

Reversible Coma Associated With Prolonged High-Dose Phenobarbital Therapy in Bilateral Sturge-Weber Syndrome

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High-dose phenobarbital therapy is an effective treatment for refractory status epilepticus in children. The advantages of this therapy include milder adverse effects without limits for maximal phenobarbital levels or doses during the initial phase of treatment. However, little is known about the safety of continuing the treatment. We describe an infant with intractable epilepsy associated with bilateral Sturge-Weber syndrome who became comatose after 1 $\frac{2}{3}$ months of high-dose phenobarbital treatment. The patient regained consciousness as serum phenobarbital concentration decreased to below 40 $\mu\text{g/mL}$. The progression and recovery were also

documented by electroencephalogram and brainstem auditory evoked potentials. The present case suggests that prolonged high-dose phenobarbital therapy may cause cerebral and brainstem dysfunction in patients with severe cerebrovascular diseases. The underlying baseline metabolic and perfusion deficit related to the disease can precipitate the neurological complication during long-term high-dose phenobarbital therapy.

Keywords: intractable epilepsy; adverse effect; electroencephalogram; brainstem auditory evoked potential

High-dose phenobarbital therapy is one of the treatment options for status epilepticus in children.¹⁻³ Compared with other medications for refractory status epilepticus, such as pentobarbital and thiopental, this treatment is preferred because of its similar efficacy and milder adverse effects without limits for maximal phenobarbital levels or doses. Respiratory distress may potentially occur during the initial phase of treatment, but little is known about the safety of continuing high doses of phenobarbital. We report on a case of intractable epilepsy associated with bilateral Sturge-Weber syndrome presenting with a comatose episode during prolonged high-dose phenobarbital therapy. In this case, electrophysiological studies demonstrated reversible

cerebral and brainstem dysfunction as the cause of the impaired consciousness, which has not previously been described as a complication of high-dose phenobarbital therapy.

Case Report

A female patient was born to nonconsanguineous parents at term after a normal pregnancy and delivery, with a birth weight of 3256 g. Because port-wine stains were noted over her left supraorbital region, a diagnosis of Sturge-Weber syndrome was suspected. At age 2 months, right-hand sided hemiconvulsive seizures began. Carbamazepine was started, which abolished the seizures. Electroencephalogram showed symmetric background rhythm and interictal sharp waves in the right occipital region. At age 6 months, hemiconvulsive seizures started to occur on the contralateral side, and then she was hospitalized because of left-hand sided partial status epilepticus. Interictal electroencephalogram showed significant asymmetry of the background with low-amplitude θ and α activities in the left hemisphere as well as high-amplitude polymorphic δ and θ activities intermixed with occipital spike waves in the right hemisphere. Gadolinium-enhanced brain magnetic resonance imaging disclosed a leptomeningeal

