Case Report

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PHACE syndrome: a case report and a comprehensive review

Munna William, MBBS[a], Amrit Bhusal, MBBS[c,*], Syed Muhammad Umar, MBBS[b], Ayesha Jamal, MBBS[b], Abdul Sattar Anjum, FCPS[a], Mudasira Habib, FCPS[a]

Introduction and importance: PHACE syndrome is a rare neurocutaneous disorder characterized by large segmental hemangiomas on the face and is associated with multiple developmental defects. PHACE stands for posterior fossa malformations, hemangiomas, arterial abnormalities, cardiac defects, and eye anomalies, with the most common manifestation being hemangioma in the cervico-facial region in early childhood.

Case presentation: The authors report a case of a 15-year-female with complaints of facial hemangioma which on multisystemic imaging showed features of central nervous system (CNS) anomalies that led to the diagnosis of PHACE syndrome. The patient was started on propanolol which decreased the size of hemangioma in follow-up visits.

Clinical discussion: The hemangioma in the frontotemporal and frontonasal area of the face are associated more with CNS and cardiovascular anomalies needing a detailed multisystem approach. CNS anomalies include posterior cerebral fossa enlargement, cystic dilation of the fourth ventricle, arachnoid cyst, and cerebellar hypoplasia which were present in our case. Propanolol is considered the first-line drug for facial hemangioma with reported evidence of remarkable improvement and good tolerance. However, regular follow-up of the patient is needed to rule out any recurrence.

Conclusion: PHACE syndrome, although being a rare occurrence, must be kept as a differential diagnosis in infants and children with facial hemangioma. Imaging modalities like MRI/magnetic resonance arteriography must be used to rule out possible associations related to PHACE syndrome and focus on early treatment to prevent possible complications.

Keywords: Case report, CNS anomalies, hemangioma, neurocutaneous disorder, PHACE syndrome, Propanolol

Introduction

PHACE syndrome is a rare neurocutaneous disorder characterized by large segmental hemangiomas on the face and is associated with multiple developmental defects[1]. The acronym PHACE stands for posterior fossa malformations, hemangiomas, arterial abnormalities, cardiac defects, and eye anomalies. When defects like sternal clefting or supraumbilical raphe are also present, the acronym PHACES is used instead[2]. The association of PHACE syndrome with brain abnormalities was first reported in 1978 by Pascual-Castroviejo. In 1996, Frieden and colleagues created the acronym PHACE to detail the most representative features of the syndrome[3]. The diagnostic criteria for PHACE syndrome was established in 2009 and was then revised in 2016[3]. The most common manifestation of PHACE syndrome is early childhood hemangioma in the cervico-facial region[4]. There are more than 300 cases of PHACE syndrome reported in literature. PHACE syndrome is observed in 2–3% of infantile hemangioma (IH) cases. Also, when the IH develops on the face and is segmental or large, the likelihood of it being associated with PHACE syndrome is 20–31%[3]. Malformations of posterior fossa are present in ~45% of the cases[5]. Diagnosis of PHACE syndrome is crucial because of its variable manifestations and complications. But the manifestations of upmost concern are that of neurological system which include neurodevelopmental delay, speech difficulties, seizures, and neurovascular complications

HIGHLIGHTS

- PHACE syndrome is a rare neurocutaneous disorder.
- It is characterized by large segmental hemangiomas on the face and is associated with multiple developmental defects.
- PHACE syndrome are associated with central nervous system and cardiovascular anomalies, and thus need a multisystemic approach.
- Propanolol is the first-line drug for facial hemangioma associated with PHACE syndrome.
- Regular follow-up is needed for patient treated with propanolol due to its recurrence pattern.

[a]Department of Diagnostic Radiology and Imaging, Nishtar Medical University, Multan, Pakistan, [b]Department of Pediatrics, Nishtar Medical University, Multan, Pakistan and [c]Department of Radio-diagnostics and Imaging, BP Koirala Institute of Health Sciences (BPKIHS), Dharan, Sunsari, Nepal

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*Corresponding author. Address: BP Koirala Institute of Health Sciences (BPKIHS), Dharan, Sunsari 56700, Nepal. Tel.: +977 984 586 4980. E-mail: Amritbhusal51@gmail.com (A. Bhusal).

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such as severe headache and acute ischaemic stroke. Therefore, early diagnosis and management of this condition is necessary to prevent any complications[6]. This case report has been reported in line with the SCARE criteria 2023[7].

