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Long-term follow-up of an individual with vitamin B₆-dependent seizures

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We report on a 31-year-old female with vitamin B₆-dependent seizures whose seizure onset was in the neonatal period. Her elder brother had the same disorder and died in infancy. Administration of vitamin B₆ was initiated in the postnatal period. At the age of 12 years 1 month, 2 months after withdrawal of vitamin B₆, visual seizures began to occur frequently. Myoclonic seizures and occasional generalized convulsive seizures were also observed. At the same time, photoparoxysmal response and spontaneous diffuse spike-wave bursts were seen on her EEG. Myoclonic seizures were provoked by intermittent photic stimulation during the EEG. It is distinctive that visual seizures were one of the main seizure types in this patient, that her clinical course was relatively benign, and that she has normal intellectual outcome.

It is well known that pyridoxine-dependency is one of the causes of neonatal seizures. The diagnosis should be made as early as possible to prevent subsequent severe encephalopathy. However, the diagnosis may not be easy as a wider spectrum of pyridoxine-dependent seizures has recently been suggested (Bankier et al. 1983, Goutières and Aicardi 1985, Haenggeli et al. 1991, Coker 1992, Baxter et al. 1996). We report on a patient with pyridoxine-dependent seizures who has presented with some distinctive clinical features during the last 31 years of observation.

Case report

The patient is a 31-year-old woman. She is the second child of non-consanguineous parents. The pregnancy and the delivery were uneventful. She had a birthweight of 3150 g. Her elder brother had convulsions, which were similar to hers, from the first week after birth and died from these at 11 months of age. There was no other family history of convulsions. The parents noticed her convulsions on the 9th day after birth. They were generalized myoclonic seizures occurring every few seconds or minutes for 10 minutes to several hours. She was admitted to Okayama University Hospital on the 13th day after birth. On the day of admission, her seizures were completely suppressed 30 minutes after an intramuscular injection of 30 mg pyridoxal phosphate. She was given this dose of pyridoxal phosphate intramuscularly every day for the next 6 days. She was then taken off pyridoxal phosphate for 8 days, without a recurrence of the seizures. While she was hospitalized, she underwent two EEGs. The initial EEG was taken during sleep before the administration of pyridoxal phosphate. It showed an atypical *tracé alternant* with some sharp waves in the bursts and relatively short burst-burst intervals (up to 3 to 4 seconds). Although she was suspected of having vitamin B₆-dependent seizures, the final diagnosis could not be reached because seizures did not recur upon withdrawal of vitamin B₆. Consequently, she was discharged on the 27th day after birth. The oral administration of pyridoxal phosphate 30 mg/day,

phenobarbital 30 mg/day, and phenytoin 30 mg/day was initiated at that time.

The patient has taken the same drugs for 6 years without a recurrence of seizures. A few times a year she had EEGs; most were normal and had neither epileptiform discharges nor photoparoxysmal response. Spontaneous diffuse spike-wave bursts without photoparoxysmal response were occasionally observed in two EEGs. At the age of 6 years 2 months, administration of pyridoxal phosphate and phenytoin was stopped, and she was given phenobarbital 40 mg/day. Two months later she had several generalized convulsions: administration of pyridoxal phosphate and phenytoin were resumed. At the age of 11 years 11 months, pyridoxal phosphate was again withdrawn because her EEGs had been normal for 4 years. She continued to take phenobarbital 30 mg/day and phenytoin 40 mg/day. Two months later (at 12 years 1 month of age) she frequently complained of brief, peculiar visual symptoms lasting from a few seconds to a few minutes; a glaring round object was approaching her which increased in size. She also began to have brief generalized myoclonus or eyelid myoclonus. These visual seizures and myoclonic seizures could be provoked in daily life by bright or flickering light.

At 12 years 2 months of age the patient underwent an EEG which occasionally showed spontaneous 6 Hz spike-wave bursts with bilateral posterior dominance (Fig. 1). The background activity was normal and a photoparoxysmal response was not observed. One month later (at 12 years 3 months of age) she had a prolonged generalized convulsion lasting for 30 minutes, after the visual symptom. She claimed that a round

glaring object was approaching her which increased in size. Finally, she lost consciousness. After the convulsion she complained of headache and vomited several times. On the following day she underwent an EEG which revealed a definite asymmetry with focal slow waves in the right posterior temporal and occipital regions (Fig. 2). This EEG also showed a photoparoxysmal response at the time of intermittent photic stimulation (12, 14, 16, 18, 20, 24, 30 flicker/s) for the first time during the clinical course, and generalized myoclonic seizures were induced by intermittent photic stimulation (16 flicker/s) during the EEG (Fig. 3). Spontaneous 3 to 4 Hz diffuse spike-wave bursts were also frequently observed during waking and sleep. The same type of discharge was also induced by hyperventilation. She continued to have frequent visual and myoclonic seizures, and at 12 years 6 months of age she had two generalized convulsions. Her EEGs frequently showed diffuse 3 to 5 Hz spike-wave bursts without a photoparoxysmal response. Myoclonic seizures were occasionally induced by sudden noise on the day of a generalized convulsion. Pyridoxal phosphate was withdrawn for 1 year 6 months (from 11 years 11 months to 13 years 5 months of age) because her current doctor thought her seizures were not vitamin B₆ dependent. In addition to phenobarbital and phenytoin, sodium valproate and carbamazepine were administered but had no effect and finally her seizures were suppressed by the resumption of pyridoxal phosphate 50 mg/day at 13 years 5 months of age. At that time her medication comprised phenobarbital 40 mg/day, phenytoin 60 mg/day, carbamazepine 500 mg/day, and sodium

