Clinicoradiological Characteristics and Outcome of Three Patients with PHACES Syndrome Associated with Intracranial Arteriopathy

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Abstract

PHACES syndrome is characterized by segmental infantile hemangiomas (IHs) accompanied by various extra-cutaneous anomalies, including cerebral artery anomalies, cardiac anomalies, ocular anomalies, sternal deformities, and posterior fossa malformations. This review article presents three case series of patients with PHACES syndrome, focusing on challenges encountered in managing stroke risk associated with propranolol therapy due to significant cerebrovascular anomalies. In each case, therapeutic strategies were tailored to individual patients, carefully considering their vascular risk and the location and potential consequences of the IH. Successful management hinged upon collaborative efforts involving a multidisciplinary team, particularly in resource-limited settings. This collaborative approach allowed pediatricians to make well-informed decisions regarding the use of oral propranolol in cases of IH with prominent cranial arterial anomalies, effectively balancing potential therapeutic benefits against the risk of stroke. Through the development of individualized treatment plans, guided by this collaborative approach, pediatricians can address each patient's unique needs and challenges. This article emphasizes the importance of personalized and comprehensive care for patients with PHACES syndrome, offering valuable insights for clinicians faced with similar cases.

Keywords: PHACEs syndrome, propranolol, Hemangioma.

Introduction

Infantile hemangiomas, which occur in 4-12% of infants, are the most frequent type of benign tumor in this age group.[1,2] PHACES syndrome (**p**osterior fossa malformations, **h**emangioma, **a**rterial anomalies, **c**oarctation of the aorta/**c**ardiac defects, **e**ye abnormalities, and **s**ternal malformations), classified as a neuro-cutaneous syndrome, was initially identified by Frieden and colleagues in 1996, [3] This syndrome is observed in 2% of patients who have segmental hemangiomas on the cervicofacial distribution, particularly in the frontotemporal or maxillary/mandibular regions. This condition is associated with additional anomalies of PHACES Syndrome, including posterior fossa abnormalities, facial hemangiomas, arterial cerebrovascular anomalies, cardiac anomalies, coarctation, ocular anomalies, and sternal defects.[4,5] The arteriopathy accompanying PHACES syndrome poses a significant concern in

the treatment of patients with high-risk vascular anomalies who may require propranolol therapy. This arteriopathy carries the potential to initiate ischemic strokes, making it a primary focus in patient management. It is essential to exercise caution when considering propranolol therapy for individuals with high-risk vascular anomalies associated with PHACES syndrome, as there is a possibility that the use of propranolol could increase the risk of stroke in such cases. We describe the clinical and radiological characteristics of three patients with PHACES syndrome who exhibited cerebrovascular arteriopathy. Our focus is on the treatment challenges and clinical outcomes. The clincoradiological findings of the three cases are summarized in Table 1.

Table 1: Summary of the clincoradiological findings of the three cases.

	Case 1	**Case 2**	**Case 3**
Age	3 weeks	5 weeks	2 weeks
Gender	Male	Male	Female
Location of hemangioma	Head & neck	Face	Face
Extra-cutaneous hemangioma	Nil	posterior paraspinal muscles from C1-C3	Intestinal intracranial
Eye	Normal	Normal	Optic disc anomaly
Cardiac	Normal	Normal	Normal
Arterio-pathy	absence of the right internal carotid artery	left internal carotid artery has a smaller caliber compared to the right side	Hypoplastic right internal carotid artery
Oral propranolol	No	Yes	Yes

Case Reports

Case one

A three-week-old late preterm neonate presented with a segmental infantile hemangioma that affected the right neck, face, and scalp. The extent of the hemangioma raised suspicion of PHACES syndrome [Figure 1]. A magnetic resonance angiogram (MRA) was performed using a time-of-flight technique and revealed a congenital absence of the right internal carotid artery (ICA) in both cervical and intracranial segments, without any significant intracranial abnormalities [Figure 1]. The patient underwent ophthalmology and cardiology evaluations, which showed no abnormalities. MRI perfusion study was attempted but was unsuccessful due to technical limitations. The multi-disciplinary team decided to monitor the patient since he was asymptomatic and had a high stroke risk. During follow-up, the patient's hemangioma showed minimal growth with no complications. As a prophylactic measure, aspirin was initiated to prevent stroke.

