# Segmental Facial Hemangiomas and Associated Structural Defects

*Margriet H. M. van Doesburg, MD,* Corstiaan C. Breugem, MD, PhD,* Johannes M. P. J. Breur, MD, PhD,† Kees P. J. Braun, MD, PhD,‡ Lucienne A. Speleman, MD,§ and Suzanne G. M. A. Pasmans, MD, PhD||*

**Abstract:** PHACE syndrome refers to the association of large segmental facial **h**emangiomas with 1 or more of the following anomalies: **p**osterior fossa malformations, **a**rterial anomalies, **c**ardiac anomalies, and **e**ye abnormalities. In this review, we present a newborn with a large segmental facial hemangioma and abnormal genesis of the cerebropetal arteries. Furthermore, we give an overview of the anomalies associated with the PHACE syndrome. Patients with large segmental facial hemangiomas are at risk for 1 of these anomalies and should be investigated accordingly. We present a clinical algorithm for screening of patients with large segmental hemangiomas suggestive of the PHACE syndrome.

**Key Words:** PHACE, hemangioma, facial hemangiomas, vascular tumor, vascular anomalies

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Infantile hemangiomas are very common vascular tumors, occurring in up to 10% of all newborns.[1] Pattern subtypes of hemangiomas include localized lesions (Fig. 1), demonstrating clear spatial containment and segmental lesions that have diffuse or plaquelike features (Fig. 2). It is well known that lesions in certain areas such as the periorbital or beard region need special attention because of functional consequences.[2] When localized in the head and neck region, the craniofacial surgeon is often involved in the management of both the cosmetic and functional consequences of these lesions.

According to the biologic classification system of Mulliken and Glowacki,[3] hemangiomas are categorized under the vascular tumor group and are not characterized under the group of structural anomalies, which consists of vascular malformations. In 1978, Pascual-Castroviejo[4] was the first to report on an association between capillary hemangiomas and craniocervical arterial anomalies. PHACE (Online Mendelian Inheritance in Man no. 606519) is an acronym that was introduced in 1996 by Frieden et al[1] to describe the association of **p**osterior fossa malformations, **h**emangiomas, **a**rterial anomalies, **c**ardiac anomalies, and **e**ye abnormalities. In case of **s**ternal clefting or supraumbilical raphe, this acronym is expanded to PHACE**S**. About 70% of the children with PHACE syndrome have only 1 extracutaneous manifestation.[5] In a prospective cohort study of 1096 children with infantile hemangiomas, 2.3% of all patients and 20% of the children with segmental facial hemangiomas met the criteria for PHACE syndrome. PHACE is therefore not a rare clinical entity, and it is suggested that it might be even more common than Sturge-Weber syndrome.[6] According to Hennedige et al,[7] Sturge-Weber syndrome is a rare syndrome, with an incidence of only 3 per 100 patients with a facial port-wine stain.

Recently, we evaluated an infant with a large facial segmental hemangioma that was also found to have agenesis and hypoplasia of the carotid and vertebral arteries. She was subsequently diagnosed with PHACE syndrome. With this review, we emphasize that segmental hemangiomas in the face are often associated with other structural anomalies. Furthermore, we provide a clinical algorithm for screening of these patients.

