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Case Report

PHACE(S) Syndrome with Ocular Involvements and No Periocular Hemangioma

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Keywords
PHACE(S) syndrome · Isolated ocular involvement · Infantile hemangioma

Abstract
PHACE(S) syndrome is a neurocutaneous disorder with a hallmark finding of an infantile facial hemangioma (IFH) >5 cm. Eye examination of patients with PHACE(S) syndrome with no IFH at periorbital region is reported to be of low yield. We report a unique case of the syndrome with ocular manifestations without periorbital IFH or systemic findings. A 3-week-old female infant with right periauricular IFH >5 cm, extending to the neck and cheek and lower lip IFH was presented. Examination revealed pseudoptosis due to microphthalmia with esotropia and hypertropia. Both corneas were clear with diameters of 5 mm and 10 mm, right eye (RE) and left eye (LE), respectively. There was a posterior polar cataract with a poor view of the fundus RE. Ocular B-scan and magnetic resonance imaging (MRI) findings were suggestive of a dysmorphic globe, vitreous hemorrhage, spherophakia and persistent fetal vasculature RE and normal findings LE. Clinical evaluation, MRI, and MR angiography revealed no other systemic abnormalities. Subsequent follow-up visits revealed progressive clouding of the cornea with neovascularization and the development of phthisis bulbi RE at which point an ocular prosthesis was placed. The IFH was managed with dye laser and with oral propranolol. At 1 year, the patient has remained stable with no development of new local or systemic anomalies, regression of the periauricular and lip IFH, and normal development of the orbital structure RE with an ocular prosthesis in situ. Ocular involvement in patients with PHACE(S) syndrome may be present

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without periorbital IFH. Regardless of the location of the IFH and the presence or absence of a periocular component, it is recommended that they receive a full initial ophthalmological assessment.

Introduction

PHACE(S) syndrome is a neurocutaneous disorder of unknown etiology; its acronym refers to the commonest features of PHACE: posterior fossa malformations, large facial hemangiomas, cerebral arterial anomalies, cardiovascular anomalies, and eye anomalies [1]. When it is associated with ventral developmental defects such as sternal cleft of the supraumbilical raphe, the acronym PHACE(S) may be used [1]. Children with PHACES syndrome may have significant ocular abnormalities and risk developing strabismus and amblyopia [2]. Although the original and revised consensus statements have established ocular anomalies in the diagnostic criteria of PHACE(S) syndrome [3], the true prevalence of ocular involvement and abnormalities are unknown. Ocular anomalies were reported to occur in 6% and 7% of cases for the posterior segment (major criterion) and anterior segment (minor criterion), respectively, based on published case reports and case series of 8 patients [4]. Samuelov et al. [5] reported that eye examination in patients with PHACE syndrome without a periocular infantile facial hemangioma (IFH) is likely of low yield. Our case is unique in the sense that the IFH was not periocular and no other systemic anomalies were noted, the presentation was early and there was monitoring of the evolving ocular features.

Case Report

We present the case of a female infant that presented at 3 weeks of age, referred by the pediatricians on account of right eye (RE) microphthalmia and ptosis. She had periauricular hemangioma that extended slightly toward the cheeks on the right (Fig. 1a) and buccal hemangioma involving the lower lip and gingival area (Fig. 1b, arrow). There were no signs or symptoms of respiratory distress. On initial ophthalmological evaluation, she had pseudoptosis of the RE with microphthalmia, esotropia, and hypertropia (Fig. 1c). Both corneas were not cloudy with a diameter of 5 mm in the RE and 10 mm in the left eye (LE) (Fig. 1d), the pupils and lens were difficult to examine and the fundus was unclear. An ocular A-scan showed an axial length of 13.3 mm RE and 18.2 mm RE. B-scan showed features of linear and punctate areas of hyperechogenicity with mild organization suggestive of vitreous hemorrhage (VH) and a hyperechoic stalk extending from the optic nerve head to the posterior capsule of a dislocated lens, suggestive of persistent fetal vasculature (PFV) (Fig. 1e, white arrow). The magnetic resonance imaging (MRI) also revealed a dysmorphic globe (Fig. 1f) with a hypo-intense stalk (Fig. 1g, arrow) extending from the optic nerve head to a dislocated spherophakic lens (Fig. 1g, arrowhead), confirming B-scan findings suggestive of PFV but no features of a staphyloma or optic nerve hypoplasia. Intraocular pressure was not measurable in the RE and 9.2 mm Hg LE by rebound tonometer. MRI and magnetic resonance angiography of the brain, head, neck, and chest revealed no other systemic malformations.