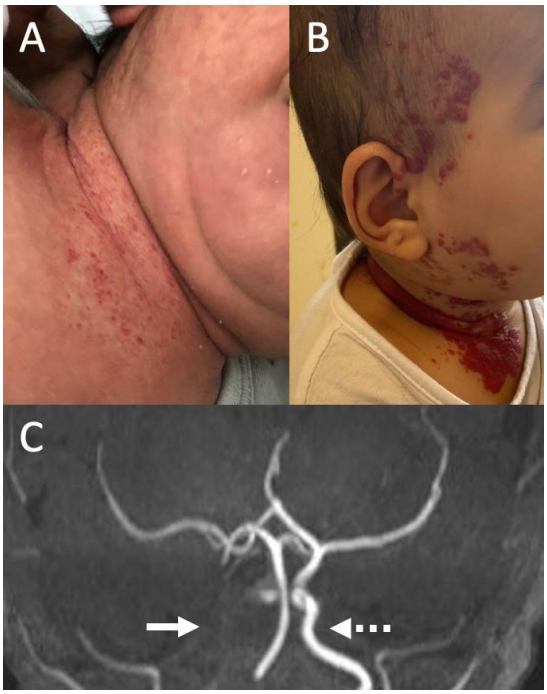

Figure 1: (A, B) Segmental infantile hemangioma involving the right neck, right face, and right scalp, which progressed over time as shown in the pictures. **(C)** Time-of-flight MR angiogram of the intracranial vessels shows an absent right intracranial internal carotid artery (solid arrow) with absence of its cervical segments (not shown here), compared to normal left internal carotid artery (dashed arrow).

Case two

An 11-week-old male infant born at term presented with progressive right facial swelling at the age of 5 weeks. The main presenting symptom was noisy breathing, without any stridor or shortness of breath. Clinical examination revealed a well-circumscribed, soft, 5 cm right cheek swelling with telangiectatic changes [Figure 2]. Ultrasound imaging revealed a hyper-vascular heterogeneously hypoechoic lesion over the right cheek consistent with a high-flow soft tissue hemangioma. Given the segmental appearance of the hemangioma, PHACES syndrome was suspected. Magnetic resonance imaging (MRI) of the head and neck showed a right-cheek mass and multiple other lobular lesions in the posterior paraspinal muscles from C1-C3, all of which had signal characteristics and an enhancement pattern consistent with hemangiomas [Figure 2]. No evidence of extension into the spinal canal was noted. Magnetic resonance angiography (MRA) revealed that the left internal carotid artery had a smaller caliber compared to the right side, with focal mild to moderate stenosis of the left internal carotid arteries just distal to the carotid bifurcation. The vertebral arteries had a mildly tortuous course. Cardiac and ophthalmology assessments were normal. The decision to initiate propranolol was debatable due to the high risk of stroke associated with intracranial arterial anomalies, leading to a multidisciplinary discussion that ultimately preferred to proceed with sclerotherapy as the best option for this infant. Several challenges delayed the intervention, given the patient's age and weight, including the unavailability of a small catheter size. Therefore, the team decided to start low-dose propranolol (1 mg/kg/day) while awaiting sclerotherapy. The infant showed a good response and improvement in symptoms while on low-dose propranolol, which was eventually tapered off and stopped after the right cheek lesion had regressed during follow-up at the age of 12 months.

