Case Report

Successful Treatment of PHACE Syndrome with Oral Propranolol

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Abstract: *An 8-week-old female infant presented with a large segmental plaque-like facial hemangioma involving her right eyelid, which caused a mechanical ptosis of the right eye with visual occlusion, and Dandy-Walker malformation, consistent with PHACE syndrome. Propranolol 2 mg/kg/day in 2 divided doses results in a dramatic change in the patient's skin color in the first week, and she could open her eyelids normally after 3 weeks. At 6 months of treatment, the skin color had returned to almost normal. The propranolol dosage was then tapered to 1 mg/kg/day for 1 month and discontinued without a relapse. No undesirable side effects were reported during the patient's follow-up visits. She had normal development and normal vision. We conclude that propranolol can be used as a front-line treatment for large facial hemangioma associated with PHACES syndrome.*

Keywords : ● *Hemangioma* ● *PHACE syndrome* ● *Propranolol*

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Introduction

Infantile hemangioma (IH) is the most common tumor in infancy.[1] In some cases, it is associated with other extracutaneous anomalies; for example, PHACE syndrome (posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, and eye abnormalities). One-third of infants with a large facial hemangioma also have extracutaneous manifestations consistent with the diagnosis of PHACE syndrome.[2] With a unique natural history, most hemangiomas are benign and have a self-limited course.[3] However, some hemangiomas may cause significant morbidity such as amblyopia from prolonged visual occlusion. Therefore, approximately 10% of infantile hemangiomas require treatment to prevent tissue destruction or sequelae.[4]

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Case report

An 8-week-old female infant presented with a large segmental plaque-like facial hemangioma involving her right eyelid, which began at 2 weeks of age. She was a full-term baby with an unremarkable birth history. On the first visit, she was unable to open her right eye (Figure 1A). Her large facial hemangioma raised concerns of PHACE syndrome (Table 1); therefore, a computerized tomography of the brain was performed and revealed a Dandy-Walker malformation (hypoplasia of both cerebellar hemispheres and a posterior fossa cyst, Figure 2A), which met the major criterion for the diagnosis of PHACE syndrome.[7] An echocardiography excluded cardiac anomaly, and an ultrasonography of the abdomen revealed no intra-abdominal hemangioma. The full blood count revealed a normal hemoglobin level (10.9 g/dL), white cell count (15,100/μL) and platelet count (527,000/μL). The coagulogram results were normal.

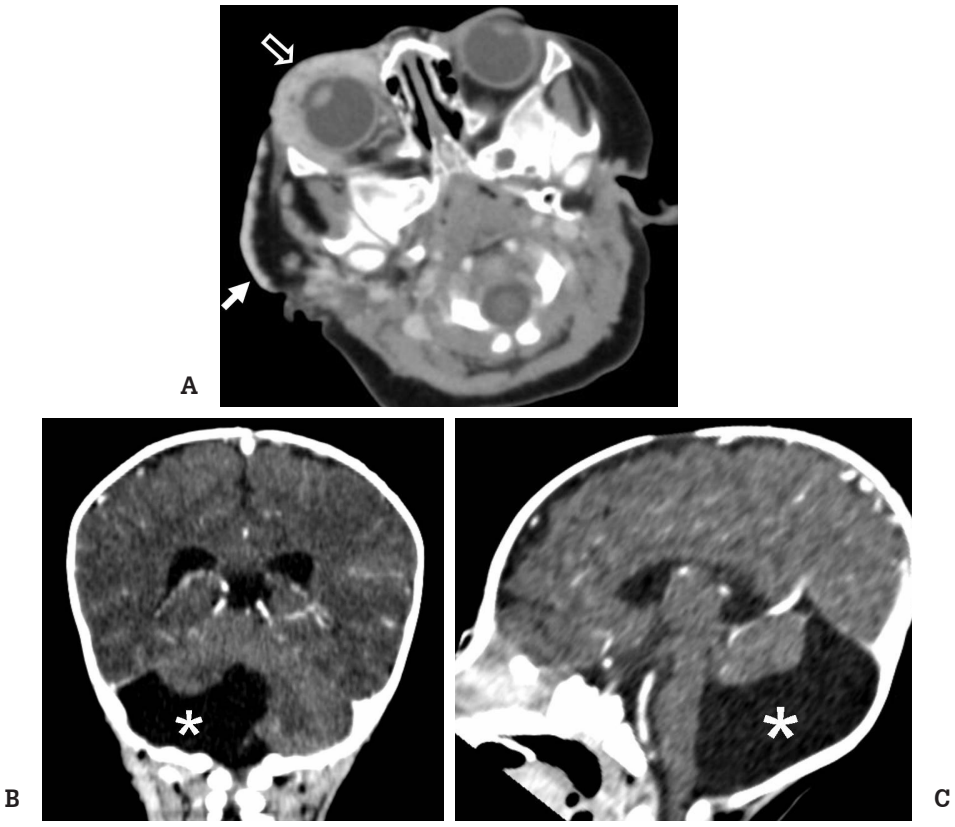
The potential benefits and risks of the treatment options, prednisolone (the standard treatment) and propranolol (the new challenging drug for IH), were