Case presentation

A 15-year-old girl presented for the evaluation of the red area over the left lateral face. A small red patch was noticed shortly after birth on the left forehead, but it was not prominent until the age of 5. Since the age of 5, it gradually started becoming prominent and occupying the whole of the left half of the face. However, no medical attention was sought until the age of 15 when the parents started becoming concerned about the cosmetic appearance of their daughter. The patient had no significant past medical history. She did not have any focal neurological deficits.

On examination, there were bright red papules and plaques over the left fronto-temporomandibular area, including the tip of the nose, lips, and left palate (Fig. 1). The area around the eye was spared and the vision was normal. There was no sternal cleft. Keeping in view the association of segmental hemangioma with PHACE syndrome, investigations like echocardiography and MRI of the head and neck were done. The echocardiography result was unremarkable. However, MRI revealed a large posterior fossa cyst communicating with the fourth ventricle and associated hypoplastic cerebellar vermis consistent with the Dandy–Walker variant; a left temporal region arachnoid cyst

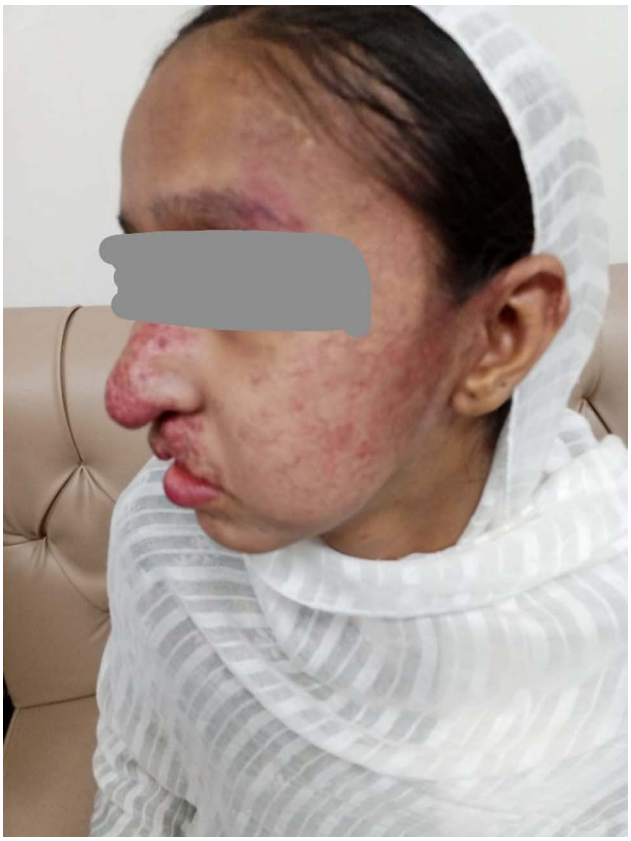

Figure 1. Multiple patchy areas of vascular malformation noted on face involving left side of nose, cheek, part of forehead and upper lip.

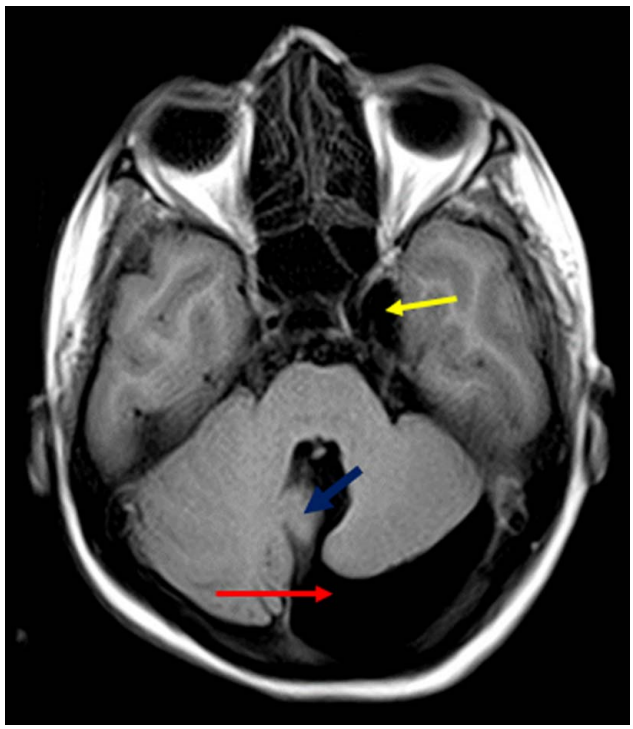

Figure 2. Axial T1 weighted MR image at the level of pons showing cerebrospinal fluid (CSF) signal intensity area (cyst) in posterior fossa communicating with fourth ventricle (red arrow) along with hypoplasia of left cerebellar hemisphere and vermis (Dandy–Walker variant) (blue arrow) and left temporal region CSF signal intensity area (arachnoid cyst) (yellow arrow).

