Special Article

PHACE Syndrome: A Review of Clinical Manifestation and Management

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PHACE syndrome is emphasized through the characteristic findings of the posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and abnormalities of the eye. This distinctive syndrome requires a multidisciplinary care team to take care of individual problems. This review article focuses on the clinical presentation of PHACE syndrome: the initial approach from the classic cutaneous presentation and the extra-cutaneous anomalies found in association with the syndrome. The recent diagnostic criteria, management surveillance, treatment, and long-term follow-up are also addressed in this presenting review.

Keywords: Craniofacial anomalies, Hemangioma, PHACE syndrome, Propranolol

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PHACE syndrome is a complex of morphologic abnormalities of unknown cause. This syndrome was first described by Dr. Ilona Freidan in 1996[1]. The acronym PHACE emphasizes the characteristic findings of the neurocutaneous syndrome: posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta, cardiac defects, eye abnormalities, and/or sternal defects. PHACE syndrome should be considered when a large segmental facial hemangioma is documented. A large segmental facial hemangioma should be further investigat to identify any associated anomalies related to PHACE syndrome. Facial hemangioma is sometimes mimicked by other vascular birthmarks[2] such as capillary malformation-also known as port wine stain (PWS)-and nevus simplex (also known as a salmon patch). The current review focuses on distinguishing between these vascular birthmarks so as to enhance their recognition and aid in early detection, further investigation, and treatment plans for individual diseases. The summary of diagnostic criteria, investigations needed, and current treatment protocols regarding PHACE syndrome are addressed. This review article was approved by institutional review board; Faculty of Medicine, Khon Kaen University# HE601220.

Clinical manifestation of PHACE syndrome

1) Cutaneous finding in PHACE syndrome

Infants with segmental hemangiomas are at known risk for PHACE syndrome. Segmental involvements are defined as areas that extend across an anatomic region of the body, while the face, neck, and scalp are the areas of most concern. There is no definition of how large the segmental involvement can be; however, the literature suggests presenting lesions of 4.5 cm x 5.0 cm or larger fit the criteria[3]. Figure 1A shows a large segmental hemangioma on a patient's face highly suggestive of PHACE syndrome.

According to presenting of vascular lesions on an infant's face at birth; other vascular birthmarks, including port wine stain[4] (PWS) and nevus simplex (salmon patch) are within the scope of a differential diagnosis[5].

Nevus simplex or salmon patch (Figure 2) characteristically present with pale pink to red patches usually located on the upper eyelids, forehead (also called angel kiss), and nape of the neck (also called stork bite). This vascular lesion usually occurs since birth, and mostly disappears spontaneously within 1 to 2 years. Salmon patch is a result of persistent fetal circulation in newborns. The lesions can present with "reappearance" phenomenon or accentuation of facial lesions during episodes of crying, breath-holding, straining with defecation, or physical exertion. Salmon patch has less extensive areal involvement and has no relation to other physical anomalies.

PWS (Figure 3) is a capillary malformation resulting from an abnormal vascular morphogenesis during embryo development. This cutaneous finding can be found since birth, and grows in proportion to patient growth with no proliferative or regressive pattern. PWS lesion can subsequently develop nodular proliferation and cutaneous hypertrophy on affected areas in adulthood. Early intervention by pulsed dye laser is suggested to prevent this long-term complication. Some PWS can be associated with other anomalies or neuro-cutaneous syndromes such as

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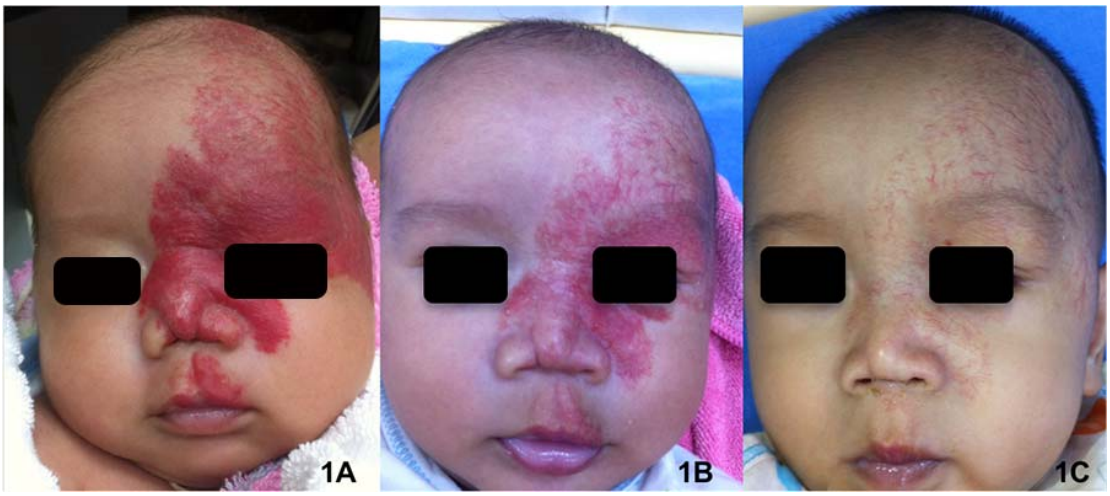

