

What Is Your Diagnosis?



A 6-week-old male infant was referred to the dermatology department for evaluation of enlarging facial lesions noted shortly after birth. The patient was delivered at 36 weeks' gestation by normal spontaneous vaginal delivery with no perinatal complications. His growth and development were otherwise normal. Physical examination revealed large, bright red, nonconfluent macules and plaques in a bilateral temporal distribution extending medially to both eyelids and laterally to the scalp.

PLEASE TURN TO PAGE 119 FOR DISCUSSION

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The Diagnosis: PHACE Syndrome



PHACE (posterior fossa brain malformations, hemangiomas, arterial anomalies, cardiac defects and coarctation of the aorta, eye and endocrine abnormalities) syndrome is a neurocutaneous disorder characterized by a spectrum of abnormalities. It also can be referred to as PHACES syndrome when sternal abnormalities (supraumbilical raphe, sternal cleft, or both) are present.¹

This syndrome should be considered in children who present with large facial hemangiomas. The majority of PHACE-associated hemangiomas are described as large, bright red plaques that occur almost exclusively on the face and scalp. Characteristic PHACE-associated hemangiomas are termed *segmental infantile hemangiomas* because they typically conform to certain facial regions that are thought to correspond with distinct developmental units of a common neuroectodermal origin rather than arising from a discrete focal point as seen in localized infantile hemangiomas.^{2,3} A consensus statement on formal diagnostic criteria for PHACE syndrome was published in 2009, which states that a definite diagnosis requires the presence of a characteristic segmental hemangioma or a large hemangioma (>5 cm) on the face or scalp plus at least 1 major criterion or 2 minor criteria. A diagnosis of possible PHACE

syndrome is made in the following scenarios: a large hemangioma greater than 5 cm plus 1 minor criteria, a hemangioma of the neck or upper torso plus 1 major or 2 minor criteria, or no hemangioma plus 2 major criteria.⁴

There are 4 distinct facial regions where segmental hemangiomas associated with PHACE syndrome generally localize. The most common site is the mandibular segment, involving the skin overlying the mandible, the lower cutaneous lip, vermilion of the lower lip, and the preauricular skin. The next most commonly involved sites are the maxillary segment, the frontotemporal segment, and the frontonasal segment.^{2,5} Although segmental hemangiomas usually present as bright red plaques or clustered papules, they occasionally can have a predominantly telangiectatic or reticular presentation, especially in newborns, and thus may be misdiagnosed as capillary vascular malformations (port-wine stains) or Sturge-Weber syndrome.⁴ In some instances, hemangiomas fail to proliferate and can maintain such an appearance.⁴ Compared to localized infantile hemangiomas, segmental hemangiomas are more likely to ulcerate, persist longer, and have poorer outcomes.³ There have been infants described with large segmental hemangiomas of the upper torso and extremities

who do not meet consensus criteria for a definite diagnosis of PHACE syndrome but do have structural anomalies similar to those reported in PHACE syndrome, suggesting a possible continuum.⁶ The majority of children with PHACE syndrome present with only 1 extracutaneous manifestation; a full-spectrum presentation is exceedingly rare.⁷ Cerebral vascular anomalies are the most common extracutaneous manifestations of PHACE syndrome, occurring in approximately three-fourths of cases. The large cerebral and cervical arteries, often ipsilateral or bilateral to the cutaneous hemangioma, usually are involved. Of note, aneurysmal dilatations and anomalous branches of the internal carotid artery and absence of the carotid artery are highly specific findings of PHACE syndrome. Structural brain anomalies primarily are composed of cerebellar and posterior fossa malformations. Of these malformations, the Dandy-Walker complex and hypoplasia or aplasia of the cerebellum, including the vermis, frequently are reported. Major criteria for the diagnosis of PHACE syndrome include the presence of an anomaly of a major cerebral artery (eg, dysplasia, hypoplasia, stenosis, aberrant origin or course) or an anomaly of the posterior fossa (eg, Dandy-Walker complex, cerebellar dysplasia). When PHACE syndrome is suspected, children should undergo baseline screening via magnetic resonance imaging and magnetic resonance angiography of the head and neck extending down to the aortic arches.^{4,7}