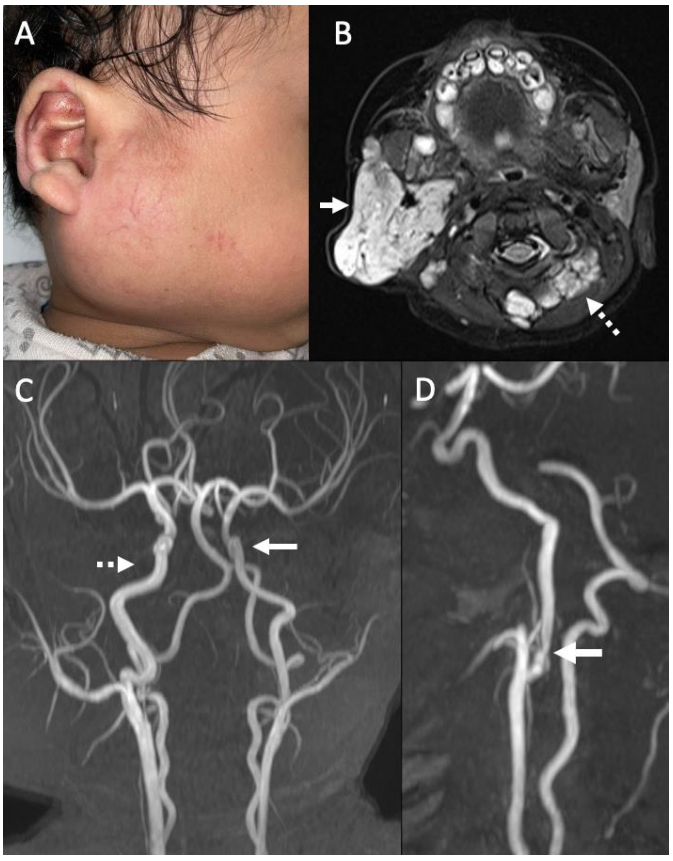

Figure 2: (A) Right cheek swelling with some telangiectatic changes over it. **(B)** Axial T2 weight image with fat saturation shows hemangiomas in the right parotid space (solid arrow) and posterior paraspinal muscles (dashed arrow). **(C)** Maximum intensity projection of time-of-flight MR angiogram shows smaller caliber of the left internal carotid artery (arrow) compared to the right internal carotid artery (dashed arrow). **(D)** Focal stenosis of the proximal left internal carotid artery just distal to the carotid bifurcation (arrow).

Case three

A three-month-old female neonate born at full-term presented with segmental hemangioma, which first appeared as a telangiectatic patch on the right periorbital area and forehead at two weeks of age. The lesion progressed to redness and swelling over time [Figure 3]. A thorough evaluation for PHACES syndrome revealed hypoplasia of the right internal carotid artery via magnetic resonance angiography (MRA) [Figure 3], an optic disc anomaly, and normal cardiac assessment. During the same hospitalization, she developed intussusception and required laparotomy after unsuccessful pneumatic reduction. The intussusception was attributed to an ileum hemangioma, which was excised. Given the presence of hemangiomas in three critical sites (i.e., orbital, intracranial, and intestinal hemangioma), a low dose of oral propranolol at 1.5 mg/kg/day was initiated. The treatment exhibited a positive response, allowing for the gradual tapering and eventual cessation of propranolol by 24 months of age.

