### EEG before pyridoxine administration

The following EEG descriptions refer to the two patients in whom treatment was delayed to four months and 10 months. EEGs of the other pre-treated patients were not available and no serial EEG studies before pyridoxine administration were available. For patient 2, a pre-pyridoxine interictal EEG at four months of age showed a burst suppression pattern that was most prominent in the frontal central regions in some segments and diffuse slowing with bilateral independent multifocal spikes and sharp waves in other segments of the EEG. For patient 1, pre-pyridoxine ictal EEG at 10 months of age revealed an intermittent right hemispheric burst suppression pattern consisting of 3-second periods of low to moderate voltage theta with 1-second periods of high voltage sharp theta

**Table 1.** Patients' characteristics.

Patient no.	Age at onset of seizure	Seizure classification	Status epilepticus	Age when pyridoxine treatment was started	Pyridoxine dose during maintenance therapy	Long-term outcome <sup>a</sup>
1	5 days	Generalized tonic clonic	Yes	10 months	250 mg twice daily	At last follow-up (five years old), patient was seizure-free with moderate mental retardation
2	4 days	Generalized tonic clonic	Yes	4 months	50 mg twice daily	At last follow-up (13 years old), patient was seizure-free with moderate mental retardation
3	2 days	Generalized tonic clonic	No	2 days	40 mg once daily	At last follow-up (17 years old), patient was seizure-free with normal development
4	5 days	Focal left sided tonic clonic	No	5 days	80 mg once daily <sup>b</sup>	At last follow-up (15 years old), patient was seizure-free with normal development

<sup>a</sup> The Denver Developmental Test was used to assess development in children of less than six years old. Standard neurological assessment and school performance were used for older children.

<sup>b</sup> Patient 4 received additional increases of pyridoxine throughout treatment but this did not affect EEG recordings.

and delta activity. The left hemisphere showed continuous semi-rhythmic spike and slow wave activity, as well as (in other segments of the EEG) generalized semi-rhythmic, usually bilaterally synchronous, sharp and slow wave activity, maximal in the right temporal area. Intermittently, the burst suppression pattern on the right side would show right-sided beta discharges in the periods of suppression (*figure 1*). During this recording, patient 1 was unresponsive with frequent generalized clonic jerks occurring every one to few seconds. Of note, both patients were receiving other anticonvulsants (patient 2 received valproate and patient 1 received phenobarbital and phenytoin) before pyridoxine treatment was started, which were later tapered off.

### EEG after pyridoxine administration

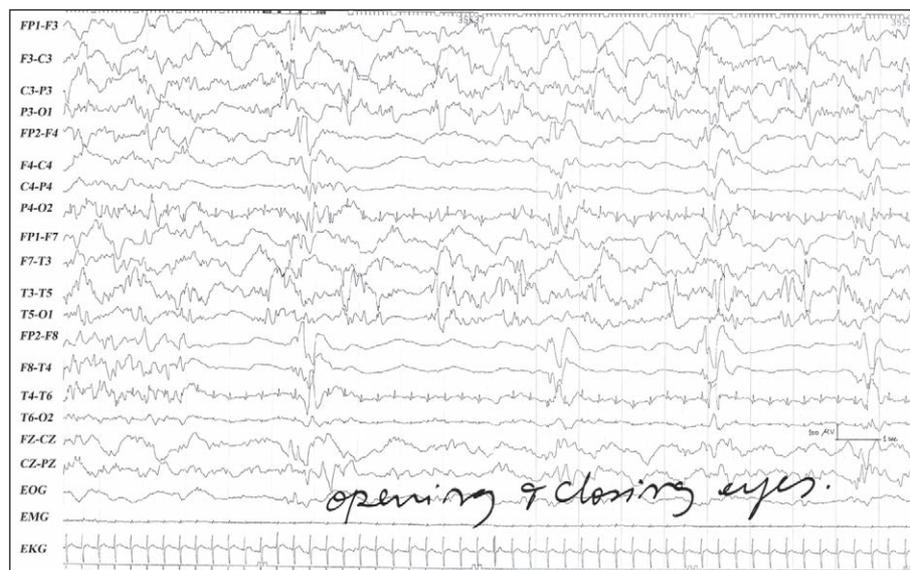
For patient 2, the post-pyridoxine EEG showed a decrease in the number of epileptiform discharges with complete resolution after one month of receiving pyridoxine.