A B C

Figure 1 **A** The patient on the first visit at 8 weeks old with a large segmental facial hemangioma involving the right eyelid and causing palpebral occlusion.

B At 3 weeks after propranolol treatment, a dramatic change in skin color and texture was noticed. She was able to open her right eye normally.

C At 6 months after propranolol treatment, only a fainted red color was noticed on the skin. Her visual acuity was equal and normal for her age.



A

B C

Figure 2 **A** Axial enhanced CT scan shows a vividly, homogeneous, enhancing lesion involving the right orbit (open arrow) and skin as well as subcutaneous fat (arrow) near the right masticator space

B and C Sagittal and coronal MPR reveals an enlarged cystic space at the posterior fossa (*) with hypoplasia of both cerebellar hemispheres (more severe on the right side) and absent cerebellar vermis, which are compatible with a Dandy-Walker malformation

Table 1 Diagnostic criteria of PHACE syndrome

PHACE Syndrome		
Facial hemangioma >5 cm in diameter PLUS 1 major criterion OR 2 minor criteria		
	Possible PHACE Syndrome	
Facial hemangioma > 5 cm PLUS 1 minor criterion	Hemangioma of neck or upper Torso PLUS 1 major criterion OR 2 minor criteria	No hemangioma PLUS 2 major criteria
Organ system	**Major Criteria**	**Minor criteria**
Cerebrovascular	Anomaly of major cerebral arteries: - Dysplasia[a] of the large cerebral arteries[b] - Arterial stenosis or occlusion with or without moyamoya collaterals - Absence or moderate-to-severe hypoplasia of the large cerebral arteries - Aberrant origin or course of the large cerebral arteries[b] - Persistent trigeminal artery - Saccular aneurysms of any cerebral arteries	Persistent embryonic artery other than trigeminal artery: - Proatlantal intersegmental artery (types 1 and 2) - Primitive hypoglossal artery - Primitive otic artery[c]
Structural brain	Posterior fossa anomaly: - Dandy-Walker complex or unilateral/bilateral cerebellar hypoplasia/dysplasia	Enhancing extra-axial lesion with features consistent with intracranial hemangioma[c]: - Midline anomaly[d] - Neuronal migration disorder[e]
Cardiovascular	Aortic arch anomaly: - Coarctation of aorta dysplasia[a] - Aneurysm - Aberrant origin of the subclavian artery with or without a vascular ring	Ventricular septal defect: - Right aortic arch (double aortic arch)
Ocular	Posterior segment abnormality: - Persistent fetal vasculature (persistent hyperplastic primary vitreous) - Retinal vascular anomalies - Morning Glory disc anomaly - Optic nerve hypoplasia - Peripapillary staphyloma - Coloboma	Anterior segment abnormality: - Sclerocornea - Cataract - Coloboma - Microphthalmia
Ventral or midline	Sternal defect or sternal cleft Supraumbilical raphe	Hypopituitarism Ectopic thyroid

Reference: Consensus statement on diagnostic criteria for PHACE syndrome. Pediatrics 2009;124:1447-56.