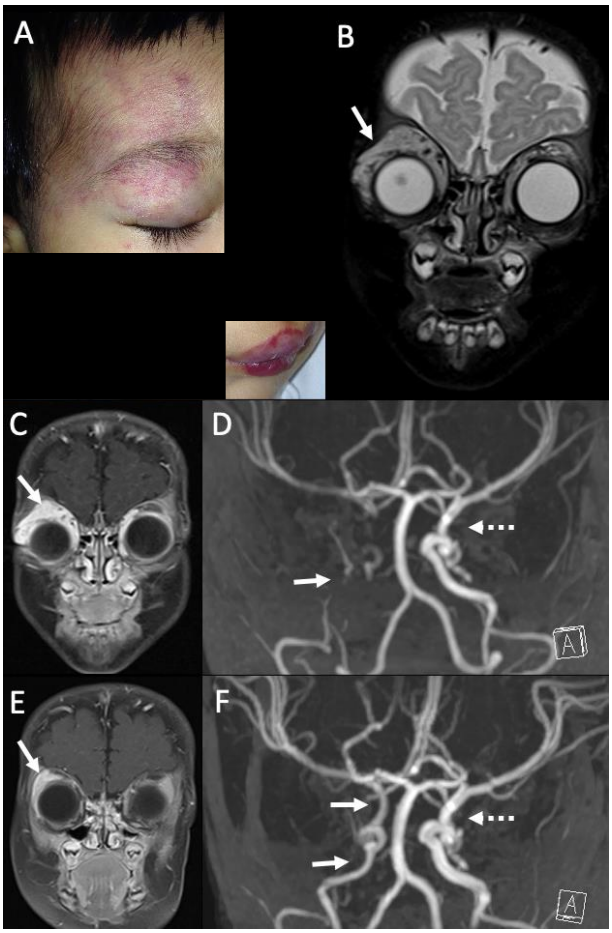

Figure 3: (A) Telangiectatic patch over the right periorbital, forehead, and lips, which then progressed to redness and swelling. **(B, C)** Coronal T2 weight image with fat suppression and post-contrast T1 weighted image, respectively, at the age of 3 months show the right orbital hemangioma (arrows). **(D)** Time-of-flight MR angiogram of the proximal intracranial arteries shows absence of the right internal carotid artery (arrow) compared to normal left internal carotid artery (dashed arrow). **(E)** At age of 6 months after treatment with propranolol, the right orbital hemangioma shows an interval reduction in size (arrow), with **(F)** marked improved recanalization of the right internal carotid artery (arrows), although it remains smaller in caliber compared to the left internal carotid artery (dashed arrow).

Discussion

PHACES syndrome is a rare disorder of unknown etiology and pathogenesis. The extracutaneous manifestations of this syndrome are well documented and include cerebrovascular anomalies, which are associated with potential comorbidities such as seizures and ischemic strokes.[6,7] The documented arteriopathy predominantly affects the medium and large-calibre cerebral vessels, giving rise to stenosis, occlusion, agenesis, hypoplasia, or anomalous origin/course of the main cerebral arteries, saccular aneurysms, and arterial dysplasia.[8-10] Furthermore, intracranial vasculopathy such as Moyamoya syndrome may cause arterial ischemic stroke.[11,12]

Patients with PHACES syndrome who present with significant narrowing (> 25%) or occlusion, aplasia or hypoplasia of main cerebral vessels, tandem or multiple arterial stenoses that diminish cerebral perfusion, and/or imaging findings suggesting chronic or silent brain ischemia are considered to be at high risk for arterial ischemic stroke.[13,14] In this context, the initiation of treatment for segmental hemangioma, which often occurs within the first few months of life, is crucial due to its aggressive proliferation, and propranolol treatment is considered the gold standard therapy for visual impairment or airway obstruction.[13,14]

However, the presence of vasculopathy in children affected by PHACES syndrome raises concerns about the potential increased risk of stroke associated with beta-blocker use, especially in those with major or multiple arterial anomalies.[13,14] While arterial anomalies are commonly observed in PHACES syndrome cases, there is limited information on the clinical outcomes of these changes after propranolol use. Two patients have reported stroke while receiving propranolol. The hypotension-induced reduction in blood flow in the stenotic, occluded, hypoplastic or absent artery is the proposed mechanism by which propranolol may trigger ischemic stroke.[15]

There are several reported cases of PHACES syndrome associated with strokes, with the average age of stroke occurrence being 13.6 months, and the most common presenting symptoms being seizure and hemiparesis.[11] Therefore, starting oral propranolol in patients with arterial anomalies is challenging and requires careful consideration of the potential risk of stroke.

Our three cases highlight the multifaceted nature of propranolol therapy decisions in PHACES syndrome, emphasizing the importance of a meticulous evaluation of individual cases and a multidisciplinary approach to treatment decision-making. In Case 1, the decision not to administer propranolol and instead opt for clinical observation was based on the assessment that the patient had a notable stroke risk, while the hemangioma did not induce functional abnormalities. For Cases 2 and 3, the high indication for propranolol therapy was driven by the potential for functional abnormalities arising from the hemangioma's location, coupled with a lower vascular stroke risk compared to Case 1.

In summary, propranolol remains a key therapeutic option for managing segmental hemangioma in PHACES syndrome, but its use must be approached with caution, especially in patients with significant arterial anomalies. The potential risk of stroke underscores the importance of thorough evaluation and a multidisciplinary approach to treatment decision-making.

Conclusion

This case series involving three PHACES syndrome patients brings to light the challenging task of deciding on propranolol administration in those with cerebrovascular anomalies due to the increased susceptibility to stroke. It emphasizes the paramount importance of interdisciplinary discussions. Regrettably, the utility of brain perfusion study to assess cerebral blood flow (CBF) before propranolol initiation as a potential predictor of stroke risk remains unclear. Additional research is imperative to determine the role of perfusion studies in the algorithm for propranolol administration in these patients.

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