For patient 1, serial EEG tracings after pyridoxine administration are summarized in *table 2* with illustrations in *figure 2*. In particular, patient 1 experienced an intermittent re-emergence of the generalized burst suppression pattern at two days after initiation of pyridoxine therapy, which

was not persistent, but continued to recur until day five (*figure 2A, B*). Moreover, after the EEG on day five that showed only diffuse slowing with a very brief period of burst suppression, a transient worsening was noticed on day 22 of therapy. This manifested as bilateral, predominantly right-sided, very frequent spikes and spike wave discharges superimposed on a high voltage slow asymmetric background in wakefulness and in sleep (*figure 2C, D*).

### EEG at long-term follow-up

The EEG of patient 1 was normal 43 months after initiation of pyridoxine therapy. At the age of 12 years, the EEG of patient 2 showed left temporal and fronto-temporal slowing in wakefulness and in sleep with left temporal and fronto-temporal focal sharp activity. At that time, patient 2 was receiving pyridoxine, 50 mg once daily. These manifestations became normalized seven months later, after increasing the dose of pyridoxine to 50 mg twice daily. The EEG of patient 3, at the age of 12, demonstrated very frequent right posterior temporal, focal, sharply contoured waves, generalized bursts of single sharp waves and rare generalized 1-second bursts of sharp and slow wave activity. Nine months later, and after increasing the dose of pyridoxine from 40 mg every other



**Figure 1.** Ictal EEG before pyridoxine treatment (patient 1) during unresponsiveness, eye fluttering and eye deviation showing: (1) left-sided semi-rhythmic sharp and slow wave activity, and (2) concurrent right temporal periodic discharges with beta discharges followed by semi-rhythmic sharp and slow waves.

**Table 2.** Serial EEG findings of patient 1 (patient 1 was an inpatient for the first week before becoming an outpatient).

Time after pyridoxine administration	EEG observations
10 minutes	Right-sided high voltage sharp theta activity with intervening periods of lower amplitude activity; left-sided semi-rhythmic delta activity that, after a few minutes, became polymorphic. Occasional spikes (less than before pyridoxine treatment) seen on the left.
20 minutes	Generalized burst suppression pattern with 1 to 2-sec burst periods followed by 5-30 sec of complete voltage suppression.
2 days	Generalized rhythmic delta activity with intermixed sharp wave activity of higher amplitude on the left side. Intermittently, for a few minutes every 5-10 minutes, the generalized burst suppression pattern <sup>a</sup> re-emerged (figure 2A).
5 days	Diffuse slowing of the background with occasional multifocal spikes seen bilaterally, most commonly over the left parietal area but also over the left frontal, right parietal, right temporal and right frontal regions. Burst suppression <sup>a</sup> recurred once on the right for one minute during the 30-minute recording (figure 2B, C).
22 days	High voltage slow asymmetric background with more slowing and higher amplitudes over the right side in wakefulness and in sleep with very frequent superimposed spikes and spike wave discharges <sup>b</sup> which were predominantly right sided (figure 2D).
8 months	Excess beta activity (probably related to concurrent phenobarbital therapy <sup>c</sup> ) and excess slowing in sleep, slightly more on the left, with intermittent 3-4 Hz, at times sharply contoured slow waves, also slightly more on the left.
20 months	Excess, almost continuous, 11 to 13-Hz frontally predominant spindle-like rhythms in sleep with a mild excess in posterior delta activity in sleep. Asymmetry in the background with more delta activity on the left and lower amplitude on the right upon arousal.
31 months	Excess beta activity with apparent lack of a well organized background in wakefulness and in sleep.
43 months	Normal EEG.