(Figs. 2–5); and vascular malformation along the upper lip, the tip of the nose, and left palate (Figs. 6 and 7). Based on the clinical and radiological findings, diagnosis of PHACE syndrome was made. The patient was initiated with Propanolol. On follow-up visits, the size of hemangioma reduced considerably.

Discussion

PHACE syndrome is an uncommon disorder with female predominance (9:1)[8]. The pathogenesis of this uncommon condition is still unknown. However, it has been postulated to develop as a result of defective embryogenesis between the 3rd to 12th week of gestation, before or during vasculogenesis[3]. Most of the cases are sporadic. But there are theories regarding its correlation with mutation in the X-linked genes, because of its female predominance and prenatal male lethality[9]. Our article also describes a 15-year-old female which matches the normal incidence of PHACE.

Hemangiomas are the most common manifestation of PHACE syndrome. About 90% of the hemangiomas in PHACE syndrome are located on the cephalic segment. The face is the most commonly affected site, but the lesions can also develop in the scalp and postauricular and cervical regions[10]. Hemangiomas in PHACE syndrome are typically segmental type and usually large (>5 cm in diameter). Segmental refers to the hemangiomas that affect one region and do not arise from a focal point. These hemangiomas may present as telangiectasias, solitary lesions, confluent plaques, small papules that assume a specific

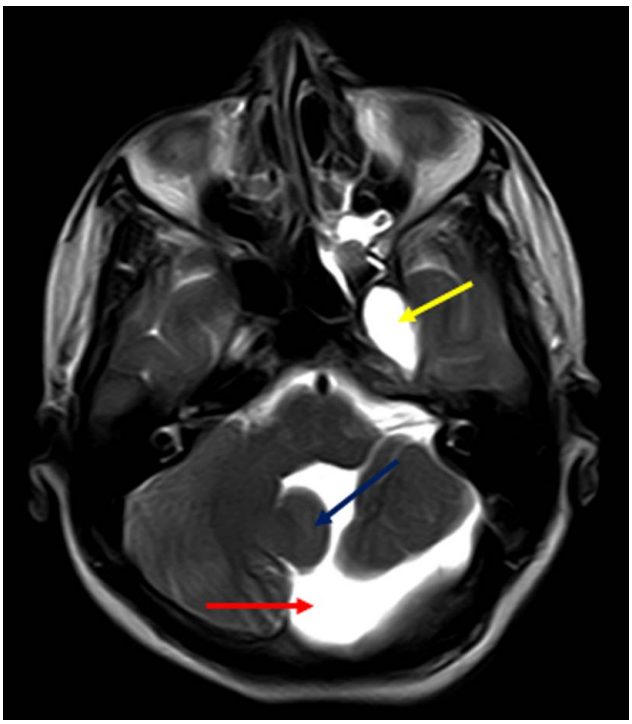

Figure 3. Axial T2 weighted MR image at the level of pons showing posterior fossa cyst communicating with fourth ventricle (red arrow) along with hypoplasia of left cerebellar hemisphere and vermis (Dandy–Walker variant) (blue arrow) and left temporal region arachnoid cyst (yellow arrow).