## CLINICAL REPORT

A 1-month-old female infant presented to the multidisciplinary clinic of our hospital for evaluation of her facial hemangioma. She was born by vaginal delivery after an uncomplicated pregnancy. Three days after birth, she developed cutaneous features consistent with a rapidly growing infantile facial hemangioma, initially located at the right side of her forehead with progression to her right ear, around her mouth, and under her chin (Fig. 2). Six weeks later, there was progressive growth of the hemangioma located below her chin, and she developed a hemangioma around her right parotid gland compressing the external ear canal. Flexible endoscopy by the otolaryngologist showed extension of the hemangioma into the mucosa of the palate, pharynx, and supraglottic larynx without airway compression. Because PHACE syndrome was suspected, she was evaluated for associated anomalies. Echocardiography showed a structural normal heart and normal great vessels. Ophthalmic evaluation showed ptosis due to the extended hemangioma as well as myopia and hypertrophy of her right eye. Audiologic evaluation by brainstem evoked response audiometry showed an abnormal function in the region of the inferior colliculus (brainstem). A cerebral magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) showed no posterior fossa malformations but did show agenesis of the left carotid and vertebral artery (Fig. 3). Furthermore, there was hypoplasia of the right carotid artery with a proximal aneurysm at the skull base. Because of endangered vision and hearing and potential airway obstruction, treatment with prednisolone 4 mg/kg per day was started. The hemangioma decreased rapidly, and the dosage was slowly tapered. To date, no complications have occurred, and the hemangioma is stable with minimal

From the Departments of *Pediatric Plastic Surgery, †Pediatric Cardiology, ‡Pediatric Neurology, §Otorhinolaryngology, and ||Dermatology/Allergology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, the Netherlands.

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Address correspondence and reprint requests to Corstiaan C. Breugem, MD, PhD, Division of Pediatric Plastic Surgery, Wilhelmina Children's Hospital, University Medical Center Utrecht, PO Box 85090, Utrecht, the Netherlands; E-mail: c.c.breugem@umcutrecht.nl



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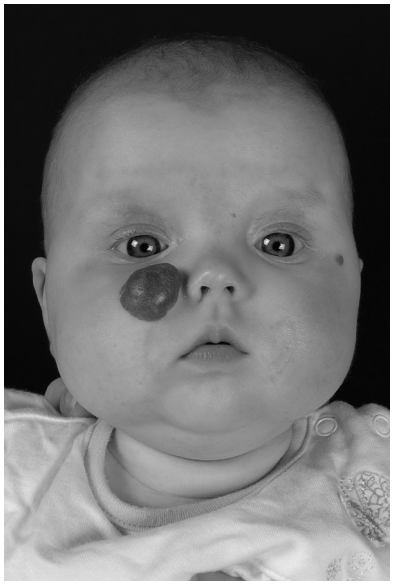

**FIGURE 1.** A localized hemangioma.

prednisone maintenance therapy (0.25 mg/kg per day). A second MRA revealed no progression of the vascular anomaly.

## DISCUSSION

Infantile hemangiomas are the most common benign tumors of infancy. Most hemangiomas need no treatment, but a minority is associated with significant morbidity. Hemangiomas can be differentiated into either localized or segmental types. The localized hemangiomas are by far the most common and consist of nodules that seem to arise from a single focal point and also demonstrate spatial containment. The segmental hemangiomas in contrast demonstrate geographic or linear patterning of the skin. There is no histologic difference between these 2 subtypes of hemangiomas; however, segmental hemangiomas are more likely to develop ulcerations and visceral involvement.[8–10] PHACE syndrome represents a spectrum of anomalies, with most patients exhibiting only 1 extracutaneous manifestation (Table 1). Although Frieden et al[1] introduced the acronym PHACE, the diagnostic criteria for this syndrome have not been clearly delineated. Poetke et al[11] used 5 diagnostic criteria and proposed to add a sixth, namely, the presence

