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Case Report

Pyridoxine-dependent status epilepticus diagnosed during infancy

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Abstract

Pyridoxine dependence is a very rare inborn error of metabolism. The disorder develops mainly during the early neonatal period, and cases diagnosed in infants are even rarer. We herein report a case of a 77-day-old boy with status epilepticus diagnosed with pyridoxine dependence. On day 2 after birth, the boy required respiratory management after entering a partial convulsive state. The convulsions did not respond to phenobarbitals and were temporarily controlled by continuous intravenous administration of midazolam. Subsequently, partial seizures occurred frequently, and the patient was observed under treatment with oral phenobarbital and phenytoin, and intravenous midazolam. However, at 65 days of age, partial convulsions of the right upper and lower limbs lasting for one minute oc-

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curred episodically in clusters every few to ten minutes. A high dose of phenobarbital was administered and the blood concentration increased to 42 μg/ml, but convulsions were not controlled. At 77 days of age, when 100 mg of pyridoxine was slowly injected intravenously during electroencephalography, the background activity flattened and spikes disappeared. Pyridoxine dependence was diagnosed and all antiepileptic agents were discontinued. Oral administration of pyridoxine at 10 mg/kg/day was started and seizures no longer occurred. Pyridoxine dependence is a treatable inborn error of metabolism. To obtain a diagnosis of pyridoxine dependence, trial administration of pyridoxine is essential, and the pyridoxine test for a definitive diagnosis should also be conducted in cases of status epilepticus during infancy.

Introduction

Pyridoxine dependence is a form of epilepsy caused by a very rare inborn error of metabolism [1]. Onset is usually manifested as intractable epilepsy during the early newborn period [2]. We examined the partial convulsive state of an infant who had been under treatment for epilepsy since the neonatal period. We then suspected pyridoxine dependence and conducted an intravenous pyridoxine test. After pyridoxine was injected intravenously, the electroencephalography and seizure symptoms of the infant improved drastically. Based on this case, pyridoxine dependence in infants is discussed.

Case report

The male infant had a gestational age of 40 weeks and 2 days, weighed 3,414 g, and was born by Cesarean section with no asphyxial signs. Forty-eight hours after birth, clonic partial convulsions occurred mainly in the right upper and lower limbs. Blood glucose, electrolytes, lactic acid, pyruvic acid, vitamin B6, amino acid, and organic acid were all normal. Brain computed tomography and magnetic resonance imaging findings of the infant showed normal findings. Auditory brainstem response also showed no abnormalities. Electroencephalography exhibited spikes in the left frontal and right parieto-occipital regions. The convulsive states did not respond to midazolam or Phenobarbital. Artificial respiratory management was no longer required at 7 days of age. The partial convulsions were temporarily controlled by phenobarbital at 7.5 mg/kg/day (blood concentration 35.6 μg/ml) and phenytoin at 10 mg/kg/day (blood concentration 5.8 μg/ml). At 56 days of age, a partial convulsive state of the right upper and lower limbs occurred. When the blood concentration of phenobarbital was increased to 44.1 μg/ml, the convulsions were stopped. At 65 days of age, partial convulsions of the right upper and lower limbs lasting one minute occurred episodically in clusters every few to ten minutes. The blood concentration of phenobarbital during the seizures was 42 μg/ml. Electroencephalogram exhibited spikes predominantly in the occipital area of the left hemisphere (Figure 1). On

77 days of age, a total of 100 mg of pyridoxine was slowly injected intravenously during electroencephalography, with an initial dose of 20 mg increasing to 30 mg after 3 minutes and 50 mg after a further 3 minutes. After 5 minutes, the background activity of the electroencephalography flattened and spikes disappeared (Figure 2). From the electroencephalographic findings, pyridoxine dependence was diagnosed, and all of the antiepileptic agents were discontinued. Oral administration of pyridoxine was started at 10 mg/kg/day and continued. Thereafter, the patient has had no seizures for more than 5 years with normal mental and physical development.

Discussion

Pyridoxine dependence is known to manifest as early-onset seizures in neurologically normal newborns. In an epidemiological study by Baxter *et al*. [1], the incidence is 1 out of 783,000 newborns, which is very rare. Some recent papers reported new genes associated with pyridoxine-dependent seizures. For example, Cormier-Daire *et al*. [2] identified a gene for pyridoxine-dependent epilepsy mapped to chromosome 5q31 region, while Mills *et al*. [3] reported mutations in antiquitin in individuals with pyridoxine-dependent seizures. Kanno *et al*. [4] reported allelic and non-allelic heterogeneities in pyridoxine-dependent seizures revealed by ALDH7A1 mutational analysis. In addition, Kure *et al*. [5] reported that GAD65 and GAD67 genes were involved in two family lines in a case of pyridoxine dependence. The main etiology has been proposed to be the absence of the inhibitory neurotransmitter GABA in the cerebrum. Glutamate dehydrogenase is an enzyme that is required when GABA is synthesized from glutamic acid. Pyridoxal phosphate, which is an active metabolite of pyridoxine, is a coenzyme of glutamate dehydrogenase that is likely to be associated with pyridoxine dependence [5]. However, in this case of pyridoxine dependence, the concentrations of pyridoxine in the blood are normal, and therefore the condition cannot be diagnosed from the clinical conditions of epilepsy or biochemical data obtained from screening of blood, urine, and spinal fluid. Therefore, trial administration of pyridoxine is the most important test for an early diagnosis.