Figure 1. Infants diagnosed with PHACE syndrome: 1A) shows a large segmental facial hemangioma at 2 weeks of age before administration of oral propranolol, 1B) (6-month-old), and 1C (9-month-old) represent residual telangiectasia after 6 months of oral propranolol treatment.

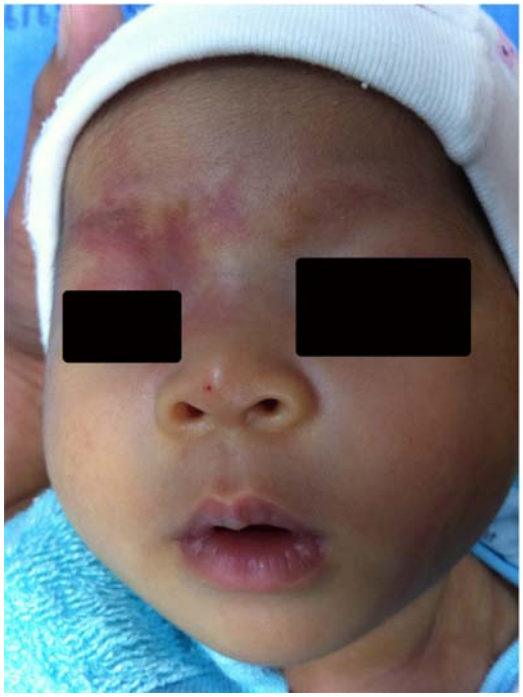

Figure 2. Picture of salmon patch demonstrating pink to red patches on upper eyelids.

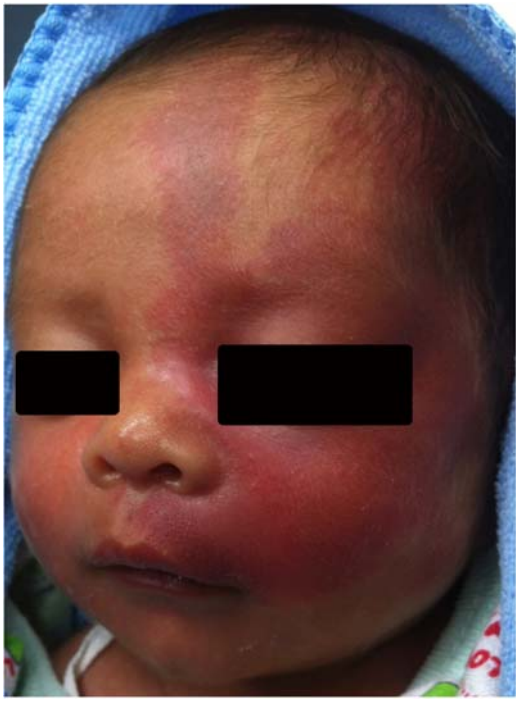

Figure 3. PWS on a patient's face representing a well-demarcated erythematous patch since birth. This lesion will not have a rapid proliferation and will persist throughout the patient's life.

Sturge-Weber syndrome, Parker Weber syndrome, and Klippel-Trenauny syndrome. The early detection of PWS may lead to prompt management of other possible associated anomalies. This cutaneous lesion will not subside by itself.