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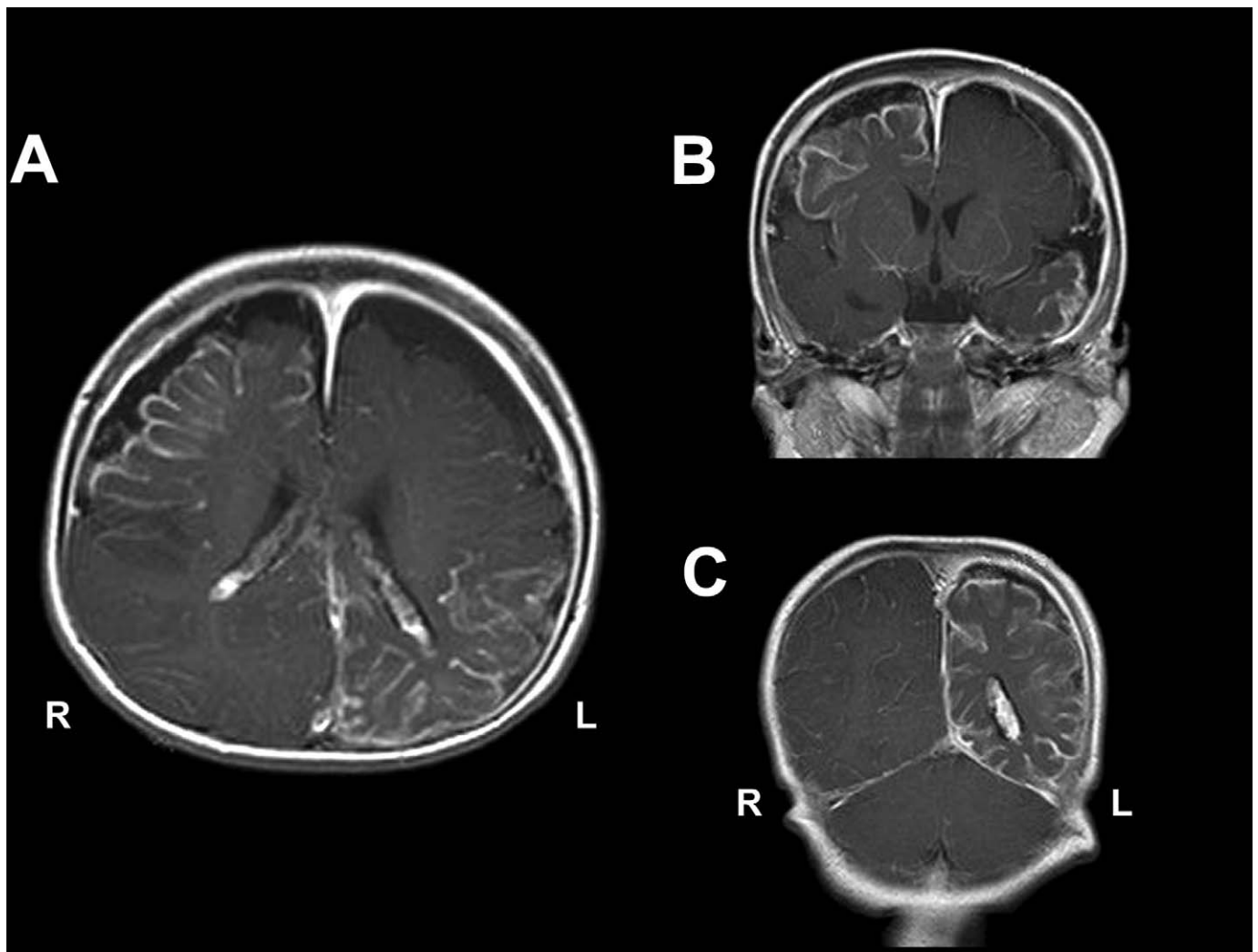


Figure 1. Gadolinium-enhanced axial (A) and coronal (B, C) brain T1-weighted magnetic resonance imagings (TR/TE = 624/17 ms) revealing a leptomeningeal angiomatosis bilaterally in the right frontal and left centroparietal areas. Note that no abnormality was detected in the right occipital region (A), which was 1 of the 3 epileptogenic foci demonstrated by ictal electroencephalogram.

angiomatosis bilaterally in the right frontal and left centroparietal areas (Figure 1). The seizures were resistant to an increased dosage of carbamazepine and to intravenous administration of phenytoin, midazolam, or lidocaine. Carbamazepine was replaced by zonisamide, which was partially helpful. Then, according to the following protocol, oral high-dose phenobarbital therapy was initiated with success (an intravenous form of phenobarbital was unavailable in Japan); phenobarbital suppositories, 15 to 20 mg/kg/d, were administered rectally for the first 7 days followed by oral phenobarbital, 20 mg/kg/d (130 mg/d). There was no cardiorespiratory failure during the initial period. After discharge at age 7 months, additional use of phenobarbital suppositories (25 mg) was effective for brief left-hand sided seizures. However, at age 8 months,

she was readmitted because of prolonged left-hand sided hemiconvulsions lasting 50 minutes. Ictal electroencephalogram demonstrated 3 independent epileptogenic foci in the left occipital, right frontal, and right occipital regions. Intravenous administration of phenytoin, midazolam, and lidocaine was ineffective again. The dosage of phenobarbital was gradually increased up to 150 mg/d (serum concentration, 76.4 µg/mL; therapeutic range, 15-40 µg/mL) until the 14th hospital day, when the patient lost consciousness. That was the 51st day after the initiation of the high-dose phenobarbital therapy. Her consciousness level evaluated using the Japan Coma Scale was 200 to 300 (ie, unrousable with slight or no movements using any forceful stimuli). Neurologic examination showed a sluggish pupil response to light, a diminished gag reflex, decreased deep