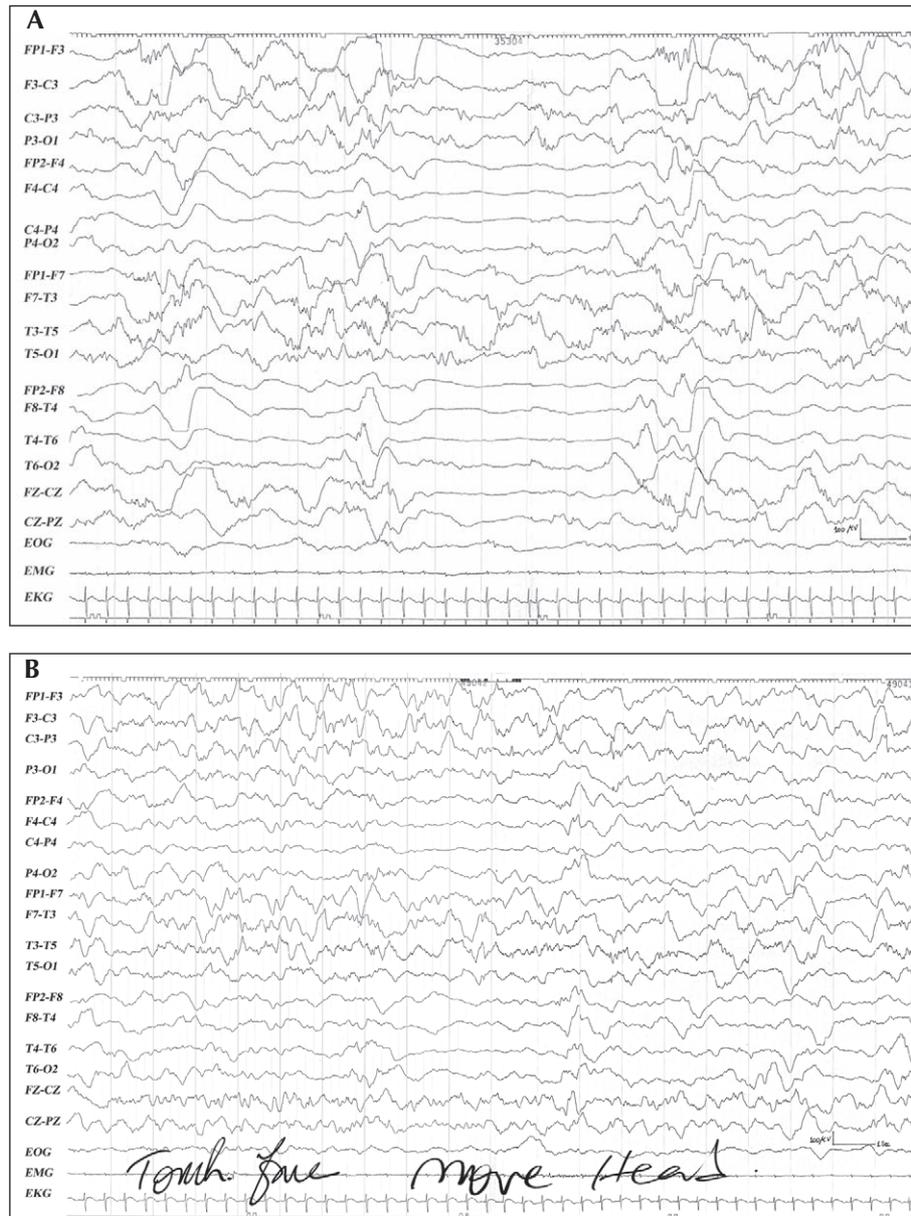
<sup>a</sup> Persistence of burst suppression.

<sup>b</sup> Transient worsening.

<sup>c</sup> Phenobarbital was being tapered off at the time and no clinical seizures were observed.

day to 40 mg once daily, the EEG was mildly abnormal with rare scattered sharp waves in the parietal and temporal regions seen in wakefulness and sleep. As for patient 4, an EEG recorded at 11 years of age showed 1 to 3-second

episodes of shifting, at times focal with sharply contoured bilateral temporo-parietal focal waves, with bursts of generalized sharp activity in drowsiness. All patients were compliant with their treatment.