Infantile hemangioma (Figure 1A) is a form of benign cutaneous vascular tumor in children. This cutaneous lesion has its own natural history of growth pattern characteristically in 3 phases: proliferative, involuting, and

Table 1. Clinical summary of nevus simplex, port wine stain and infantile hemangioma

	Nevus simplex	Port wine stain	Hemangioma
Etiology	Result of persistent fetal circulation	Abnormal vascular morphogenesis during embryo development	Form of benign vascular tumor
Onset	At birth	At birth	Absent or preliminary light patches before turning into rapid growth
Location	Usually on forehead, nape of neck and upper eyelids	Can be located on face and other areas of body	Head and neck common areas Can be found on other areas of body
Characteristic	Faint erythematous patch usually with ill-defined border	Well-defined erythematous patch. Cutaneous hypertrophy can be found subsequently	Preliminary light patches before turning into rapid growth to proliferative plaque and nodule
Natural history of growing pattern	Disappear spontaneously within 1 to 2 years	Grow proportionately to patient growth. Nodular proliferation and cutaneous hypertrophy on affected area can be found subsequently	Rapid proliferation of lesion within first year of life, stop growing and spontaneously regress over time
Treatment	None	Pulsed dye laser	Oral propranolol is first line therapy for problematic hemangiomas

involuted. The cutaneous lesions usually occur as preliminary light patches before turning into rapid growth in the proliferative phase. This pattern can be seen within a few weeks to a few months of birth. It is essential, therefore, to follow-up the presence of any proliferative cutaneous lesion growth at 1 to 2 months of age to confirm a diagnosis of infantile hemangioma. The majority of infantile hemagioma regresses spontaneously over time; however, some problematic hemangiomas-especially a large segmental pattern-indicate a risk for PHACE syndrome and need further investigation and rapid treatment.

A clinical description of nevus simplex, PWS, and infantile hemangioma are summarized in Table 1.

2) Structural brain abnormalities associated with PHACE syndrome

Many structural brain lesions have been documented in association with PHACE syndrome. The common findings are posterior fossa brain malformation[6], Dandy-Walker complex[7], hypoplasia/dysplasia of the mid or hind brain, and cerebella abnormalities[8]. Some less common structural brain include malformation of cortical development (i.e., polymicrogyria and heterotopia, hypoplasia/agenesis of corpus callosum, absent pituitary or partially empty sella turcica and intracranial hemangioma)[9,10]. Figure 4 shows ipsilateral cerebellar atrophy on an MRI in a patient diagnosed with PHACE syndrome.

According to the structural brain abnormalities, neurological symptoms in PHACE syndrome can vary from asymptomatic, to migraine-like headache to severe (including seizure, tremor, dysphagia, and developmental delays).

3) Arterial and cardiovascular abnormalities associated with PHACE syndrome

There are several arterial abnormalities related to

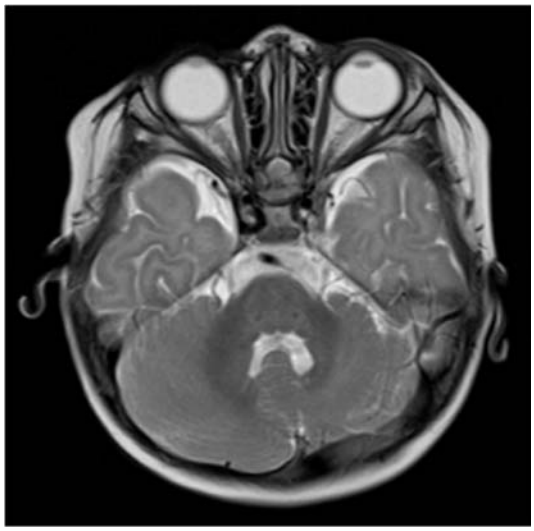

Figure 4. Imaging of ipsilateral cerebellar atrophy on an MRI in a patient diagnosed with PHACE syndrome.

PHACE syndrome[9,11-13]. Common findings include dysplasia, narrowing, and aberrant origin of the cervical, cerebral and brachiocephalic arteries. Some less common findings include Moyamoya-like arteriopathy, aneurysms, and agenesis of the cervical, cerebral, and brachiocephalic arteries. Other documented findings include arteriovenous dural fistulae[11] in association with this syndrome.

The prevalence of congenital heart disease in PHACE syndrome is incompletely described, but ranges between 41 and 67%[14]. Aberrant origin of the subclavian artery and coarctation of the aorta are the two most common

cardiac conditions. Since cardiovascular anomalies do not infrequently occur in association with PHACE syndrome, all suspected patients should undergo cardiac and aortic arch imaging to determine arch patency and brachiocephalic origins.