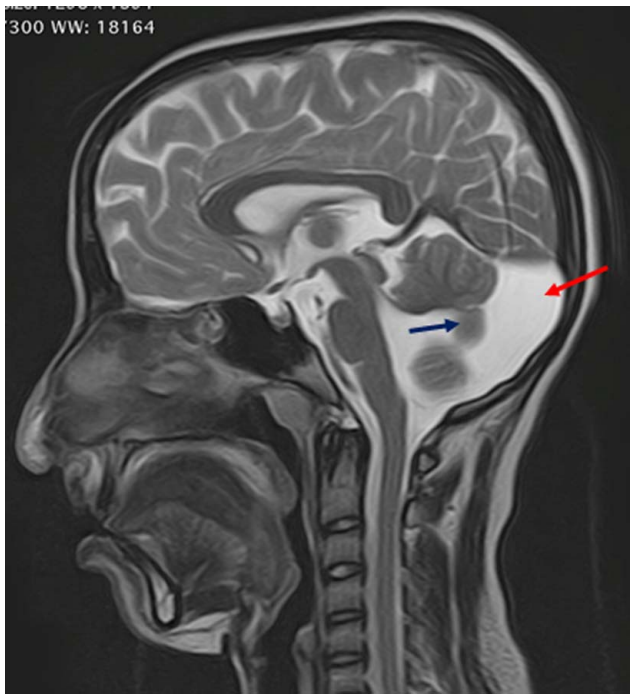

Figure 5. Mid-sagittal T2 weighted MR image showing cerebrospinal fluid signal intensity area in posterior fossa communicating with fourth ventricle (red arrow) along with hypoplasia of left cerebellum and vermis (blue arrow).

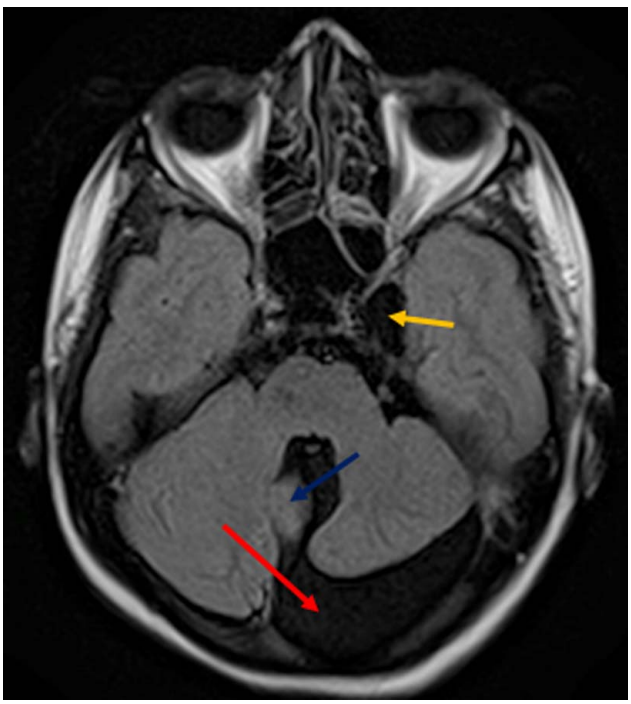

Figure 4. Axial FLAIR MR image at the level of pons showing posterior fossa cyst communicating with fourth ventricle (red arrow) along with hypoplasia of left cerebellar hemisphere and vermis (Dandy–Walker variant) (blue arrow) and left temporal region arachnoid cyst (yellow arrow).

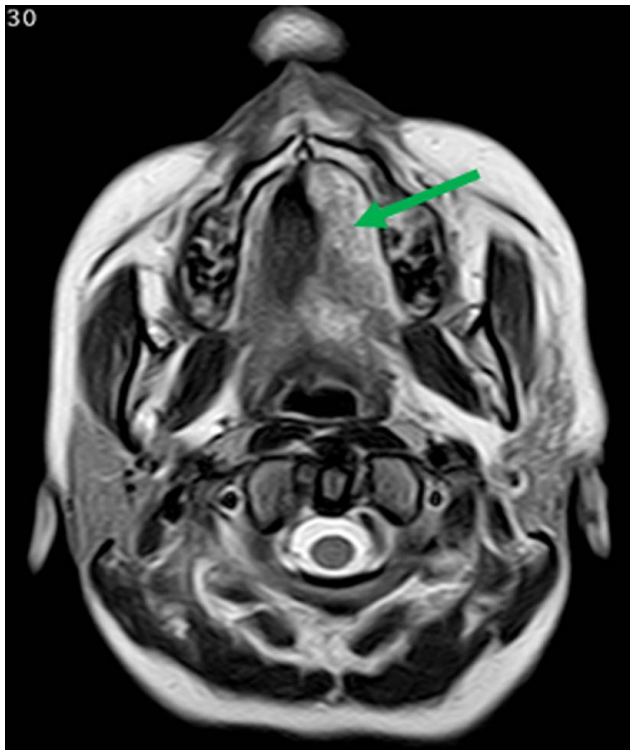

Figure 6. Axial T2 weighted image at the level of atlas/C1 showing high T2 signal intensity area with internal flow voids along left side of palate (green arrow) suggestive of vascular malformation.