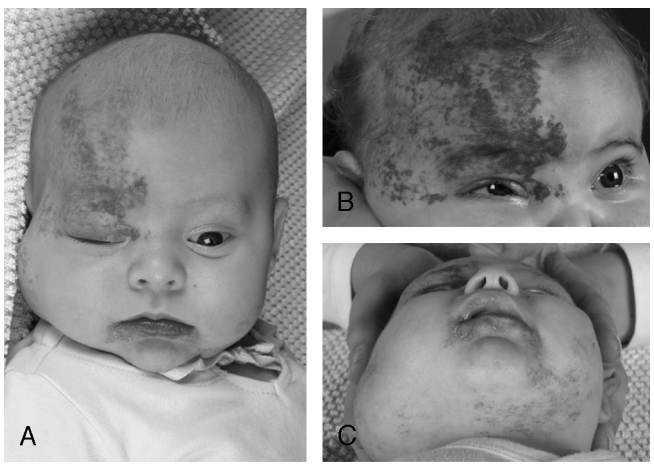


**FIGURE 2.** Patient with segmental hemangioma.

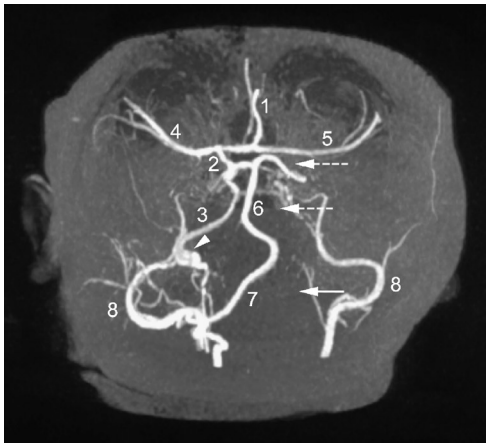


**FIGURE 3.** Magnetic resonance angiography of abnormal left carotid and vertebral artery. The other structures are (1) anterior cerebral artery, (2) right internal carotid artery, (3) right internal carotid artery, (4) right medial artery, (5) left medial cerebral artery, (6) basilar artery, and (7) vertebral artery. The 2 striped arrows demonstrate the location of the absent left internal carotid artery, and the normal arrow shows the absent left vertebral artery. The arrowhead demonstrates the dilated right internal carotid artery and a stenosis just proximal to this dilatation.

of arterial abnormalities and/or intracranial hemangiomas. According to Metry et al,[6] the conditions of patients are diagnosed as PHACE syndrome by having a large, plaquelike, segmental hemangioma of the face, with 1 or more of the anomalies listed in Table 1. Occurring in 2.3% of all hemangiomas and in 20% of children with segmental facial hemangiomas, this syndrome is not a rare clinical entity, and infants having such hemangiomas should be carefully evaluated for associated structural anomalies.[6]

### Structural Brain Malformations

Posterior fossa malformations occur in 43% to 81% of children diagnosed with PHACE.[1,5,6,11,12] Two categories of anomalies are observed: congenital malformations of the cerebellum and cerebrum and arterial anomalies of the cerebral vasculature. A spectrum of posterior fossa lesions has been described, ranging from Dandy-Walker malformation to hypoplasia of the corpus callosum or septum pellucidum. Most recently, Pointdexter et al[13] described 2 cases of periventricular heterotopia, features that were not previously emphasized and may suggest a further expansion of the spectrum of PHACE. Although the acronym includes a "P" for "posterior fossa malformations," many of the described lesions are supratentorial brain malformations and are subsequently not "pure" posterior fossa malformations.

### Hemangiomas

The presence of a large segmental facial hemangioma is the hallmark of PHACE syndrome. They can be unilateral or bilateral, and unlike port-wine stains, they are not strictly dermatomal in their distribution.[1] Four primary facial segments have been identified: the frontotemporal region (segment 1); the maxillary region respecting the nasomedial sulcus (segment 2); the preauricular region, mandible, chin, and lower lip (segment 3); and the frontonasal region, comprising the medial frontal scalp, nasal bridge, and philtrum (segment 4).[9] Metry et al[6] stated that there is a strong correlation between hemangiomas in segment 1 or 4 and structural brain, cerebrovascular, and ocular anomalies. Hemangiomas occurring in