The infant who had been treated for epilepsy since the neonatal period developed a partial convulsive state, and we suspected the possibility of pyridoxine dependence. We performed a pyridoxine test by intravenous injection of a total of 100 mg/kg of pyridoxine in three step-wise increasing doses. Subsequently, the abnormal waves on electroencephalogram of the infant were improved and the seizures were well controlled. Many of the initial symptoms of pyridoxine dependence lead to the development of partial convulsions in the early postnatal period. Occasionally, convulsive seizures develop *in utero* during late pregnancy and are perceived by the mother [6, 7]. In addition, some cases are diagnosed as pyridoxine dependence after the neonatal period as in our case, or even after

Fig. 1. Electroencephalogram recorded at 65 days of age. Spikes were observed in the occipital area of the left hemisphere.

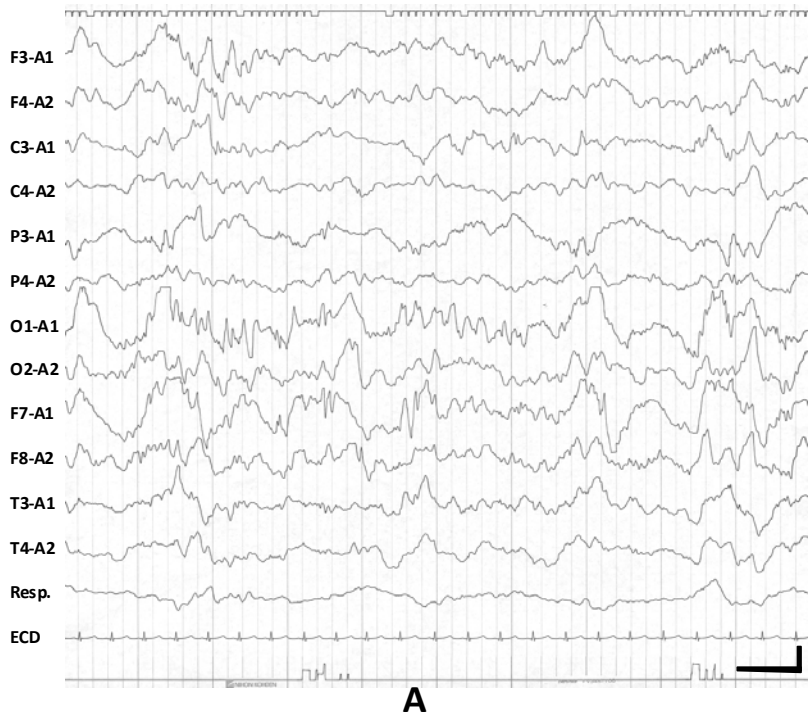
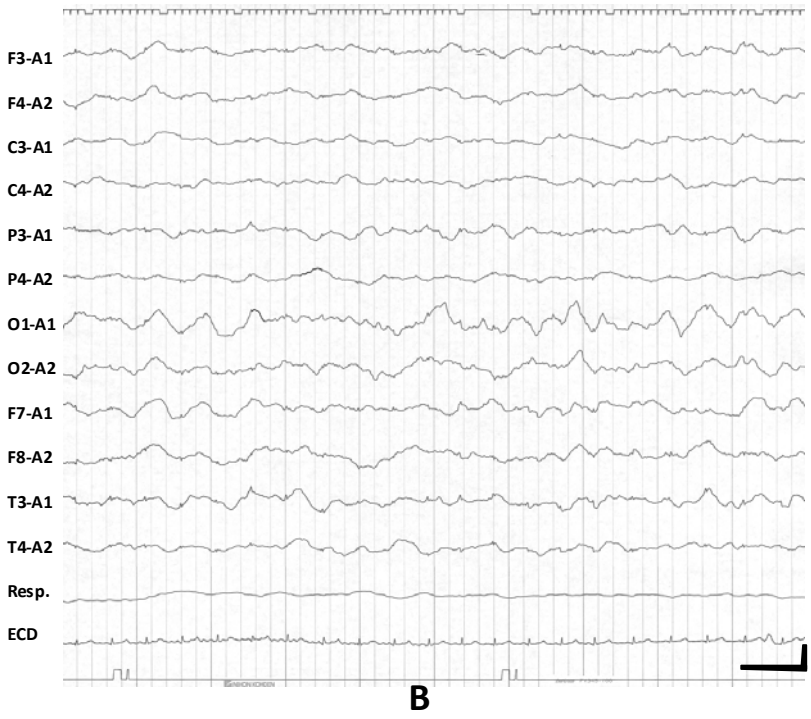


Figure 2: Electroencephalogram recorded after the injection a total 100 mg of pyridoxine at 77 days of age. Background activity flattened and focal occipital spikes disappeared



the first year of life [8-10]. In a review of 63 cases of pyridoxine-dependent seizures in North American, seizures were observed during the neonatal period in only 70% of the cases [11]. Moreover, it has been reported that pyridoxine-dependent epilepsy after the age of 1 year commonly manifests status epilepticus [12]. Therefore it is very important to exclude pyridoxine-dependent seizure even in patients with convulsions during the infantile period. Trial administration of pyridoxine is the most useful method for diagnosing pyridoxine dependence. However, including our case, one cannot distinguish pyridoxine-responsive seizures from pyridoxine-dependent seizures only from the observation that convulsions are stopped by prescribing pyridoxine. Ohtsuka *et al*. [13] reported relapse of seizure by discontinuation of pyridoxine. Our patient has continued pyridoxine treatment. Since pyridoxine dependence can be treated by administering pyridoxine, early diagnosis of pyridoxine dependence can prevent intellectual impairment of an infant [9]. The present case highlights that although very rare, it is very important to suspect pyridoxine dependence in infants with status epilepticus.

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