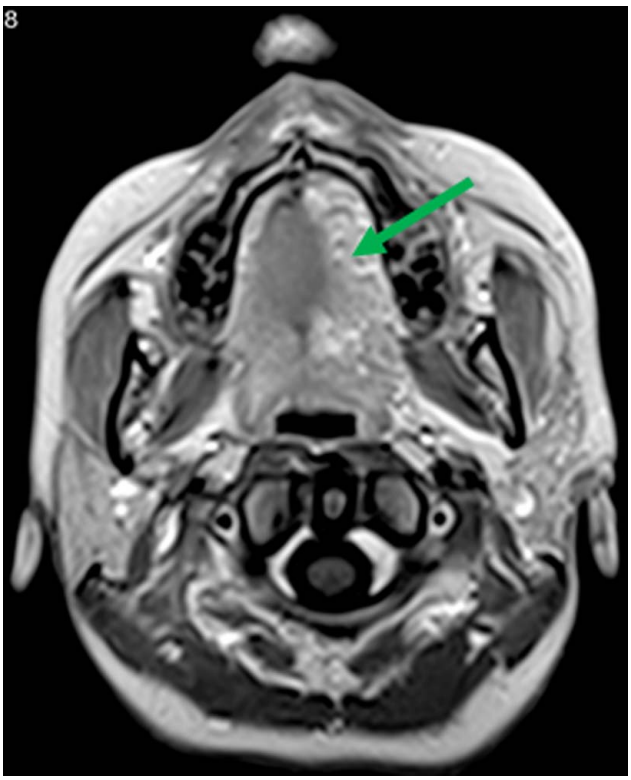

Figure 7. Axial T1 weighted post contrast image at the level of Atlas/C1 showing enhancing area along left side of palate (green arrow) suggestive of vascular malformation.

distribution, and tumours with deeper involvement[11]. IH may either be absent or manifest as a precursor lesion characterized by a pale, slightly erythematous, or telangiectatic area at birth. However, the majority of IHs become visibly apparent by the end of the first month of life[12]. In our case, the facial hemangioma was present since birth, but it became prominent after 5 years of age and was a matter of concern after she turned 15 years of age due to cosmetic concerns.

Facial hemangiomas located in the upper half of the face exhibit an elevated susceptibility to concurrent structural brain, cerebrovascular, and ocular anomalies. In contrast, those positioned elsewhere are more prone to the development of cardiac defects[13]. Haggstrom *et al.*[14] suspected a relationship between the facial location and extracutaneous involvement of an IH, which states that the IHs on the frontotemporal and frontonasal segments bear a higher risk of ocular and central nervous system (CNS) involvement, whereas those on the mandibular segment are linked to a greater risk of midline and cardiovascular defects. In our case as well, the hemangioma was present in the frontonasal and frontotemporal aspect of the face and was associated with CNS malformations.

The range of potential differential diagnoses of PHACE syndrome encompasses Sturge–Weber syndrome, Wyburn–Mason syndrome, infantile hemangioma, and LUMBAR syndrome. LUMBAR syndrome manifests as lower body hemangiomas, urogenital anomalies, myelopathy, bone deformities, anorectal malformations/arterial anomalies, and renal anomalies[6].

The initial physical examination for the suspected PHACE syndrome includes an assessment for ocular and sternal midline abnormalities, in addition to neurological and cardiac evaluations. Standard echocardiography is imperative, and upon detection of anomalies, additional evaluation employing cardiac MRI and magnetic resonance arteriography (MRA) is advised for a comprehensive analysis of cardiac and brachiocephalic structures. However, no visual, cardiovascular, or sternal abnormalities were present in our case. To thoroughly assess suspected PHACE syndrome instances, diagnostic imaging should encompass gadolinium-enhanced MRI and MRA of the brain, neck, and aortic arch. It is noteworthy that although MRI holds significance, its efficacy in identifying all arterial abnormalities is constrained, prompting the supplementary utilization of MRA[6]. For a case to be diagnosed with "definitive PHACE", a hemangioma of the face or scalp larger than 5 cm must be associated with one major diagnostic criterion, or a large segmental hemangioma of the neck, upper trunk, or trunk and proximal upper extremity must be associated with two other major criteria (Table 1)[15]. The absence of cutaneous hemangioma does not preclude the diagnosis of PHACE. The concept of "possible PHACE" was established to accommodate patients lacking hemangiomas but presenting with two major criteria[6]. Our case had features like facial hemangioma and posterior fossa anomaly fulfilling the major criteria that led us to the diagnosis of PHACE syndrome. Primary neuroimaging characteristics