**TABLE 1.** Incidence and Reported Anomalies in PHACE Syndrome

| Category of Anomaly | Incidence, % | Reported Defects |
|---|---|---|
| Structural brain malformations | 43–81 | Dandy-Walker malformation, hypoplasia of the corpus callosum, septum pellucidum or cerebrum, polymicrogyria, microcephaly, frontal lobe calcifications, absent foramen lacerum, cerebral hyperplasia, arachnoid cysts |
| Hemangiomas | 100 | Extracutaneous 7%–22%, mostly in subglottic region |
| Arterial anomalies | 41–57 | Aneurysmal dilatation, stable or progressive arterial stenosis or occlusion, aberrant origin or course of carotids, moyamoya syndrome, hypoplasia of carotids, subclavian and vertebral arteries, abnormal course and kinking of brainstem arteries |
| Cardiovascular anomalies | 33–50 | Aortic anomalies: coarctation, dilatation, stenosis, aberrant origin of subclavian artery, aneurysms, congenital valvular aortic stenosis, cervical aortic arch, dextroposition of aorta, absent right aortic arch, hypoplastic descending aorta, double aortic arch, double aortic coarctation |
| | | Other: steal syndrome, patent ductus arteriosus, ventricular septal defect, atrial septal defect, pulmonary stenosis, cor triatriatum, valvular anomalies, tetralogy of Fallot, atrial enlargement, ventricular hypertrophy, patent foramen ovale, anomalous left superior vena cava |
| Eye anomalies | 16–31 | Microphthalmos, optic atrophy, iris hypoplasia, optic nerve hypoplasia, sclerocornea, lens coloboma, exophthalmos, congenital cataract, increased retinal vascularity, bilateral retinal hyperemia, morning glory deformity of retina, glaucoma, esotropia, ablatio retinae, amblyopia, strabismus, trichiasis, heterochromia, esotropia, Horner syndrome |
| Ventral developmental defects | 5–26 | Sternal clefting, subumbilical raphe, sternal pit, cleft palate, omphalocele |
| Miscellaneous | Few reports | Lingual thyroid, congenital hypothyroidism, micrognathia, auricular hypoplasia or agenesis, esophageal diverticulum |

Adapted from Metry and Hebert[2] and Wendelin et al.[20]

segment 3 seem to be associated with sternal defects and/or supraumbilical raphe. Our patient illustrates the risk of extension of the hemangioma in the intraoral, pharyngeal, and laryngeal mucosa when the lips or chin is involved. In 7% to 22% of the patients, extracutaneous hemangiomas were reported, mostly located on the upper trunk and/or extremities.[5] Poetke et al[11] found that 12% of the PHACE patients had intracranial hemangiomas, although recent reports suggest that this is a more common finding than previously recognized. Subglottic hemangiomas do also occur and should be considered in patients with respiratory distress.[11,14]

## Arterial Anomalies

Structural vascular anomalies occur in 41% to 57% of the patients. They include persistent trigeminal artery, absence or hypoplasia of carotid or vertebral arteries, and aneurysm of the carotid.[1,5] In 25 new cases reported by Metry et al,[6] cerebrovascular anomalies occurred in 55% of the patients, most commonly an aberrant origin or course of the carotid arteries or aneurysm formation. Occlusion or narrowing of the internal carotid and/or anterior middle cerebral arteries can cause arterial ischemic stroke with hemiplegia and new-onset seizures as most common symptoms. However, stroke may be missed in children because of subtle or transient manifestations. Symptoms develop early, and the age of symptom onset ranges from 3 to 18 months.[6,12,15] Metry et al[6] also reported 2 patients with evidence of resolution of their vascular anomalies, suggesting a possibility of both progressive and regressive phenomena within the vascular anomalies.[16] Two categories or phases of cerebrovascular disease among PHACE patients seem to be observed: congenital or developmental anomalies of the cervical and cerebral vessels and progressive or acquired changes when vascular occlusions and stenoses can progress to ischemic stroke.[12,17]

## Cardiovascular Anomalies

One third to one half of the patients have cardiac anomalies. Coarctation of the aorta is the most common anomaly, but other malformations of the great arteries and intracardiac defects can also occur.[5,6,11] An ipsilateral relationship might exist between the location of the hemangioma and the side of aortic arch anomaly.[18] Potential complications of aortic aneurysms are of concern, although the risk among PHACE patients is unknown.