4) Ocular abnormalities in PHACE syndrome

There are many ocular abnormalities[15] found in association with PHACE syndrome but they are less frequent than brain structural abnormalities and arterial cardiovascular anomalies. The ocular findings reported with PHACE syndrome include microphthalmia, congenital oculomotor nerve palsy[16], posterior segment anomalies; persistent fetal vasculature, retinal vascular anomalies, morning glory disc anomaly, optic nerve hypoplasia, peripapillary staphyloma, and coloboma[17]. Since multiple eye abnormalities have been found, ophthalmic evaluation should be performed in every case of suspected PHACE syndrome.

5) Other miscellaneous manifestations in PHACE syndrome

Some other miscellaneous manifestations associated with PHACE syndrome include: anomaly of the midline chest and abdomen, sternal defect[18], sternal pit, sternal cleft, and supraumbilical raphe[19]. These presentations should be screened and can be found during a routine physical examination.

Endocrine abnormalities have been documented to be association with PHACE syndrome including: hypopituitarism, hypogonadism, hypothryroidism, and growth hormone deficiency[20]. These endocrine abnormalities may be caused by defects in the hypothalamus and pituitary glands, resulting from structural brain abnormalities.

Some other clinical findings associated with PHACE syndrome are ear anomalies, auricular hypoplasia[21], and dental abnormalities[22]. These findings do not affect the general physical health of the patient, but the long-term quality of life can be affected so these abnormalities should be monitored.

Diagnostic criteria of PHACE syndrome

Diagnosis of PHACE syndrome is addressed when the patient presents a large segmental facial hemangioma together with other clinical findings of posterior fossa malformations, arterial anomalies, coarctation of the aorta and cardiac defects, eye abnormalities, and/or sternal defects. There are, however, some reports regarding PHACE syndrome with no facial hemangioma but having hemangioma elsewhere (i.e., on the neck, scalp, upper extremities, and/or trunk) or even without clinical findings of cutaneous hemangioma. This variation makes this syndrome even more difficult to diagnose. A consensus statement on the diagnostic criteria for PHACE syndrome was developed in 2009[23] and revised criteria were proposed in 2016[24]. The criteria include definite and possible PHACE syndrome by counting the number of major and minor criteria. Each individual criterion was classified by the presentation of clinical findings in each organ system. The lists of major and minor criteria for PHACE syndrome were proposed for a consensus-derived diagnosis and care recommendations among the PHACE syndrome community group[24] (Table 2).

Definite PHACE syndrome is defined as: (a) Hemangioma >5 cm in diameter of the head including the scalp PLUS 1 major or 2 minor criteria; or (b) Hemangioma of the neck, upper trunk, or trunk and proximal upper extremity PLUS 2 major criteria.

Possible PHACE syndrome is defined as: (a) Hemangioma >5 cm in diameter of the head including the scalp PLUS 1 minor criteria; (b) Hemangioma of the neck, upper trunk, or trunk and proximal upper extremity PLUS 1 major or 2 minor criteria; or, (c) No hemangioma PLUS 2 major criteria.

Management

According to multiple associated findings, a multidisciplinary approach should be used with patients with PHACE syndrome. Multidisciplinary teams vary among institutions but should include a general pediatrician, a pediatric dermatologist, a hemato-oncologist, a neurologist, and a pediatric surgeon. The following management should be utilized in all patients with suspected PHACE syndrome.

1) Physical examination searching for noticeable abnormalities

Identification of hemangioma lesion must be differentially-diagnosed from other vascular birthmarks as described in Table 1. When a large segmental facial hemangioma is diagnosed suggestive of PHACE syndrome, a physical examination should be carefully performed to identify any potentially associated anomalies especially of noticeable findings such as a sternal and/or abdominal defect. Early detection of a sternal and/or abdominal defect and early referral to a pediatric surgeon will lead to a prompt, specific surgical correction.

2) Ophthalmology examination

Since many ocular abnormalities can be found in association with PHACE syndrome, performing an ophthalmology examination is necessary in all cases. Some early correction of ocular abnormalities can prevent long-term ocular complication.

3) Echocardiogram

Performing echocardiogram should be addressed in all cases of suspected PHACE syndrome since multiple associated cardiac anomalies are possible. Besides the structure of the heart, the arteries and braches should be evaluated since dysplasia, narrowing, and aberrant origins of the cervical, cerebral and brachiocephalic arteries are common findings.