[a] Includes kinking, looping, tortuosity, and/or dolichoectasia

[b] Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system

[c] See structural brain anomalies section for discussion

[d] Callosal agenesis or dysgenesis, septum pellucidum agenesis, pituitary malformation, or pituitary ectopia

[e] Polymicrogyria, cortical dysplasia, or gray matter heterotopia

discussed with the parents, who then chose propranolol. Propranolol was then administered orally 2 mg/kg/day in 2 divided doses, which were adjusted as the baby grew. Blood pressure and heart rate were monitored every hour during the first 4 hours of treatment and at every follow-up visit. There was no immediate cardiovascular effect observed. The patient was maintained on this dosage and followed up at our Outpatient Clinic 1 week after treatment, then every 2 weeks for a month, and monthly afterwards.

A dramatic change in the patient's skin color was noted in the first week, and after 3 weeks, the baby could open her eyelids normally (Figure 1B). At 6 months of treatment, the skin color had almost returned to normal, with only residual faint red discoloration on the right side of her face (Figure 1C). The follow-up sagittal and coronal MPR still showed an enlarged cystic space at the posterior fossa with hypoplasia of both cerebellar hemispheres and absent cerebellar vermis which were compatible with Dandy-Walker malformation (Figure 2B, 2C).

The dosage of propranolol was tapered to 1 mg/kg/day, then discontinued 1 month later with no skin discoloration. However, at 2 months after treatment discontinuation, the hemangioma lesion started to reappear, with a slight reddish color and reproliferation was noticed at the edge of the hemangioma. After discussion with the parents, propranolol was resumed at a lower dosage (1 mg/kg/day) and continued for 9 months. At the age of 20 months, she had only faint red discoloration of the right face, propranolol was discontinued. No adverse effects, including bradycardia, hypotension or hypoglycemia, were detected during the treatment period. She had normal development and normal vision.

Discussion

Since a consensus on its diagnostic criteria was reached, PHACE is no longer a rare clinical syndrome. However, its pathogenesis is still unknown. A cohort study has reported that infants with PHACE syndrome are more likely to be female,[5] born to slightly older mothers and at a slightly older gestational age than other hemangiomas. No correlation between the hemangioma incidence and prenatal illness or drug use has been demonstrated.[6]

Following a consensus criteria in 2009, the diagnosis of PHACE syndrome require presence of a facial hemangioma (> 5 cm) plus one other major criterion or two minor criteria. The diagnosis of a possible PHACE syndrome requires the presence of a facial hemangioma > 5 cm plus one minor criterion or hemangioma of the upper torso plus one major criterion/two minor criteria (Table 1).[7]

The presence of a large segmental facial hemangioma in our patient raised the concern of PHACE syndrome. A previous report has described facial hemangioma patterns into four segments: frontotemporal (S1), maxillary (S2), mandibular (S3) and frontonasal (S4) segments. The majority of PHACE patients have hemangioma involving the S1 segment regardless of other segment involvement.[2] The facial segmental involvement is also associated with clinical manifestation. Hemangiomas located in the S1 & S4 segments are associated with structural brain, cerebrovascular and ocular anomalies, while those located in the S3 segment are associated with sternal defects or supraumbilical raphes.[6] Most affected children have only one extracutaneous manifestation to fulfill a diagnosis of PHACE syndrome, most commonly CNS anomalies.[8] Currently, ocular, cerebrovascular and cardiovascular evaluations should be undertaken in patients presenting with segmental facial hemangioma. Additionally, an MRI and magnetic resonance angiography of the head and neck and echocardiography should be evaluated in infants at risk for PHACE syndrome. There is a significant association between aortic arch and hemangioma laterality.[9]