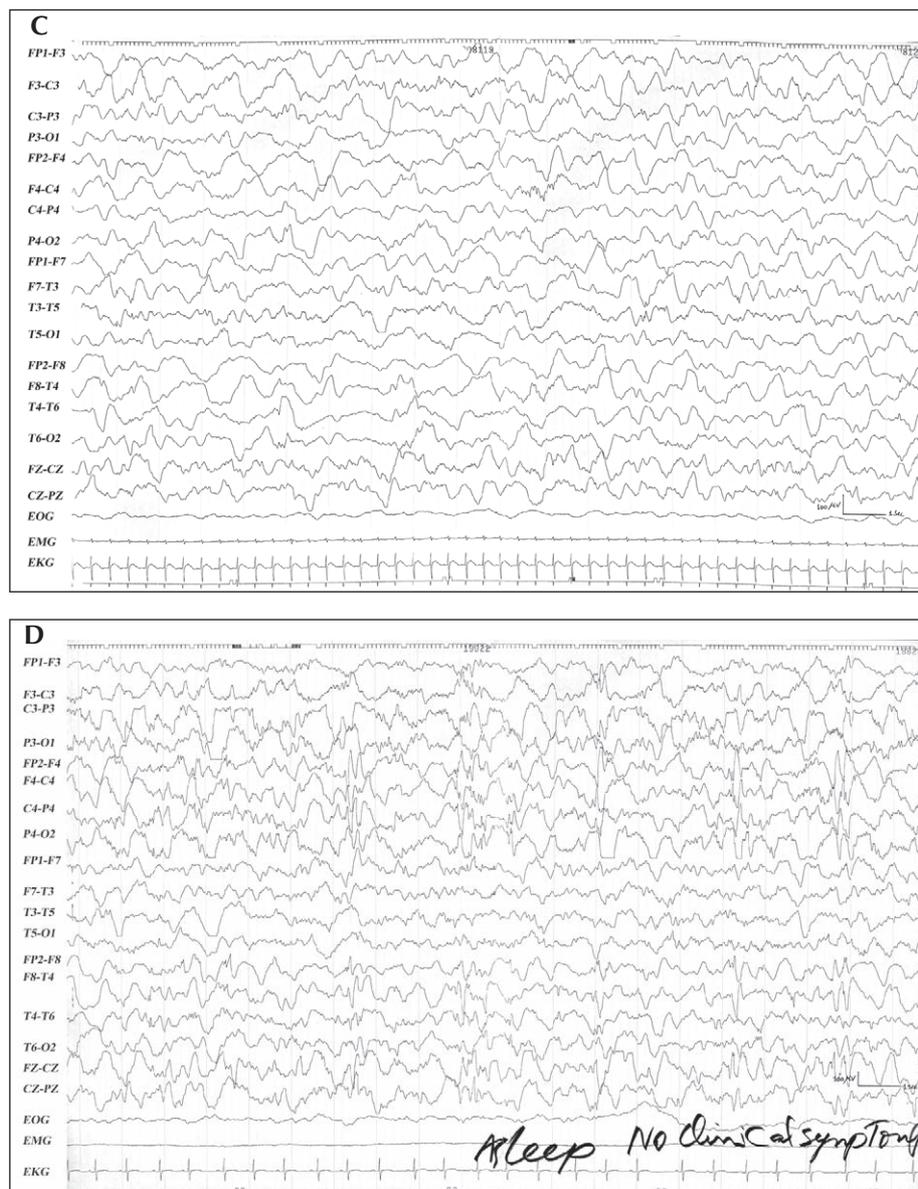


**Figure 2.** EEGs after pyridoxine treatment (patient 1). **A)** Two days post-pyridoxine treatment showing presence of burst suppression mainly on the right with some ongoing left semi-rhythmic delta activity. **B)** Three days post-pyridoxine treatment showing presence of burst suppression on the right for one minute during a 30-minute EEG, the rest of the EEG being as in C.

## Discussion

Most of the available information of EEGs from patients with PDE in the literature is based on a few case series and case reports. Below is a discussion of the above findings in the context of a review of the literature. Of note, although the patients we studied fulfilled Baxter's criteria for PDE, they presented some atypical features, notably, no documented abnormal intra-uterine movements or

breakthrough seizures with intercurrent illnesses and normal to moderate impairment of school progress. Neonatal EEG in the pre-pyridoxine treatment phase was not available that would otherwise have been informative. Although the effect of concomitant antiepileptics was not specifically studied, our prior experience suggests that antiepileptic drugs can control the seizures transiently but may not necessarily correct the EEG (Mikati *et al.*, 1991). The dose and route of administration of pyridoxine



**Figure 2** (continued). EEGs after pyridoxine treatment (patient 1). **C**) Five days post-pyridoxine treatment showing diffuse slowing of the background with occasional sharp waves and some spindle activity. **D**) 22 days post-pyridoxine treatment showing transient worsening (as compared to day five in **C**): asymmetric background with more slowing and higher amplitude over the right side in wakefulness and in sleep, with very frequent discharges which were predominantly right-sided with superimposed very frequent spikes and spike wave discharges.

was different for each patient and a dose-dependent effect could have influenced the EEG patterns discussed below. Although we did not specifically set out to study the difference between pyridoxine administered orally and intravenously, our prior experience shows that EEG changes may occur earlier after intravenous administration, but may still persist for hours or days (Mikati *et al.*, 1991).

#### Ictal EEG before pyridoxine administration

Ictal EEG patterns observed in PDE patients are consistent with previous reports:

- generalized bilaterally synchronous 1-4 Hz spike and slow wave complexes (Coursin, 1954);
- runs of unilateral/bilateral intermixed spikes, sharp waves and slow waves (Mikati *et al.*, 1991);

– focal rhythmic sharp theta waves (Mikati *et al.*, 1991). For patient 1, our findings confirm both the ictal spike and slow wave complexes and the increase in theta activity.