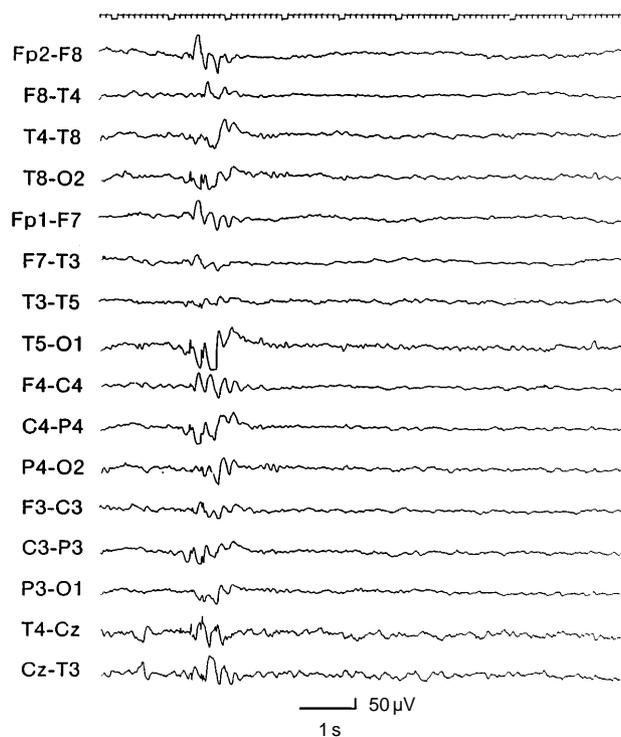


Figure 1: EEG at 12 years 2 months of age, 11 weeks after withdrawal of vitamin B₆. Spontaneous diffuse 6 Hz spike-wave burst with bilateral posterior dominance appeared during light sleep.

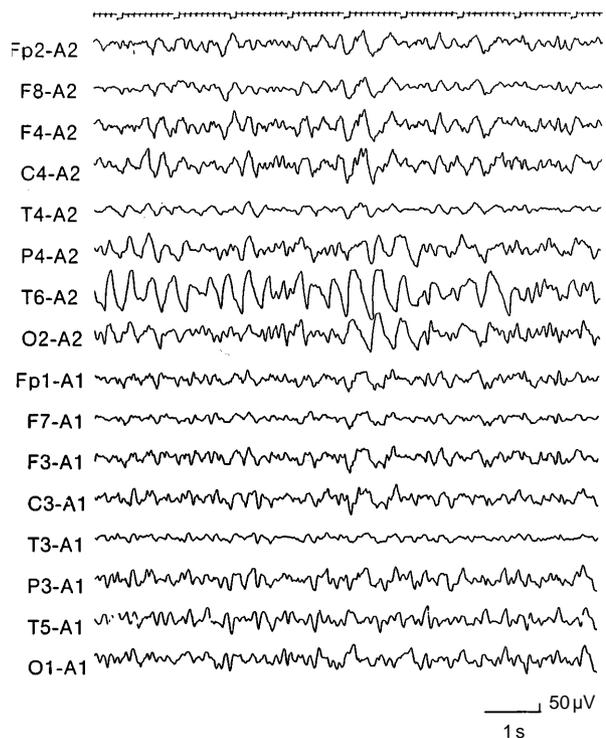


Figure 2: EEG at 12 years 3 months of age. The basic pattern of the EEG revealed focal slow waves in the right posterior temporal and occipital regions on the day following a prolonged generalized convulsion preceded by a visual seizure.

valproate 800 mg/day in addition to pyridoxal phosphate 50 mg/day. Since then her EEGs have shown neither epileptiform discharges nor a photoparoxysmal response. In the meantime phenytoin, phenobarbital, carbamazepine, and sodium valproate were withdrawn, and she has been given only pyridoxal phosphate from the age of 20 years 3 months. She is free from seizures on pyridoxal phosphate 50 mg/day orally, with recurrence of visual seizures when she forgets to take it. She has neither cognitive nor psychiatric disturbances. She works at a hospital as a registered nurse.

Discussion

Pyridoxine-dependent seizures are a relatively rare autosomal recessive disorder that cause neonatal seizures. The elder brother of our patient was considered to have had the same disorder. The seizures of our patient started around the first week after birth. They were promptly suppressed by an intramuscular injection of pyridoxal phosphate and recurred due to its discontinuation. Our patient is a typical case of pyridoxine-dependent seizure in these aspects.