The conventional therapeutic approach for problematic infantile hemangioma involves the use of systemic corticosteroids as the first-line therapy, and then vincristine, interferon or laser therapy as a second-line therapy. However, corticosteroid use often leads to serious side effects. Recent studies have found that propranolol, a well-known β-adrenergic receptor blocker, can have dramatic

effects in controlling hemangioma growth. The proposed action mechanisms of propranolol on hemangiomas include the control of hypoxic stress with upregulated hypoxia inducible factor 1 (HIF-1), apoptosis induction, and decreased production of vascular endothelial growth factors (VEGF) and fibroblastic endothelial growth factors (FGF-β).[10] Its related excellent outcomes suggest that propranolol should now be used as a first-line treatment for severe infantile hemangioma.

Although it is not known how long propranolol should be continued in children with severe hemangioma, most reports have used propranolol at a duration of 6-12 months or until the hemangioma showed spontaneous regression.[11] Most hemangiomas have a cessation of growth after 9 months of age and spontaneous involution typically begins at 1 year of age, while segmental hemangioma has a persistently higher rate of a longer growth than localized hemangioma.[4] In our case, propranolol was used for 6 months. However, the patient's age at the time of propranolol discontinuation may be another factor to be considered, since reproliferation might occur if propranolol is discontinued during the proliferative phase.

We report the use of propranolol as a front-line treatment for large facial hemangioma associated with PHACES syndrome with promising results. However, for infants with intracranial arterial anomalies and thus high risk for stroke, propranolol should be use with caution. The significant risk factors for ischemic stroke in children with PHACE syndrome are aplasia, hypoplasia or occlusion of a major cerebral artery, especially in those with coarctation of the aorta.[12] Recently, propranolol is recommended in large facial hemangioma like in our case if the benefits outweigh the risks. The consensus group recommends a target dose to treat infantile hemangioma at the median of 2 mg/kg/day with slow titration from a low starting dose to achieve the desired treatment effect.[13] Collective reviews of propranolol use in 32 infants with PHACE syndrome have reported no significant ischemic strokes during propranolol use. Worsening hemangioma (ulceration/ tissue necrosis) has been reported in 3 patients, all of whom received concurrent oral corticosteroids.[14] Other reports on propranolol monotherapy as a treatment for ulcerated hemangioma in PHACE syndrome patients have reported excellent outcomes.[15] Although the correlation of propranolol with worsening hemangioma is not clearly understood, we should be careful on repeat skin evaluations during propranolol therapy.

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ผลการรักษา PHACE Syndrome ด้วยยา Propranolol

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บทคัดย่อ *เด็กหญิงไทยอายุ 8 สัปดาห์ มีปื้นแดงหนาขนาดใหญ่ บริเวณใบหน้าและเปลือกตาด้านขวาตั้งแต่แรกเกิด ขยายขึ้นเรื่อยๆ จนผู้ป่วยไม่สามารถเปิดตาได้ และพบ Dandy-Walker malformation ในสมองเข้าได้กับการวินิจฉัยกลุ่มอาการ PHACE การรักษาด้วยยา propranolol ขนาด 2 มิลลิกรัมต่อกิโลกรัมต่อวัน สามารถทำให้สีของก้อนจางลงใน 1 สัปดาห์ ผู้ป่วยเปิดตาได้หลังจากเริ่มยาประมาณ 3 สัปดาห์ และผิวหนังเรียบและสีจางลงหลังเริ่มยาไป 6 เดือน จึงหยุดการรักษา ผู้ป่วยไม่มีปัญหาเรื่องการมองเห็นและมีพัฒนาการปกติตามวัย*

Keywords : ● *Hemangioma* ● *PHACE syndrome* ● *Propranolol*

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