She had been started on oral propranolol at 1 mg/kg (3.75 mg) at 2 months of age to help with the regression of the hemangioma and also to limit further possible growth. The dose is being adjusted as per her body weight. With monthly ophthalmological examinations, the RE

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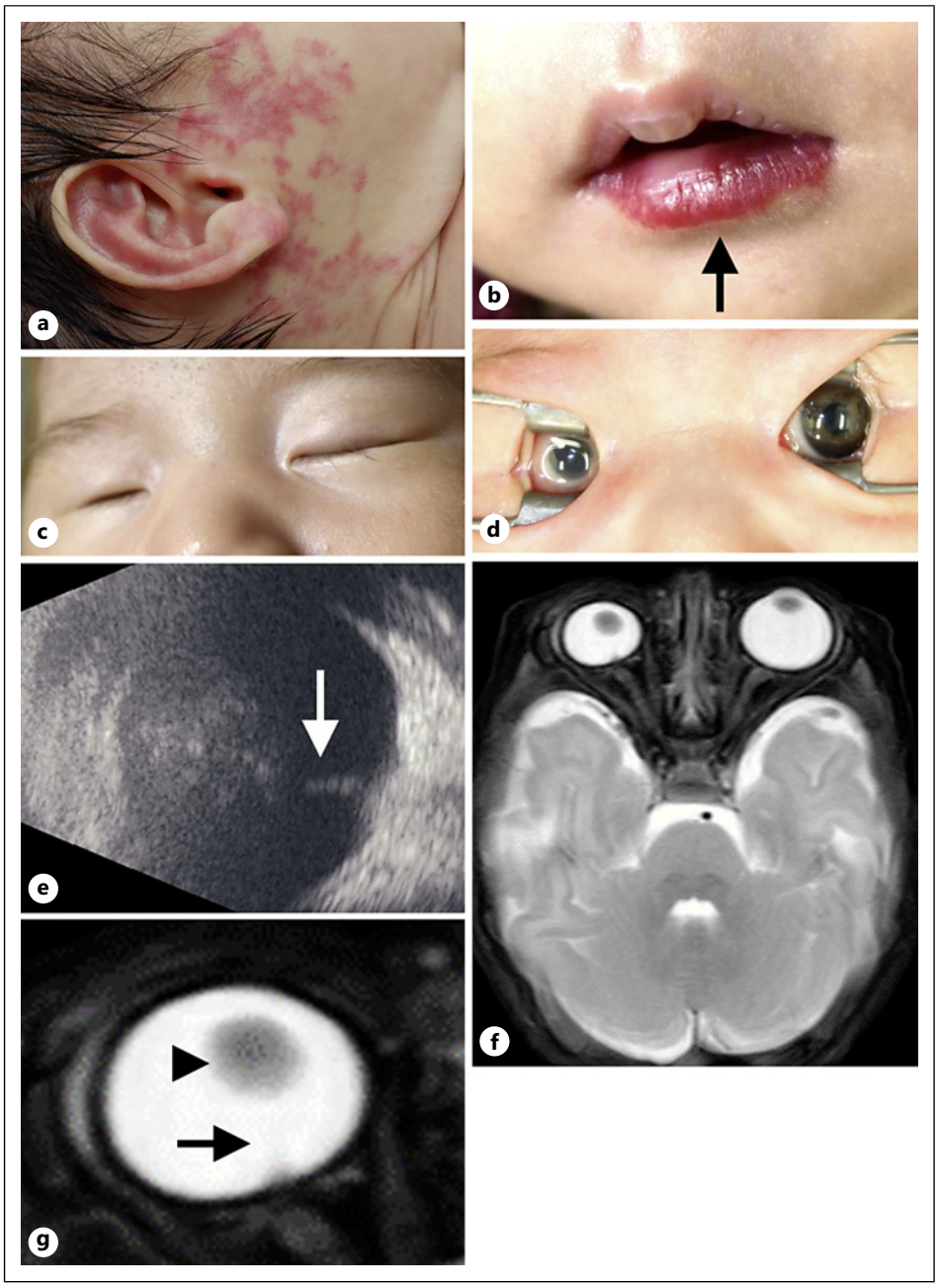