Cardiovascular abnormalities are reported in approximately 40% of patients, with the most common findings being coarctation of the aorta; right-sided aortic arch; and aberrant origin of brachiocephalic arteries, especially the right subclavian artery. These abnormalities are considered major diagnostic criteria for PHACE. Coarctation of the aorta, the most commonly reported cardiovascular defect, generally occurs proximal to and at times involves the great vessel origins. This presentation is in contrast to classic coarctation, which occurs distal to the brachiocephalic vessel origins. Detection of blood pressure gradients between the upper and lower extremities is not possible with PHACE-associated coarctation, highlighting the utility of a screening echocardiogram, which should be performed in all patients suspected to have PHACE syndrome. The most common cardiac abnormalities reported include patent ductus arteriosus, atrial and ventricular defects, and pulmonary stenosis; however, complex congenital disease rarely is seen. Ventral septal defects or a right-sided aortic arch are considered minor criteria for diagnosis.^{4,5,7}

Eye abnormalities are seen in a minority of cases. It is felt that most of these anomalies can be explained

as secondary events to other primary vascular and/or neurologic phenomena.⁵ The most commonly reported finding is microphthalmia (a small malformed eye) ipsilateral to the facial hemangioma, which is considered a minor criterion in diagnosis. More serious posterior segment ocular defects such as retinal vascular anomalies and morning glory disc anomaly are major criteria. It is recommended that patients with head and neck hemangiomas at risk for PHACE syndrome be referred to an ophthalmologist for thorough screening. Patients with periocular hemangiomas will require close follow-up to screen for potential amblyopia with surgical correction if it is caused by mechanical ptosis secondary to the hemangioma.^{4,5} Endocrinopathies including congenital hypothyroidism and growth hormone deficiency have been reported in infants with PHACE syndrome and a low index of suspicion should be maintained for endocrine disorders.⁵ The pathogenesis of PHACE syndrome is not known. No disease-causing genetic mutations have been identified. An extraordinary female predominance (9:1 ratio) has been reported, prompting speculation that it may be an X-linked dominant condition with lethality in males⁸; however, a prospective study showed disease severity to be equal in males and females.⁹ A recent study of X-chromosome inactivation patterns also did not support this X-linked dominant inheritance and authors concluded that genetic heterogeneity is likely in PHACE syndrome.¹⁰ Additionally, there are no known reports of familial cases of PHACE syndrome; thus vertical transmission seems an unlikely cause. The current hypothesis is that a developmental field defect occurring early in gestation could be the cause.¹¹ This theory is supported by the observation that underlying vascular anomalies in PHACE syndrome occur ipsilateral to cutaneous hemangiomas. The association between genitourinary, spinal, and lower body hemangioma reported in the PELVIS (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, vesicorenal abnormalities, imperforate anus, and skin tag), SACRAL (spinal dysraphism and anogenital, cutaneous, renal, and urologic anomalies associated with an angioma of lumbosacral location), and LUMBAR (lower body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies) syndromes also supports this theory. The pathogenesis of PHACE syndrome currently is an active subject of research in addition to the establishment of more formal management guidelines, which likely will be published as more prospective studies are completed.

CONTINUED ON PAGE 154

CONTINUED FROM PAGE 120

Hemangiomas of PHACE syndrome historically have been treated with oral steroids. As propranolol has become first-line treatment of hemangiomas, it is critical to recognize that there is an increased risk for acute ischemic stroke in infants with PHACE syndrome and propranolol may potentiate that risk. There have been 2 reports of acute ischemic stroke in PHACE syndrome patients taking propranolol.¹² In a retrospective study of 32 infants with PHACE syndrome, only 1 patient developed a change in neurologic status during propranolol treatment (hemiparesis), which improved with continued treatment.¹³ Neuroimaging should be performed prior to initiation of propranolol. Patients with severe, long-segment narrowing or nonvisualization of major cerebral or cervical arteries in the setting of inadequate collateral circulation, especially when there are coexisting cardiac and aortic arch anomalies, seem to be at greatest risk for acute ischemic stroke.¹³ In patients with high-risk neuroimaging findings, comanagement with a neurologist, use of the lowest possible dose, slow titration, close observation with inpatient hospitalization, and 3 times daily dosing are recommended.¹⁴

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