However, our patient had some unusual clinical features: the main seizure type was visual; she had frequent myoclonic seizures and rare major convulsions. Major convulsions were often preceded by visual seizures. According to a review of a large group of subjects with pyridoxine-dependent seizures (Haenggeli et al. 1991), various types of seizures have been described; generalized tonic-clonic seizures evolving into status epilepticus occur most frequently. Myoclonic seizures are also common. Seizures are often provoked by external stimuli. These features were also found in our patient. However, there have been no case reports in which visual seizures were the dominant seizure type. In photosensitive epilepsy, generalized spike-wave discharges induced by intermittent photic stimulation are frequently preceded by occipital spikes (Jeavons and Harding 1975), or parieto-occipital spikes with biphasic slow wave are induced by intermittent photic stimulation (Quirk et al. 1995). In patients with Lafora disease, visual seizures are commonly observed in addition to photosensitive and spontaneous myoclonic seizures (Tinuper et al. 1983). These facts indicate that photosensitive cases can show occipital spikes in addition to generalized spike-waves or they can have visual seizures in addition to generalized seizures such as myoclonic seizures. In our patient, major seizures were often preceded by visual seizures. The EEG on the day following a prolonged seizure, which was preceded by a visual seizure, showed focal slow waves on the right posterior temporal and occipital regions. These findings suggest that the visual seizures of this patient arise from the occipital lobe.

Mikati et al. (1991) reported EEG features of pyridoxine-dependent epilepsy in detail. They described that pre-pyridoxine EEG manifested a unique EEG pattern of generalized bursts of 1 to 4 Hz sharp and slow activity in most cases. They also described the specific sequential EEG changes upon vitamin B₆ withdrawal. The initial EEG of our patient did not show the unique EEG pattern as described by Mikati. During vitamin B₆ therapy, her EEGs only rarely showed spontaneous diffuse spike-wave discharges with normal background activity. Our patient and one of Mikati's patients showed stimulus-induced myoclonus (sound and light), a photoparoxysmal EEG response, spontaneous generalized epileptiform discharges, and subsequent spontaneous

myoclonus and major seizures after discontinuation of vitamin B₆. This phenomenon was observed within 5 days of withdrawal in Mikati's patient, and it was observed within a few months in our patient.

It is known that seizures recur within several days after discontinuation of pyridoxine in typical cases. Our patient did not have seizures for a few months after its discontinuation. Recently some atypical cases of pyridoxine-dependent seizures have been reported (Bankier et al. 1983, Goutières and Aicardi 1985, Haenggeli et al. 1991, Coker 1992, Baxter et al. 1996). Those atypical cases have unusual findings: later onset of initial seizures; a seizure-free period after taking of anticonvulsants, but before taking of pyridoxine; a long remission after withdrawal of pyridoxine; and atypical seizure type. Since pyridoxine-dependent seizures are considered to be caused by an inborn error of metabolism, it is likely that the degree of symptoms might depend on the degree of enzyme defect. Another possibility is that the presence of atypical cases suggests that pyridoxine-dependent seizures are a heterogeneous disorder. It is distinctive that the long-term cognitive outcome of this patient is favourable and that she has a relatively benign clinical course, although her elder brother belonged to a typical severe form of vitamin B₆-dependent seizures and died in infancy. The variable expression of this disorder in the same family has not yet been described. Our observation of this patient indicated that a mild form of vitamin B₆ dependency is rather difficult to diagnose because of the delayed recurrence of seizures upon withdrawal of vitamin B₆.

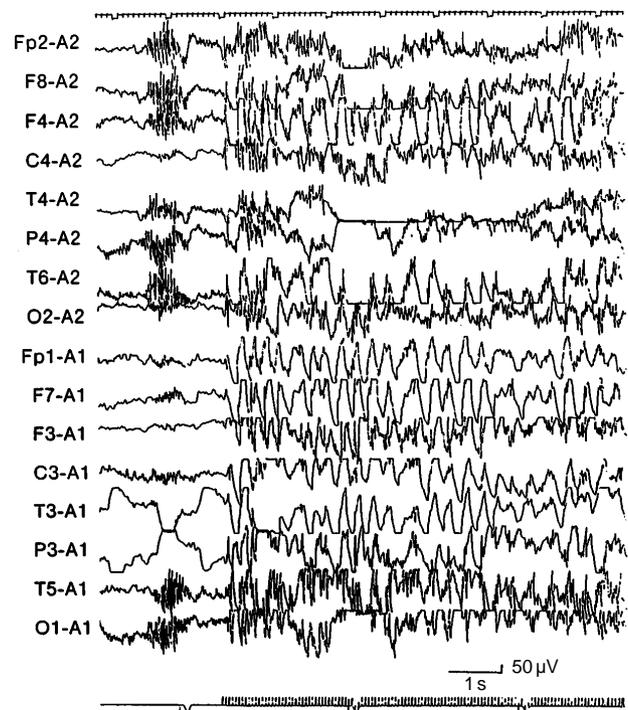


Figure 3: EEG at 12 years 3 months (the same as Fig. 2). Generalized myoclonic seizures were provoked by 16 flicker/s intermittent photic stimulation.

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