Fig. 1. Findings at 3 weeks of age. **a**, **b** A female infant with IFH over the right periauricular area extends down the neck and cheek area (**a**) and lower lip (**b**, arrow). **c** A right small globe, pseudoptosis, and a narrow palpebral fissure. **d** A right microphthalmia and a clear microcornea. **e** Ocular B-scan showing hyperechoic lesions in the vitreous cavity and stalk extending from the ONH (white arrow). **f** MRI showing right microphthalmos with dysmorphic globe. **g** Right globe on MRI showing a dislocated spherophakic lens (arrowhead) and hypo-intense stalk extending from the ONH to the posterior lens capsule (arrow). ONH, optic nerve head.

was noticeably shrinking, phthisis bulbi was progressing, and at 8 months of age, the cornea became cloudy, and developed neovascularization (Fig. 2a). The decision was made to insert an ocular prosthesis device (Kajiyama Prosthesis, Kyoto, Japan) to maintain the orbital space and facilitate the development of the facial bony structure. The size of the prosthesis was

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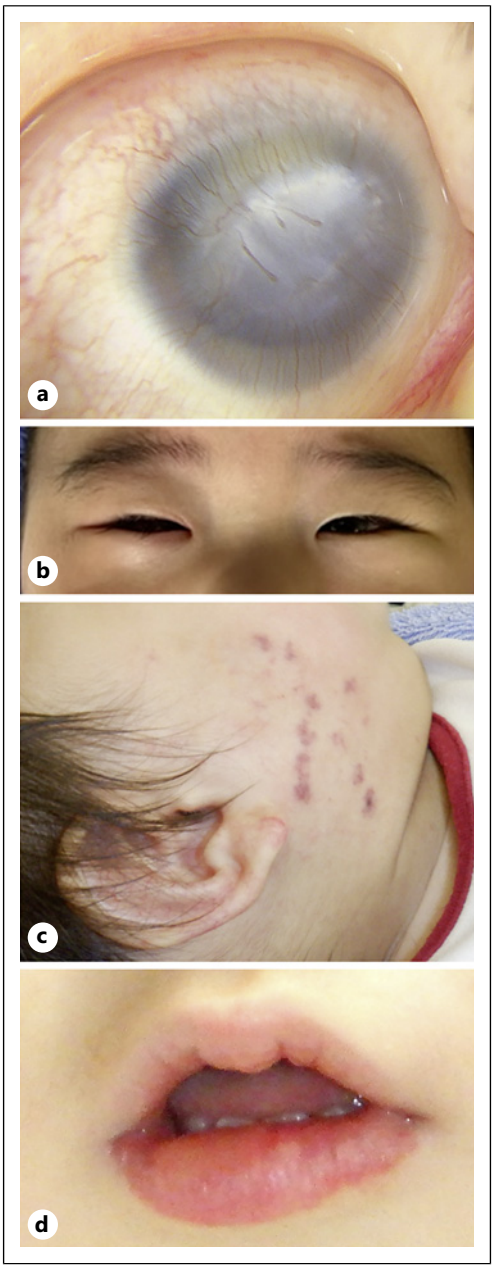

Fig. 2. Findings on follow-up. **a** RE corneal opacity with neovascularization at 8 months of age. **b** At 1 year of age with an ocular prosthesis fitted in the RE, good development and symmetry of palpebral fissure. **c** At 1 year of age with an obvious reduction in periauricular IFH. **d** At 1 year with a reduction of IFH of the lower lip.

checked and adjusted as necessary (Fig. 2b). She had laser therapy with dye laser (V-beam, Syneron Candela, Marlborough, MA, USA) starting at 7 months of age for the hemangiomas on the periauricular area, neck, and cheeks administered by the plastic surgeons. After three sessions (applied energy of 11 J/session), significant regression of the superficial component of the hemangioma had been noted. At 1 year of age, she has had normal developmental milestones and is currently stable on oral propranolol at a dose of 3 mg/kg daily. Interventions by pediatricians and plastic surgeons have resulted in regression of the IFH in both the periauricular and lower lip area (Fig. 2c, d). The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533887).

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Discussion

Although the exact cause of PHACE(S) syndrome is unknown, it appears to occur sporadically from an unknown post-zygotic somatic mutation [2]. The specific symptoms and their severity vary greatly from one individual to another. The hallmark finding in this widely varying disease spectrum is the presence of large plaque-like facial hemangiomas that occupy at least one facial segment (https://rarediseases.org/rare-diseases/phace-syndrome/) [1–3]. The presence of PFV in PHACE(S) syndrome was first reported in 2004 by Lasky et al. [6], and since then, few cases have been reported, particularly cases with periocular hemangiomas [3, 5].

