



## A Newborn Girl With a Large Red Plaque on Her Face

Denise W. Metry, MD

A 6-week old Caucasian girl presented with an extensive red plaque on the face. The parents recalled seeing a pink “stain-like” area of the left face at birth that within days began to thicken and proliferate, becoming bright red in color. Left visual axis obstruction became apparent at age 3 weeks.

This infant was born at term, after an uncomplicated pregnancy, and had a normal birth weight of 7 pounds, 15 ounces. Neither she nor her mother had any known medical problems, and there was no family history of similar skin lesions.

Physical examination showed a large, erythematous plaque of the left face, scalp and ear (see image). Fullness of the left upper lid was noted, with moderate ptosis and mild proptosis. The remainder of the physical examination, including neurologic evaluation, was normal.

The infant was started on 3 mg/kg/day of oral prednisolone, along with oral ranitidine at 2 mg/kg/dose twice daily,

and sent for appropriate diagnostic evaluation. Magnetic resonance imaging (MRI) of the head showed a vascular lesion in the suprazygomatic masticator space overlying the temporalis muscle, extending inferiorly in a patchy fashion into the left cheek. Additional involvement of the left orbit, both intra- and extraconally, was noted, most pronounced superiorly but also surrounding the anterior aspect of the optic nerve in the intraconal space. Moderate hypoplasia of the left cerebellar hemisphere was seen, as well as moderate hypoplasia of the cerebellar vermis.

Magnetic resonance angiography (MRA) of the head showed prominent left internal maxillary artery branches supplying the vascular lesion, as well as a persistent left stapedial artery giving rise to the left middle meningeal artery. Formal ophthalmologic examination showed no additional ocular anomalies, and echocardiogram and liver ultrasound studies were normal.

## DIAGNOSIS

### Large, segmental facial hemangioma in association with PHACE syndrome

## DISCUSSION

Infantile hemangiomas (IH) are the most common benign tumors of infancy. Known risk factors for their development include female gender, Caucasian ethnicity, low birth weight, and multiple gestation. Unique in their behavior, IH classically undergo an initial phase of growth, the majority of which typically occurs within the first 3 to 4 months of life. This is followed by a period of slow regression, generally over years.<sup>1</sup>

While the majority of IH remain uncomplicated and do not need treatment, a substantial minority can be associated with significant complications. Recently, it has been recognized that complication risk can be correlated with lesion morphology, and that two morphologic types of hemangiomas exist: localized and segmental. Localized IH are by far the most common type and consist of papules or nodules that appear to arise from a single focal point and demonstrate clear spatial containment. In contrast, segmental IH are plaque-like and show linear or geo-

graphic “patterning” over the skin. The patterns observed in facial segmental IH do not appear to correspond to facial dermatomes or lines of Blaschko, but do correspond, at least partially, to developmental facial prominences (Figure).<sup>2</sup>

While segmental IH show no histopathologic differences from localized lesions, they are much more likely to be associated with complications such as ulceration, birth defects and visceral hemangiomas. Segmental IH also are more likely to require more intensive and prolonged therapy and have a poorer overall outcome.<sup>3</sup>

PHACE syndrome (OMIM #606519) is a neurocutaneous association.

The acronym refers to the combination of large, segmental hemangiomas, most commonly located on the face, with one or more of the following congenital anomalies: posterior fossa or other structural brain malformations, arterial anomalies, coarctation of the aorta, cardiac defects, or eye abnormalities.<sup>4</sup> The syndrome is sometimes referred to as PHACES when ventral midline defects such as sternal clefting or supraumbilical raphe (typically a linear, scar-like lesion that extends upward from the umbilicus) are present. The diagnosis of PHACE requires the presence of a typical segmental, facial IH in association with only one other congenital anomaly, as affected infants rarely suffer from the complete spectrum.<sup>5</sup>

PHACE is uncommon but not rare. It is now recognized that PHACE is probably even more common than Sturge-Weber syndrome, a disorder with which PHACE sometimes is confused. However, the vascular birthmark associated with Sturge-Weber syndrome is a port-

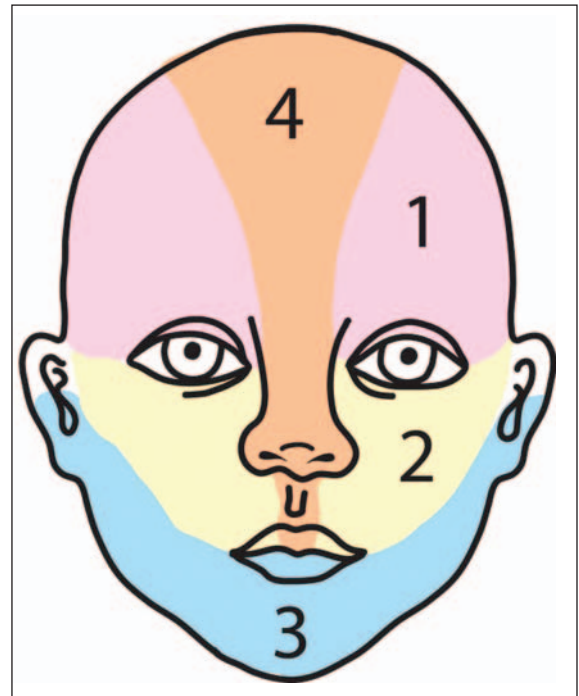


Figure. Proposed hemangioma segment map.<sup>2</sup> (Image © 2006, American Academy of Pediatrics. All rights reserved. Used with permission.)

wine stain, which, unlike IH, is a capillary-like vascular malformation that is fully present at birth, shows no signs of proliferation during infancy, undergoes minimal (if any) expansion over time, and does not regress.