## Eye Anomalies

Children with PHACE syndrome may have periocular and ocular abnormalities. Reported incidences range from 16% to 75% of the patients.[19] Most abnormalities are ipsilateral to the facial hemangioma and can include microphthalmos (most common), retinal vascular abnormality, lens coloboma, exophthalmos, and optic nerve hypoplasia.[1,5,6,19] These children also have an increased risk

**TABLE 2.** Evaluation for PHACE Manifestations

| Investigation | Time |
|---|---|
| MRI—brain | First 3 mo of life |
| MRA—brain (MRA of circle of Willis and neck arteries) | First 3 mo of life |
| Echocardiography | First month of life |
| MRA—cardiac | Along with MRA of the brain |
| Consultation with ophthalmologist | First 3 mo of life |
| Consultation with otolaryngologist | First 3 mo of life |

for amblyopia and strabismus, especially when there is periocular and ocular involvement of the hemangioma.[19]

## Miscellaneous Anomalies

When ventral developmental defects, including sternal clefting and/or a supraumbilical raphe, are present, the syndrome may be referred to as PHACES syndrome. These defects occur in 5% to 26% of patients and can be readily visible at physical examination but may be easily overlooked when anomalies are minor such as sternal pits.[1,6,11]

Endocrine abnormalities include lingual thyroid with hypothyroidism, absent pituitary, or partially empty sella turcica.[1,6,16] Recently, Pointdexter et al[13] reported 2 cases of pituitary dysfunction, suggesting that endocrinopathy may be a feature of PHACE syndrome too.

## Pathogenesis

The pathogenesis of PHACE is poorly understood. Infants with infantile hemangiomas are more likely to be female, white, premature, and a product of multiple gestation. Patients with PHACE syndrome, on the other hand, are even more likely to be female (90%), tend to be term babies from single pregnancies, and are born to slightly older mothers.[5,6] X-linked inheritance is suggested because of the clear female predominance.[6] This suggests a possibility of lethality in males; however, there is no evidence of familial tendency.[6] It has also been suggested that vascular growth factor may contribute to the pathogenesis of vascular stenoses and occlusions in PHACE syndrome because the development of obstructive vascular disease and stroke in PHACE seems to correspond with the proliferative phase of the hemangioma.[6,12]

## Recommendations

Structural and vascular anomalies of the brain are the most common features of PHACE syndrome, and infants should be evaluated accordingly. Therefore, we recommend early brain MRI or MRA of the brain and aortic arch and its main vessels within the first 3 months of life.[1,11,12] This should also include gadolinium to detect possible intracranial hemangiomas. If vasculopathy is present, we recommend follow-up with MRA to investigate possible progression. Because it is possible for cerebrovascular changes to progress, the question remains whether patients where no structural cerebrovascular anomalies have been found should have a second MRA some months later. PHACE patients are at increased risk of cardiac anomalies, and they should undergo full cardiologic examination, including blood pressure measurements in arms and legs and echocardiography, preferably in the first month of life.[1,19] Infants with PHACE syndrome need an ophthalmologic evaluation within the first 3 months of life and careful monitoring by an ophthalmologist because ocular morbidity can potentially lead to blindness.[10,19] Because of the risk of hearing impairment by compression of the ear canal or respiratory distress due to involvement of the laryngeal mucosa, an otolaryngologic evaluation is recommended especially when the lips or chin is involved. Because abnormalities such as endocrinopathy have recently been reported, we also recommend a full examination by a pediatrician in all patients with a segmental facial hemangioma (Table 2).[6,13]

# CONCLUSIONS

Craniofacial surgeons often encounter hemangiomas. They should be aware that PHACE syndrome is not a rare clinical entity in children with facial hemangiomas. We therefore stress that this syndrome should always be considered in infants with large segmental facial hemangiomas and recommend appropriate screening in these patients.