In our case, the diagnosis of PHACE(S) syndrome was made based on the presence of IFH >5 cm, PFV, which is a major criterion, and microphthalmia with mild posterior polar cataract, both minor criteria (Table 1) [3, 5]. As our case, female predominance of PHACE(S) syndrome with a 3.6:1 female-to-male ratio was reported [6–9]. Most patients reported Caucasian (82%) or Hispanic (16%) ethnicity and a majority (85%) were younger than 1 year [9]. Steiner et al. [9] detected globe malformations in only 4 (7%) of the patients and similar to our case, only in the globe ipsilateral to the hemangioma. Two of their patients had posterior staphyloma and 2 had microphthalmos [9]. One of the patients with microphthalmia also demonstrated choroidal hemorrhage and lens dislocation, 3 patients had hypoplasia of the optic nerve(s) or chiasma [9]. In our case, there was microphthalmia and a dislocated lens, and with PFV as a posterior ocular anomaly was noted. In a case series of 43 patients by Soliman, ocular anomalies were always associated with other PHACE(S) major criteria and were ipsilateral to facial hemangioma [8]. This finding was not the case in our patient, although the ocular anomaly was ipsilateral to the IFH, the lack of other major criteria was noteworthy. They also reported that all eyes having a posterior segment anomaly (major criteria) had associated intracranial vascular anomalies [8], however, our patient did not.

Our findings were not in keeping with those observed by Samuelov et al. [5]. Even though ocular abnormalities are part of PHACES syndrome, Samuelov et al. [5] reported that most ocular complications observed in their cohort of 30 patients over 15 years, were secondary to the presence of the large periocular hemangioma itself and were not specific to PHACE(S) syndrome. Nayak et al. [10] reported a case similar to ours, an 11-month-old female presented with facial IFH involving the lower lid only, with PFV, VH, and congenital cataract with microphthalmia. She had no associated systemic anomalies. They were however able to salvage vision after cataract extraction and diathermy of the intraocular vascular stalk despite the late presentation. They concluded that the outcome would have been better with early presentation and intervention. In our case, on account of the possible severity of the PFV, VH, and subsequent progressive haziness of the cornea from phthisis bulbi that developed, the visual outcome was poor as the severity of congenital eye abnormalities rendered the eye inoperable.

The ongoing management of our patient is multidisciplinary and aimed at ensuring normal development and acceptable cosmesis. Since the PHACE syndrome is associated with cerebrovascular and cardiovascular anomalies, monitoring of life-threatening diseases is also important. The ophthalmologist facilitated the symmetric development of facial bone structure and palpebral fissure, with the use of ocular prosthesis; the plastic surgeons monitored the facial hemangioma and administered laser therapy, while the pediatricians routinely assessed the effectiveness of the propranolol therapy, checked for possible progression of hemangioma and development of any anomalies.

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Table 1. Consensus-derived diagnosis of PHACE(S) syndrome

Diagnostic criteria	Current case
IFH	Right periauricular (>5 cm)
	Lower lip
Arterial anomalies	Absent
Structural brain	Absent
Cardiovascular	Absent
Ocular	PFV (major), microphthalmos (minor), posterior polar cataract (minor)
Ventral/midline	Absent
Definite case	Hemangioma >5 cm in diameter of the head including scalp plus 1 major criterion

Conclusion

Ocular involvement in patients with PHACE(S) syndrome may be present without periorbital IFH. It may even be the only association. In patients with IFH, >5 cm regardless of the location of the hemangioma and the presence or absence of a periocular component, it is recommended that patients receive a full ophthalmological assessment and an MRI/magnetic resonance angiography to rule out possible associations. It is also important to have a multidisciplinary approach to treating patients with PHACES.

Statement of Ethics

This study adhered to the tenets of the Declaration of Helsinki. The Institutional Review Board of Shimane University Hospital did not require an Ethics Committee review process to report this case. Ethical approval is not required for this study in accordance with national guidelines of Japan. This retrospective review of patient data did not require ethical approval in accordance with national guidelines of Japan. The patient's guardian provided written informed consent for the publication of this case report and any accompanying pictures.

Conflict of Interest Statement

The authors have no conflicts of interest associated with this case report.

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Author Contributions

All authors attest that they meet the current ICMJE criteria for authorship. A.S.K., K.S., K.Y., S.K., C.O., T.T., K.H., and M.T. treated the subject, collected the clinical data, approved the final version of the manuscript, and agreed to be responsible for all aspects of this work. A.S.K. and M.T. wrote the manuscript, and K.Y., S.K., C.O., T.T., and K.H. revised the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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