Recent studies estimate that PHACE probably represents about 2% to 3% of patients with IH overall, and at least 20% of patients with segmental IH of the face. Notably however, these numbers, as well as the incidence of reported PHACE anomalies, very likely are underestimated, as the vast majority of at-risk patients with segmental facial IH have not undergone complete evaluations.<sup>6</sup>

The list of PHACE anomalies continues to expand as the spectrum becomes more fully defined (Table, see page xxx). Structural and vascular anomalies of the brain are the most common features, followed by cardiovascular anomalies, ventral developmental defects, and ocular anomalies. Due to the potential for acute and chronic neurologic sequelae,

## CME EDUCATIONAL OBJECTIVES

1. Identify and discuss management of infantile hemangiomas.
2. Describe the association of hemangiomas with PHACE syndrome.

*Dr. Metry is associate professor of dermatology and pediatrics, Texas Children's Hospital, Baylor College of Medicine, Houston, TX.*

*Address reprint requests to: Denise W. Metry, MD, Texas Children's Hospital, Clinical Care Center, Dermatology Department, 6701 Fannin, ST CCC 620.16, Houston, TX 77030; or e-mail [dwmetry@texaschildrenshospital.org](mailto:dwmetry@texaschildrenshospital.org).*

*Dr. Metry disclosed no relevant financial relationships.*

TABLE.

### Type and Approximate Incidence of Reported Anomalies in PHACE Syndrome

Category of Anomaly	Approximate Incidence	Specific Defects Reported
Structural Brain	40%	<ul style="list-style-type: none"> <li>• Posterior fossa, including Dandy-Walker complex, cerebellar hypoplasia/atrophy/encephalomalacia, and dysgenesis/agenesis of vermis</li> <li>• Hypoplasia or agenesis of cerebrum, corpus callosum, or septum pellucidum</li> <li>• Subependymal and arachnoid cysts</li> <li>• Frontal lobe calcifications</li> <li>• Absent foramen lacerum</li> <li>• Polymicrogyria</li> <li>• Microcephaly</li> </ul>
Cerebrovascular	40%	<ul style="list-style-type: none"> <li>• Carotid arterial anomalies               <ul style="list-style-type: none"> <li>• Primary anomalies: Hypoplasia/agenesis, anomalous branches, aberrant origin or course</li> <li>• Secondary phenomena: Stenosis/occlusion (including Moyamoya-like collaterals), aneurysm formation, fusiform or dolicho change, kinking and looping</li> </ul> </li> <li>• Persistent embryonic arteries (eg, trigeminal, carotid-vertebrobasilar anastomoses)</li> </ul>
Cardiovascular	33%	<ul style="list-style-type: none"> <li>• Aortic coarctation</li> <li>• Aneurysms of the ascending aorta, aortic arch, subclavian or innominate arteries</li> <li>• Right, left, double, interrupted aortic arch</li> <li>• Congenital valvular aortic stenosis</li> <li>• Dextroposition of the aorta</li> <li>• Anomalous coronary arteries</li> <li>• Ventral and atrial septal defects</li> <li>• Patent ductus arteriosus</li> <li>• Pulmonary stenosis</li> <li>• Anomalous pulmonary veins</li> <li>• Other: patent foramen ovale, cor triatriatum, tetralogy of Fallot, tricuspid atresia/stenosis, dextrocardia, persistent left superior vena cava</li> </ul>
Ocular	< 20%	<ul style="list-style-type: none"> <li>• Microphthalmos, retinal vascular abnormality, persistent fetal retinal vessels</li> <li>• Optic atrophy, iris vessel hypertrophy, iris or optic nerve hypoplasia</li> <li>• Congenital cataracts, sclerocornea, lens coloboma, exophthalmus, congenital 3rd nerve palsy, excavated optic disc anomalies, lens coloboma, "morning-glory," peripapillary staphyloma, Horner syndrome</li> </ul>
Ventral Developmental	20% to 25%	<ul style="list-style-type: none"> <li>• Sternal defects, including partial or complete agenesis and cleft or pit</li> <li>• Supraumbilical raphe</li> <li>• Omphalocele</li> </ul>
Miscellaneous	Few reports	<ul style="list-style-type: none"> <li>• Micrognathia, auricular hypoplasia or agenesis/"low-set" ears, orofacial clefting</li> <li>• Endocrine: absent pituitary or partially empty sella turcica, lingual ectopic thyroid</li> <li>• Structural pituitary anomalies + optic disc anomalies/optic nerve hypoplasia + moyamoya + multiple endocrinopathies</li> <li>• Other: spina bifida occulta, widely-spaced nipples, polydactyly, esophageal diverticulum, cervical cyst, inguinal and umbilical herniae</li> </ul>

brain anomalies are not only the most common association but also the most potentially worrisome.