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# REFERENCES


1. Frieden IJ, Reese V, Cohen D. PHACE syndrome: the association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. *Arch Dermatol* 1996;132:307–311
2. Metry DW, Hebert AA. Benign cutaneous vascular tumors of infancy: when to worry, what to do. *Arch Dermatol* 2000;136:905–914
3. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg* 1982;69:412–422
4. Pascual-Castroviejo I. Vascular and nonvascular intracranial malformations associated with external capillary hemangiomas. *Neuroradiology* 1978;16:82–84
5. Metry DW, Dowd CF, Barkovich AJ, et al. The many faces of PHACE syndrome. *J Pediatr* 2001;139:117–123
6. Metry DW, Haggstrom AN, Drolet BA, et al. A prospective study of PHACE syndrome in infantile hemangiomas: demographic features, clinical findings, and complications. *Am J Med Genet A* 2006; 140A:975–986
7. Hennedige AA, Quaba AA, Al-Nakib K. Sturge-Weber syndrome and dermatomal facial port-wine stains: incidence, association with glaucoma, and pulsed tunable dye laser treatment effectiveness. *Plast Reconstr Surg* 2008;121:1173–1180
8. Chamlin SL, Haggstrom AN, Drolet BA, et al. Multicenter prospective study of ulcerated hemangiomas. *J Pediatr* 2007;151:684–689
9. Haggstrom AN, Lammer EJ, Schneider RA, et al. Patterns of infantile hemangiomas: new clues to hemangioma pathogenesis and embryonic facial development. *Pediatrics* 2006;117:698–703
10. Chiller KG, Passaro D, Frieden IJ. Hemangiomas of infancy: clinical characteristics, morphologic subtypes, and their relationship to race, ethnicity, and sex. *Arch Dermatol* 2002;138:1567–1576
11. Poetke M, Frommeld T, Berlien HP. PHACE syndrome: new views on diagnostic criteria. *Eur J Pediatr Surg* 2002;12:366–374
12. Heyer GL, Millar WS, Ghatan S, et al. The neurologic aspects of PHACE: case report and review of the literature. *Pediatr Neurol* 2006;35:419–424
13. Pointdexter G, Metry DW, Barkovich AJ, et al. PHACE syndrome with intracerebral hemangiomas, heterotopia, and endocrine dysfunction. *Pediatr Neurol* 2007;36:402–406
14. Judd CD, Chapman PR, Koch B, et al. Intracranial infantile hemangiomas associated with PHACE syndrome. *Am J Neuroradiol* 2007;28:25–29
15. Bhattacharya JJ, Luo CB, Alvarez H, et al. PHACES syndrome: a review of eight previously unreported cases with late arterial occlusions. *Neuroradiology* 2004;46:227–233
16. Burrows PE, Robertson RL, Mulliken JB, et al. Cerebral vasculopathy and neurologic sequelae in infants with cervicofacial hemangioma: report of eight cases. *Radiology* 1998;207:601–607
17. Drolet BA, Dohil M, Golomb MR, et al. Early stroke and cerebral vasculopathy in children with facial hemangiomas and PHACE association. *Pediatrics* 2006;117:959–964
18. Bronzetti G, Giardini A, Patrizi A, et al. Ipsilateral hemangioma and aortic arch anomalies in posterior fossa malformations, arterial anomalies coarctation of the aorta, and cardiac defects and eye abnormalities (PHACE) anomaly: report and review. *Pediatrics* 2004;113:412–415
19. Kronenberg A, Blei F, Ceisler E, et al. Ocular and systemic manifestations of PHACES (posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects and coarctation of the aorta, eye abnormalities, and sternal abnormalities or ventral developmental defects) syndrome. *J AAPOS* 2005;9:169–173
20. Wendelin G, Kitzmüller E, Salzer-Muhar U. PHACES: a neurocutaneous syndrome with anomalies of the aorta and supraaortic vessels. *Cardiol Young* 2004;14:206–209