4) MRI/MRA of head, neck, arch

Many vasculatures anomalies on the head and neck area as well as structural brain abnormalities are the most common extra-cutaneous manifestation in PHACE

Table 2. Revised criteria for PHACE syndrome; Garzon et al[22]

Organ systems	Major criteria	Minor criteria
Arterial anomalies	- Anomaly of major cerebral or cervical arteries - Dysplasia of large cerebral arteries - Arterial stenosis or occlusion with or without moyamoya collaterals - Absence or moderate-severe hypoplasia of l arge cerebral and cervical arteries - Aberrant origin or course of large cerebral or cervical arteries except common arch variants such as bovine arch - Persistent carotid-vertebrobasilar anastomosis (proatlantal segmental, hypoglossal, optic, and/or trigeminal arteries)	- Aneurysm of any cerebral artery
Structural brain	- Posterior fossa brain anomalies - Dandy-Walker complex - Other hypoplasia/dysplasia of the mid and/or hind brain	- Midline brain anomalies - Malformation of cortical development
Cardiovascular	- Aortic arch anomalies - Coarctation of the aorta - Dysplasia - Aneurysm - Aberrant origin of subclavian artery with or without vascular ring	- Ventricular septal defect - Right aortic arch/double aortic arch - Systemic venous anomalies
Ocular	- Posterior segment abnormalities - Persistent hyperplastic primary vitreous - Persistent fetal vasculature - Retinal vascular anomalies - Morning glory disc anomaly - Optic nerve hypoplasia - Peripapillary staphyloma	- Anterior segment abnormalities - Microphthalmia - Sclerocornea - Coloboma - Cataracts
Ventral/midline	- Anomaly of midline chest and abdomen - Sternal defect - Sternal pit - Sternal cleft Supraumbilical raphe	- Ectopic thyroid hypopituitarism - Midline sternal papule/hamartoma

syndrome[25,26]. Performing MRI/MRA can identify these abnormalities. Due to the risk of acute ischemic stroke (AIS) vis-a-vis vasculatures abnormalities on the head and neck, imaging is needed to identify and grade the risk of AIS in each patient. The risk classification for AIS (low, intermediate, or high) informs further treatment plans.

Treatment

With respect to standard infantile hemangioma treatment, the first line therapy is oral propranolol. The optimal dose of oral propranolol ranges between 1 to 3 mg/kg/day, divided to twice to three times daily for at least 6 months[26-31]. In PHACE syndrome, the same recommendation as infantile hemangioma is applied[27]. There are, however, some concerns about the occurrence of ischemic stroke in patients with PHACE syndrome when being treated with oral propranolol[33], so a lower target dose than the standard 2 mg/kg/day and/or a slower titrating schedule are recommended. Additionally, the total daily dose should be divided into 3 times/day to minimize fluctuations in peak blood levels.

Long-term monitoring

The long-term cutaneous lesion of PHACE syndrome patients depends on how large and deep the hemangioma is. The cutaneous lesion has its own natural history of growth and will regress over time. Early treatment, however, with oral propranolol should result in a good cutaneous outcome since propranolol can arrest the proliferation of the cutaneous lesions. Long-term cutaneous findings can, however, result in superficial telangiectasia (Figures 1B and 1C), redundant of the soft tissue and can also cause scarring.

There is limited literature regarding the long-term follow-up of neurological development in PHACE syndrome. Long-term follow-up will vary depending upon the severity of the vasculature abnormalities and structural brain involvement. Common long-term neurological sequelae include headache and/or migraine-like headache. Most patients benefit from simple analgesic medication, however, those who do

not respond to standard treatment may require vasoconstrictive headache medicines. Triptans, dihydroergotamine, and ergotamine tartrate are relatively contraindicated and should be used with caution in those having cerebral vasculopathy in PHACE syndrome[24]. Suggestions for long-term follow-up-especially developmental monitoring-should be used on an individual basis.

Conclusion

PHACE syndrome has a distinctive clinical manifestation and should be considered when a large facial segmental hemangioma is present. Due to multiple associated anomalies, a thorough physical examination and relevant investigations should be performed to identify a patient's individual risk and treatment plans. Propranolol treatments are effective but long-term follow-up is needed.

What is already known on this topic?

Propranolol is a first line treatment in infantile hemangioma in children.

What this study adds?

Since there are multiple associated anomalies with PHACE syndrome, a thorough physical examination and associated investigations should be performed to identify a patient's individual risk and treatment plans. Propranolol is safe and can be used to treat PHACE syndrome.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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