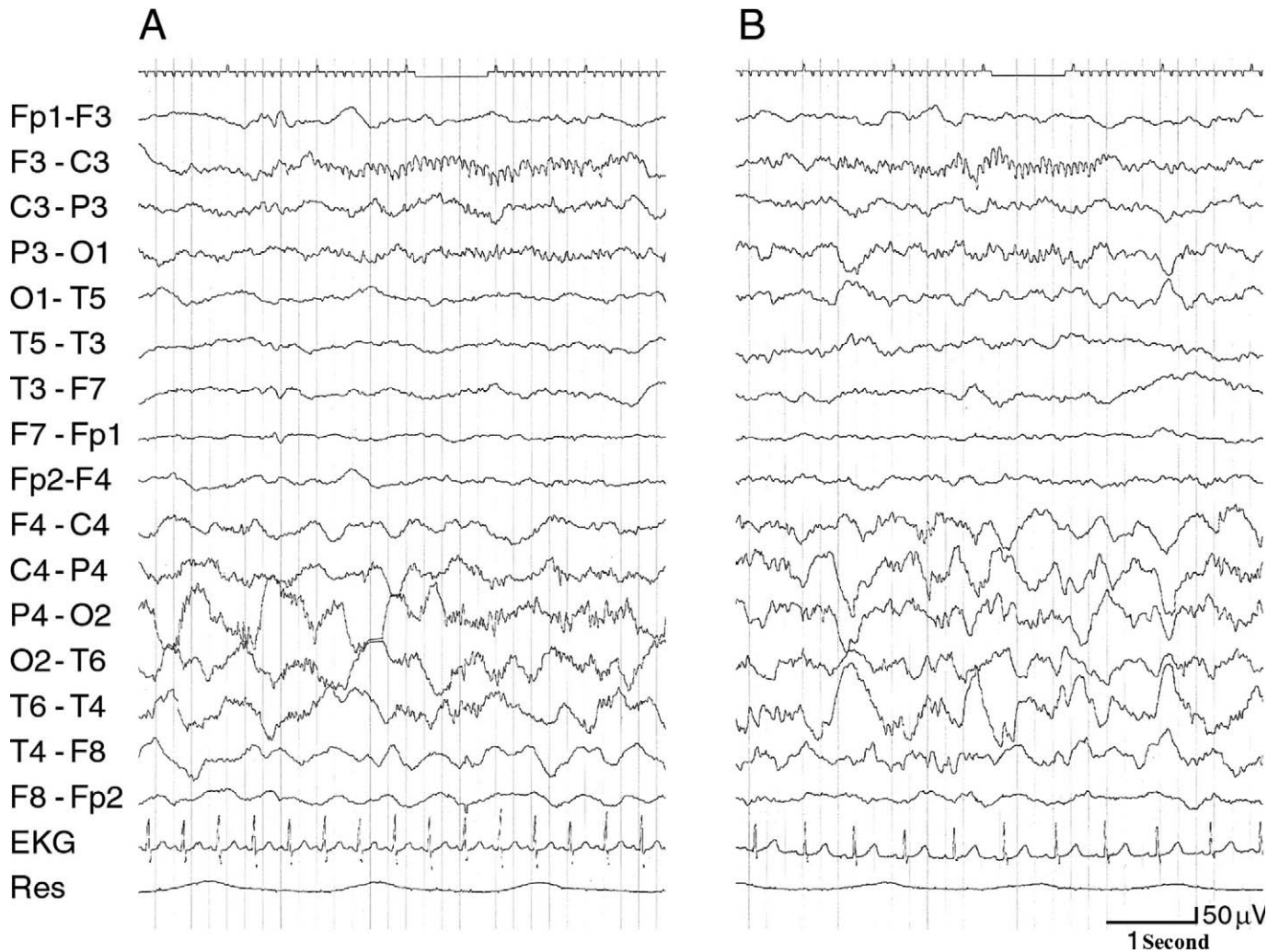
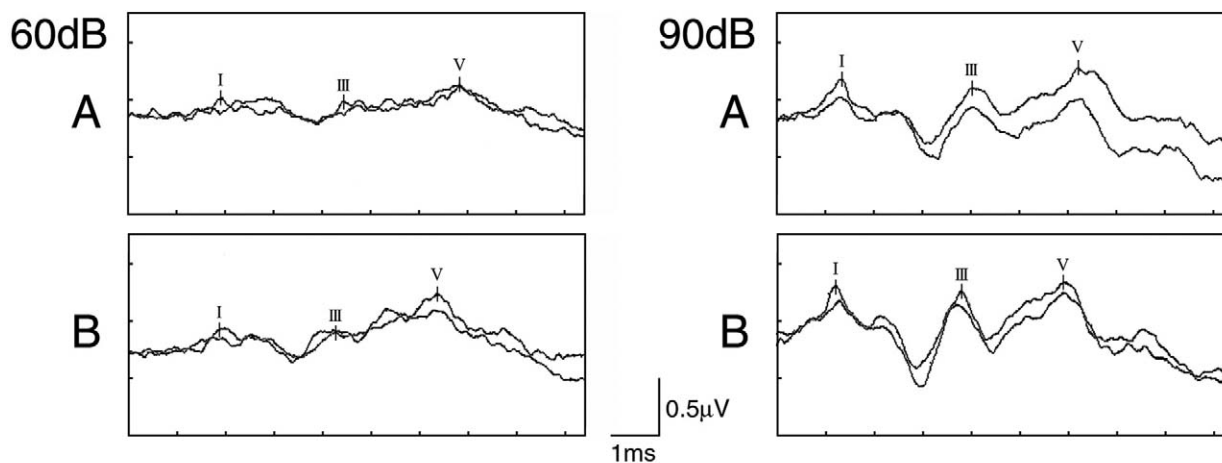


