Infantile hemangiomas are the most common benign tumors occurring in infancy, and more than 10% of infantile hemangiomas are facial segmental hemangiomas [1]. In infants with large facial segmental hemangiomas, various nervous system, cerebrovascular, eye, cardiovascular, and chest wall abnormalities can occur, a condition known as “Posterior fossa malformations, Hemangioma, Arterial anomalies, Cardiac defects, Eye anomalies” (PHACE) syndrome. In PHACE syndrome, hemangiomas are large and often have functional problems. About 80% of patients with PHACE syndrome need aggressive hemangioma treatment and additional treatment for associated malformations [1].

After the effects of propranolol on infantile hemangiomas were reported in 2008, propranolol became the first-line therapy for infantile hemangiomas [2]. Propranolol has...
been carefully tested in patients with PHACE syndrome due to the risk of stroke and has recently been reported to be efficacious as a first-line treatment [3-6]. We have experienced the effectiveness of first-line propranolol treatment for facial hemangioma in patients with PHACE syndrome.

### Case Report

A 26-day-old girl was admitted to our hospital with a red skin lesion widely spread over her left forehead and eyelids. The infant was born without any problems at 40 weeks of gestation at a birth weight of 3.3 kg. Magnetic resonance imaging (MRI) was performed at 2 days postnatally due to suspicion of cerebellar hypoplasia by prenatal ultrasonography. Brain MRI showed that the left hemisphere of the cerebellum was pushed down, and an arachnoid cyst was suspected. At birth, there was a salmon patch on the left eyelid; 2 weeks after birth the lesion became broad and dark red. When the patient first visited our hospital, the lesion had progressed to the form of segmental hemangiomas distributed around the eyes, left forehead, left auricle, and scalp (Fig. 1). The lesion initially thought to be an arachnoid cyst was confirmed as left cerebellar hypoplasia on brain MRI performed at 47 days of age. Also, magnetic resonance angiography (MRA) showed absence of the left A1 segment of the anterior cerebral artery (Fig. 2). The patient was diagnosed with PHACE syndrome. There were no abnormalities on both echocardiography and abdominal ultrasonography performed to identify other co-morbid abnormalities. There was no intrinsic eye anomaly, but the hemangioma had invaded the upper eyelid conjunctiva and the eye was not fully open, causing amblyopia.
There was no major cerebral vessel narrowing or occlusion, which is associated with high risk of stroke. There were no abnormalities on electrocardiogram. On the 48th day of life, the patient was started on oral propranolol at a dose of 0.5 mg/kg. On the next day, the dose was increased to 1 mg/kg and on the third day the dose was raised to 1.5 mg/kg. However, asymptomatic hypotension developed at a propranolol dose of 1.5 mg/kg, so the patient was treated with 1-1.5 mg/kg until the end of treatment. After treatment, the lesion range decreased and it was light pink and flattened.

At 14 months of age, the lesion was significantly improved. The medication was tapered over 5 weeks and then stopped. However, the lesion reddened again at age 16 months, and the medication was resumed at the same dose and finally stopped at 20 months of age. At that time, only a telangiectatic patch remained (Fig. 3). The patient had normal development and growth up to 24 months of age and ophthalmologic examination showed no abnormal findings.

Discussion

PHACE syndrome is not a widely known disease, but the incidence is reported to be higher than that of Sturge-Weber syndrome, a well-known neurocutaneous disorder [1]. Metry et al., reported that 20% of those presenting with facial segmental hemangiomas were diagnosed with PHACE syndrome [1]. However, they suggest that the actual prevalence rate might be higher because radiological examinations are not performed on all patients. In fact, the diagnosis rate may be lower because of neglect of subtle anomalies such as sternal pits, insufficient examination, and misdiagnosis of hemangioma as capillary malformation [3,7].

In a prospective study in which MRI, MRA, echocardiography, and ophthalmologic examinations were performed in all patients with large facial hemangiomas, 31% of patients with facial hemangiomas greater than 22 cm² were diagnosed with PHACE syndrome [8]. Of these patients, 50% with hemangiomas greater than 100 cm² were diagnosed with PHACE syndrome [8]. In a study by Forde et al., 58% of patients with plaque-like infantile hemangioma met the diagnostic criteria for PHACE syndrome, suggesting that there is high prevalence of PHACE syndrome in patients with large facial segmental hemangiomas [9]. Therefore, patients with large facial segmental hemangiomas should be suspected to have PHACE syndrome and should be thoroughly evaluated for comorbid anomalies.

In a study by Heggastrom et al., all patients with PHACE syndrome showed a high incidence of brain structure abnormalities (52%), cerebral vascular abnormalities (90%), and cardiovascular abnormalities (67%) [8]. Bayer et al., reported that 62 patients (42%) out of 155 patients with PHACE syndrome showed cardiovascular abnormalities [10]. Among them, coarctation of the aorta (CoA) and an interrupted aortic arch were diagnosed in 28 patients (18%) and other cardiac anomalies were seen in 19 patients (12%) [10]. Of patients with cardiovascular abnormalities, 37% received surgery or intervention [10].

In patients with PHACE syndrome, early treatment of facial hemangioma is necessary. Propranolol has been the most widely used first-line treatment for hemangioma since 2008 [2]. Although propranolol can cause side effects such as hypoglycemia, asymptomatic hypotension, and bradycardia, these side effects can be prevented through predrug evaluation and patient education. The therapeutic effect of propranolol is excellent. However, physicians have been hesitant to use this drug in patients with PHACE syndrome because of the risk of stroke. In patients with...
PHACE, arterial ischemic stroke (AIS) is caused by several factors, including progressive steno-occlusive disease, blood flow-limiting arterial narrowing, and thromboembolism [11]. In a recent study of 22 patients with PHACE syndrome and AIS, symptoms occurred at mean age 13.6 months of age, and the main symptoms were seizures and hemiparesis [12]. Among stroke patients, 95% of patients who underwent cerebral angiography had narrowing or nonvisualization of major vessels. CoA was identified in 13 patients (59%) and was higher than the CoA ratio of 18-30% seen in all PHACE patients [8,10,12]. In this study, the majority of patients were treated with steroids. Only one patient who treated with steroids and propranolol, had uncontrolled hypertension [12].

Although there has been no previous analysis of the association between propranolol therapy and AIS, there is concern that propranolol may reduce cerebral blood flow and increase the risk of stroke. However, a previous study of PHACE patients treated with propranolol included seven patients with high-risk stroke-related vascular abnormalities, and no stroke occurred [13]. In addition, propranolol use was reported in a high-risk patient with CoA and an absent right vertebral artery, and another patient with absent right intracranial internal carotid artery without serious adverse effects [5,6]. Additional studies on the association of propranolol therapy with stroke in high-risk stroke patients are needed, but propranolol has been increasingly used in high-risk patients.

There have been reports of ulcerations, severe scarring, continued use of a ventilator, and decreased visual acuity in patients with prior steroid use [14,15]. Considering the complications of steroid therapy and long-term side effects, propranolol could be used instead as a first-line treatment with close monitoring of stroke in patients with PHACE syndrome.

References

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