Developmental delays (motor more than language) can result from structural brain anomalies, possibly as a result of cerebellar defects. Cerebrovascular anomalies also are of concern because of known progressive vasculopathies

that can occur within such anomalies, which can lead to seizures or acute arterial ischemic stroke (AIS), generally during infancy.<sup>6</sup> In fact, although the mechanism is unknown, it is now believed that PHACE may represent an under-recognized cause of pediatric AIS, which is overall a relatively rare event.<sup>7</sup> Serial neuroimaging during in-

fancy should be considered in PHACE patients with significant cerebrovascular anomalies (particularly those of the carotid artery), with the reasoning that if progressive cerebrovascular changes are identified early, neurosurgical revascularization procedures can be performed to potentially reduce AIS-related morbidity and mortality.

In addition to cerebrovascular anomalies, a number of especially unique and complex aortic anomalies have been described in association with PHACE, and although the potential for progressive changes within these anomalies is also of concern, the real risk is not currently known. Of note, in addition to progressive vascular changes in PHACE, cases of regressive phenomena (normalization) of such anomalies also have been reported.<sup>6</sup>

A correlation appears to exist between IH located over the upper half of the face (S1 or fronto-temporal segment or S4 or frontonasal segment) and the presence of structural brain, cerebrovascular, and ocular anomalies. In contrast, there appears to be a strong correlation between ventral developmental defects (sternal defects, supraumbilical raphe, or both) and IH located over the lower half of the face (S3 or mandibular segment) (Figure). There may be a correlation between S3 IH, as well as large segmental IH covering the trunk and arm, and cardiovascular anomalies, but this needs further study.

Because such correlations are not absolute, with definite exceptions reported, it is recommended that all patients with segmental facial IH undergo complete evaluation for all potential anomalies, including MRI and MRA imaging of the head and neck vasculature, echocardiogram or MRI/MRA imaging of the cardiovascular, and a formal ophthalmologic examination.<sup>6</sup> Prospective studies are ongoing in an effort to help further define the true scope of disease and correlate IH anatomic location with disease burden.

The pathogenesis of PHACE is poorly understood. In contrast with IH overall, the syndrome is even more common among female infants, with a nearly 90% female incidence, and tends to occur in term, singleton pregnancies of normal birth weight. A recent study of infant and maternal demographic features

showed that mothers of infants affected with PHACE were of slightly older age but found no increased incidence of any other factors that might suggest an environmental or other influence.<sup>6</sup>

The spectrum of anomalies in PHACE, and general ipsilateral relationship between such anomalies and the cutaneous IH, strongly suggests a “developmental field defect,” as proposed by Opitz et al.,<sup>[REFERENCE]</sup> whereby an insult at a critical time in embryogenesis gives rise to similar developmental outcomes. The precise timing of such an insult in PHACE is speculative, but both the anatomic IH patterns corresponding to developmental prominences and several of the associated structural abnormalities point to timing early during the first trimester, probably within the first 3 to 12 weeks of gestation prior to or during early vasculogenesis.<sup>5</sup>

Because PHACE has a reproducible pattern of structural and functional anomalies, it likely has a genetic basis. Based on recent findings that multi-organ syndromes are caused by micro deletions, it is hypothesized that PHACE may result from a very small (submicroscopic) copy number aberration; molecular genetic studies for this are currently in progress. The marked female predominance is also of interest, suggesting the possibility of X-linked inheritance with lethality in males, although there is no evidence of a familial tendency in PHACE.<sup>6</sup>

Although IH undoubtedly are birthmarks, and as such represent “birth defects,” their lack of presence at birth has resulted in omission from study in formal birth defect registries and other birth defect research, where ascertainment generally occurs in the newborn nursery. As a result, IH research has lagged behind many other, much less common, tumors. Further understanding of PHACE will best be served by collaborative research efforts between related clinical specialties such as dermatology, genetics,

cardiology, neurology, and developmental biology. A PHACE patient registry has recently been established at Texas Children’s Hospital to provide a much-needed resource in this regard.

## REFERENCES

1. Haggstrom A, Drolet B, Baselga E, et al. Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. *Pediatrics*. In press.
2. Haggstrom AN, Lammer EJ, Schneider RA, Marcucio R, Frieden IJ. Patterns of infantile hemangiomas: new clues to hemangioma pathogenesis and embryonic facial development. *Pediatrics*. 2006;117(3):698-703.
3. 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(12):1567-1576.
4. 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(3):307-311.
5. Metry DW, Dowd CF, Barkovich AJ, Frieden IJ. The many faces of PHACE syndrome. *J Pediatr*. 2001;139(1):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;140(9):975-986.
7. Drolet BA, Dohil M, Golomb MR, et al. Early stroke and cerebral vasculopathy in children with facial hemangiomas and PHACE association. *Pediatrics*. 2006;117(3):959-964.