Figure 2. Electroencephalogram performed during the comatose episode (A) showing a diffuse amplitude reduction and slowing of the background, which returned to the baseline after recovery of consciousness (B). Note that the baseline electroencephalogram was quite disorganized, exhibiting significant background asymmetry with low-amplitude on the left as well as high-amplitude polymorphic activities intermixed with occipital spike waves on the right.

tendon reflexes, and positive Babinski reflexes bilaterally. No ventilatory support was required. Routine hematological and chemical profiles were normal, including blood glucose and plasma ammonium. Cerebrospinal fluid analysis was normal. Cranial magnetic resonance imagings showed no structural changes compared with the previous ones. Interictal electroencephalogram revealed a diffuse amplitude reduction and slowing of the background, which was poorly reactive to external stimuli (Figure 2A). A brainstem auditory evoked potential study was performed using a computerized evoked potential recorder (MEB 2204; Nihon-Kohden, Tokyo, Japan). The methods and settings for the brainstem auditory evoked potential recording were described previously elsewhere.⁴ The brainstem auditory evoked potential study results

demonstrated prolonged interpeak latencies of waves III to V and waves I to V (Figure 3A). These electroencephalogram and evoked potential findings suggested neuronal dysfunction of the cerebrum and brainstem possibly due to the protracted high-dose phenobarbital therapy. Then, valproic acid was newly added with a rapid response. Thereafter, the dosage of phenobarbital could be gradually decreased to 60 mg (8 mg/kg/d), whereas that of valproic acid was increased up to 260 mg (35 mg/kg/d). Once the serum phenobarbital level had declined to below 40 μg/mL, the patient regained consciousness. Babinski reflexes then disappeared. Otherwise, there was no remarkable change in her neurodevelopmental status before and after the comatose episode. The seizures remained well controlled. Electroencephalogram performed after the recovery showed that the



		Latency (ms)			Interpeak Latency (ms)		
		I	III	V	I-III	III-V	I-V
60dB	A	1.95	4.34	6.67	2.39	2.33	4.72
	B	1.90	4.24	6.29	2.34	2.05	4.39
Control (Mean±SD)		1.88±0.11	4.27±0.13	6.31±0.13	2.39±0.12	2.04±0.13	4.43±0.12
90dB	A	1.39	3.98	6.21	2.59	2.23	4.84
	B	1.36	3.88	5.88	2.52	2.00	4.52
Control (Mean±SD)		1.42±0.10	3.92±0.15	5.92±0.14	2.50±0.12	2.00±0.14	4.50±0.13

Figure 3. Brainstem auditory evoked potential studies demonstrating prolongation of the interpeak latencies of waves III to V and waves I to V during the coma (A) and normalization of the finding after recovery of consciousness (B).

background activity had returned to the baseline (Figure 2B). A repeat brainstem auditory evoked potential study revealed resolution of the abnormalities present in the first examination (Figure 3B). At age 10 months, the patient was transferred to another hospital, where she underwent pre-surgical evaluation followed by surgical excision of a right anterior epileptogenic area underlying the angiomas. After surgery, she has been experiencing weekly seizures comprising mild eyelid myoclonus. Recent electroencephalogram showed that the degree of the interhemispheric background asymmetry was slightly improved, but that interictal polyspike waves were frequently seen in the right occipital region.