### Interictal EEG before pyridoxine administration

Interictal EEG patterns observed in PDE patients are consistent with previous reports:

- bursts and runs of high voltage bilaterally synchronous 1-4 Hz sharp and slow wave and spike and slow wave activity (Mikati *et al.*, 1991);
- focal sharp waves, multifocal spikes, single sharp waves and bursts of focal 3-Hz sharp and slow wave complexes (Mikati *et al.*, 1991; Coker, 1992). Although some of these findings have been reported, they refer to late onset PDE which differs from neonatal PDE (Nabbout *et al.*, 1999);
- bursts of generalized rhythmic delta of shifting voltage predominance (Mikati *et al.*, 1991);
- fronto-central bilaterally synchronous single polyspikes during sleep (Mikati *et al.*, 1991);
- continuous diffuse high voltage rhythmic delta slow waves and slow low voltage (Mikati *et al.*, 1991);
- suppression of burst-like patterns with suppression periods lasting up to 14 seconds (Nabbout *et al.*, 1999);
- poorly organized monotonous background with paroxysmal features (Lott *et al.*, 1978);
- hypsarrhythmia (Lott *et al.*, 1978).

Our observations confirm the burst suppression pattern previously observed. However, a normal pre-pyridoxine interictal EEG has also been observed in one patient with PDE (Coker, 1992).

### Interictal EEG directly after pyridoxine administration

Following pyridoxine administration, EEG patterns observed in PDE patients are consistent with previous reports:

- slow background and slow rhythm, occasional sharp waves in the posterior quadrant (Mikati *et al.*, 1991);
- very poorly developed slow and low voltage background, often, but not always resulting in normality (Mikati *et al.*, 1991).

In addition to previous observations, our study has identified the presence of a burst suppression pattern that occurs for up to five days following pyridoxine treatment and fluctuations with transient worsening of electrographic discharge (including an increased frequency of spike wave discharges) observed at day 22 of pyridoxine treatment. The persistence of the burst suppression pattern was previously observed as an incidental finding and not highlighted as a new observation (Nunes *et al.*, 2002). Similar to our studies, the burst suppression pattern was reported to disappear after six days of pyridoxine administration in a one-day-old female neonate (Nunes *et al.*, 2002). Interestingly, the occasional multifocal spikes, seen most commonly over the left parietal area at five days post-pyridoxine treatment in patient 1, were demon-

strated previously by Yoshii *et al.* (2005) in a seven-month-old female infant with a delayed diagnosis of PDE, before seven months of age. Hence, based on our above observations, transient worsening of the EEG during the first month and persistence of burst suppression for several days should not rule out a diagnosis of PDE.

Possible reasons for the delay in complete improvement of the EEG include:

- a lag in formation of the active form (pyridoxal phosphate) of pyridoxine;
- a lag in crossing the blood brain barrier;
- a lag due to clearing of excess glutamate or secondary long-term potentiation;
- a lag due to structural changes (secondary to the recurrent seizures), the effects of which cannot be overcome until levels of GABA increase and glutamate decrease with time.

Determining the exact mechanism awaits future studies.

### Interictal EEG at long-term follow-up

The EEG at long-term follow-up has been previously described to normalize with therapy over a period of up to two years after initiation of pyridoxine therapy (Mikati *et al.*, 1991). For patient 1, our observations point to an even longer time to complete normalization (43 months), not previously reported. In one patient of 12 years of age, we observed right posterior temporal, focal, sharply contoured waves and slow waves. The same finding has previously been reported by Ohtsuka *et al.* (1999) following a long-term 12-year follow-up of a girl with PDE. However in this case report, the EEG was recorded the day following a prolonged generalized seizure, preceded by a visual aura.

## Conclusion

Based on new EEG findings of patients with PDE, the study of this case series aims to consolidate our knowledge of EEG patterns associated with PDE. These findings include: the presence of burst suppression patterns for up to five days following pyridoxine treatment, fluctuations with transient worsening of electrographic discharges following pyridoxine treatment at day 22 and a long period (43 months) between initiation of pyridoxine treatment and normalization of the EEG. Observation of one or more of the above phenomena should not lead to a diagnosis of PDE being ruled out. We also demonstrate that abnormal EEGs observed during long-term pyridoxine therapy can often be normalized by increasing the dose of pyridoxine. These findings should complement the currently available use of biochemical and genetic tests available to diagnose and manage these patients. □

### Disclosure.

None of the authors has any conflict of interest to disclose.

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