Table 1

Diagnostic criteria for PHACES syndrome[15]

System	Major criteria	Minor criteria
Brain (vascular)	Anomalies of larger brain vessels • Arterial dysplasia, occlusion or stenosis. • Absence or hypoplasia • Aberrant origin or course • Persistence of trigeminal artery • Saccular aneurysms	Persistence of embryonic arteries • Pro-atlantal intersegmental artery • Primitive hypoglossal artery • Primitive ophthalmic artery
Brain (structural)	Posterior fossa anomaly • Dandy–walker • Unilateral/bilateral hypoplasia/ dysplasia of the cerebellum	Extra-axial lesion compatible with intracranial hemangioma
Cardiovascular	Aortic arch anomaly • Coarctation of aorta • Aneurysm • Aberrant origin of subclavian artery with or without vascular ring	• Defect of ventricular septum • Right sided aortic arch (double aortic arch)
Ocular	Posterior segment anomalies • Persistence of foetal vascularization • Vascular anomalies of the retina • Optic disc anomalies, morning glory type • Optic nerve hypoplasia • Coloboma • Peripapillary staphyloma	Anterior segment changes • Sclerocornea • Cataracts • Coloboma • microphthalmia
Midline	Sternal deformities • sternal cleft • supraumbilical raphe • sternal defects	Hypopituitarism Ectopic thyroid

encompassed unilateral cerebellar hypoplasia, elevation of the affected cerebellar hemisphere and tentorium, as well as hypoplasia and upward rotation of the cerebellar vermis[16]. Predominantly, central neurological malformations in PHACE syndrome manifest in the posterior fossa, frequently presenting as Dandy–Walker syndrome characterized by posterior cerebral fossa enlargement, elevation of the cerebellar tent, and cystic dilation of the fourth ventricle[17]. The neuroimaging features noted in our patient were posterior fossa anomaly, hypoplastic cerebellar vermis consistent with the Dandy–Walker variant, left temporal region arachnoid cyst, and vascular malformation along the upper lip, tip of the nose, and left palate. These features are consistent with the available literature on PHACE syndrome. Other abnormalities of the posterior cerebral fossa have been reported such as arachnoid cyst and mega cisterna magna[17].

Propanolol is considered the first-line drug for IH. It should be administered gradually starting with 0.5–1 mg/kg/day in the first week, increasing progressively to 2–3 mg/kg up to optimum dose so as not to disturb blood pressure. In the case of cerebral vascular disease, neurosurgical treatments should be appropriate[17]. Initially, it was thought that β-blockers could decrease cardiac output, reducing perfusion in the cerebral arteries and causing infarction in areas with absent, stenosed, or occluded arteries[1]. However, a cohort study in 2019 done on 76 PHACE patients showed no patients with stroke, who were on oral propranolol therapy[1]. Several studies show remarkable improvement and good tolerance with oral propranolol therapy. Also, there has been reported incidence of IH recurrence and tumour growth upon discontinuation of propranolol treatment, particularly if the treatment was halted prematurely[3]. Follow-up of the patient after treatment discontinuation is crucial, as re-initiating treatment may be necessary in cases of recurrence[3].

Conclusion

PHACE syndrome, though being a rare occurrence, must be kept as a differential diagnosis in infants and children with facial hemangioma. Imaging modalities like MRI/MRA must be used to rule out possible associations related to PHACE syndrome and focus on early treatment to prevent possible complications.

Ethical approval

The study is exempt from ethical approval in our institution.

Consent

Written informed consent was obtained from the patient's parents/legal guardian for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

All the authors were involved in manuscript preparation, review of literature and final approval of manuscript.

Conflicts of interest disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Dr. Amrit Bhusal.

Data availability statement

Yes the data analyzed during current study are publicly available, available upon reasonable request, or if data sharing is not applicable to this article.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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