Discussion

This is the first report of reversible cerebral and brainstem dysfunction associated with prolonged high-dose phenobarbital therapy that was demonstrated by sequential

electroencephalogram and brainstem auditory evoked potential recordings. It is well known that primary dose-related side effects of phenobarbital usually appear when the serum concentration is more than 40 µg/mL.⁵ Similarly, the neuronal dysfunction in our patient disappeared clinically and electrophysiologically when the serum phenobarbital level had decreased to below 40 µg/mL. Experimental studies have shown that phenobarbital at therapeutic dose produces minimal and transient decreases in cerebral blood flow and brain oxygen consumption, but that phenobarbital at a higher dose generates greater and longer-sustained reductions in them.⁶ It was evident that such ischemic and hypoxic effects of phenobarbital were attributable to suppressive changes seen in the electroencephalogram of our patient.

The efficacy of high-dose phenobarbital therapy for childhood refractory status epilepticus was first reported by Crawford et al,¹ who studied 50 patients with a variety of etiologic but apparently no severe cerebrovascular diseases such as Sturge-Weber syndrome. In that study, patients underwent treatment with no limits for maximum

phenobarbital doses and achieved serum levels of 70 to 344 $\mu\text{g/mL}$ for up to 48 days.¹ Most of them were initially intubated but recovered good spontaneous respiration despite persistently high serum phenobarbital levels. No severely impaired consciousness was reported. Those authors suggested that cardiorespiratory adverse effects are strongly influenced by the severity of the seizures and underlying disease. It has been reported that patients with Sturge-Weber syndrome tend to have cerebral perfusion and metabolic insufficiency.⁷ In our patient, a large leptomeningeal angiomas occupied the cerebral hemispheres bilaterally, and an additional nonlesional epileptogenic area was present in the right occipital region (Figure 1). Therefore, it is reasonable to consider that this patient primarily had a marked reduction of the baseline reserve capacities for cerebral blood flow and metabolism related to the underlying bilateral Sturge-Weber syndrome. Furthermore, frequent repetitive status epilepticus most likely produced more significant decreases in these capabilities, which might have caused the neurological complication in our patient. This hypothesis was strengthened by the fact that in the report of Crawford et al,¹ comatose episodes did not occur in any of their patients without severe cerebrovascular diseases.

Previous electrophysiological evidence has suggested that brainstem auditory evoked potential can be affected by various antiepileptic drugs, such as carbamazepine and valproic acid.⁸ However, it has been reported that phenobarbital usually has minimal depressive effects on brainstem auditory evoked potential.^{5,8} Brinciotti examined brainstem auditory evoked potential in 8 epileptic children with chronic high serum levels of phenobarbital ranging from 40 to 80 $\mu\text{g/mL}$.⁵ Those children exhibited drowsiness, nystagmus, ataxia, and changes in behavior and cognitive functions. As a result, it was found that the majority of the patients showed no significant interpeak latency changes in brainstem auditory evoked potential studies. Therefore, compared with the previous reports, the brainstem auditory evoked potential abnormalities seen in our patient were so exceptional that the effect of phenobarbital was difficult to establish as a predominant factor for the brainstem dysfunction. Instead, as already discussed above, it could be speculated that the baseline hemodynamic compromise and secondary deterioration might have contributed together to progression of the

neuronal dysfunction in our patient. However, it remains to be elucidated whether brainstem is actually included in the baseline hemodynamic compromise because direct brainstem involvement is usually not seen in Sturge-Weber syndrome.

In summary, the present case demonstrated a rare adverse effect of phenobarbital, which is generally considered a safe drug to treat status epilepticus. Patients with severe cerebrovascular diseases may be prone to having significant cerebral and brainstem dysfunction when their high-dose phenobarbital therapy is protracted. Once seizure control is achieved with this treatment, the dosage should be reduced to that equivalent to the serum level below 40 $\mu\text{g/mL}$. Further studies are required to determine the safety of long-term high-dose phenobarbital therapy for epileptic children with or without brain perfusion and metabolic abnormalities.

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