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KEY WORDS

PHACE syndrome, PHACES syndrome, hemangioma, diagnostic criteria

ABBREVIATION

MRA—magnetic resonance angiography

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abstract

OBJECTIVES: A subgroup of patients with infantile hemangiomas have associated structural anomalies of the brain, cerebral vasculature, eyes, sternum, and/or aorta in the neurocutaneous disorder known as PHACE syndrome. The diagnosis has been broadly inclusive by using a case definition of a facial hemangioma plus ≥1 extracutaneous features, leading to numerous reports of potential associated disease features, many of uncertain significance. This consensus statement was thus developed to establish diagnostic criteria for PHACE syndrome.

METHODS: A multidisciplinary group of specialists with expertise in PHACE syndrome drafted initial diagnostic criteria on the basis of review of published, peer-reviewed medical literature and clinical experience. The group then convened in both executive and general sessions during the PHACE Syndrome Research Conference held in November 2008 for discussion and used a consensus method. All conflicting recommendations were subsequently reconciled via electronic communication and teleconferencing.

RESULTS: These criteria were stratified into 2 categories: (1) PHACE syndrome or (2) possible PHACE syndrome. Major and minor criteria were determined for the following organ systems: cerebrovascular, structural brain, cardiovascular, ocular, and ventral/midline. Definite PHACE requires the presence of a characteristic segmental hemangioma or hemangioma >5 cm on the face or scalp plus 1 major criterion or 2 minor criteria. Possible PHACE requires the presence of a hemangioma >5 cm on the face or scalp plus 1 minor criterion. The group recognized that it may be possible to have PHACE syndrome with a hemangioma affecting the neck, chest, or arm only or no cutaneous hemangioma at all. In such cases, fulfillment of additional required criteria would also lead to a possible PHACE diagnosis.

CONCLUSIONS: These criteria represent current knowledge and are expected to enhance future assessments of PHACE syndrome. It is understood that modifications are to be expected over time to incorporate new research findings. *Pediatrics* 2009;124:1447–1456

Infantile hemangioma is the most common benign tumor of infancy, with an incidence estimated between 4% and 5%.[1] A subgroup of patients with infantile hemangiomas exhibit associated structural anomalies of the brain, cerebral vasculature, eyes, aorta, and chest wall in the neurocutaneous disorder called PHACE syndrome (OMIM 606519). The PHACE acronym, coined by Frieden et al[2] in 1996, refers to posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities/aortic coarctation, and abnormalities of the eye. Although formal guidelines for care have not been established, it is recommended that infants who have large hemangiomas of the face or scalp and are at risk for PHACE undergo imaging of the head, neck, and chest and ophthalmologic and skin examinations.[3]

Recent clinical studies have detailed the associated features of PHACE syndrome; however, very little is known about the natural history of this disease or outcomes of affected infants. Brain and cerebral vascular anomalies constitute the most common extracutaneous features; accordingly, neurologic and cognitive impairments constitute the greatest source of potential morbidity in this neurocutaneous disorder.[3] Clinicians must rely on personal experience when counseling parents on the implications of abnormal neuroimaging, cardiac findings, or other abnormalities.

There are no standardized criteria for the diagnosis of PHACE syndrome. A broadly inclusive case definition of "facial hemangioma plus 1 or more extracutaneous features" has been proposed.[2,3] Infantile hemangiomas occur frequently; the significance of their association with other common extracutaneous anomalies such as an arachnoid cyst, a cerebral vascular "variant," or a patent foramen ovale is uncertain. It is essential that basic criteria for the diagnosis of PHACE syndrome be developed, particularly as investigators move to establish large clinical trials and search for the underlying cause of this syndrome, genetic or otherwise. The aim of this report is to create diagnostic criteria for PHACE syndrome on the basis of the consensus of an expert panel and analysis of all available peer-reviewed data. Although the diagnostic criteria will continue to evolve as we incorporate new research findings, the establishment of guidelines will enhance clinical care by improving screening, detection, and awareness of this neurocutaneous disorder. In addition, it will improve phenotype uniformity among PHACE syndrome cohorts and registries, allowing investigators to assess clinical features, outcomes, and potential treatments in a standardized manner.

The development of the diagnostic criteria for PHACE syndrome followed the standard consensus method and is based on the review of published clinical data and the experience of a multidisciplinary expert panel. This multidisciplinary expert panel included the following specialties: pediatric dermatology (7), pediatric neurology (1), neuroradiology (2), pediatric oncology (1), genetics (1), pediatric cardiology (1), ophthalmology (2), and representatives from patient support groups (2). Panel members constituted the writing committee. No external funding was accepted for this project. The evidence gathered was based on clinical experience and a review of published, peer-reviewed medical literature by query of Medline and PubMed databases. The expert panel drafted the initial diagnostic criteria and revised the document by electronic communication. The panel convened in an executive session at the PHACE Syndrome Research Conference and Workshop November 7, 2008, where key features of the disorder were discussed in a panel setting and a basic consensus statement was drafted. This was followed by 1 day of scientific presentation with a larger audience of medical professionals that focused on the clinical and basic science aspects of PHACE syndrome (November 9, 2008). During this conference, the diagnostic criteria were circulated to the audience for comments and revisions. After the conference, the expert panel resolved all conflicting recommendations via electronic communication and teleconferencing.

HISTORY, NOSOLOGY, AND INCIDENCE OF PHACE SYNDROME

The association between infantile hemangiomas and brain anomalies was first recognized by Pascual-Castroviejo,[4] and a variety of terms have been used to describe this association: OMIM 606519, PHACES syndrome, PHACE association, Pascual-Castroviejo type II syndrome, sternal malformation/vascular dysplasia association, and cutaneous hemangioma: vascular anomaly complex. PHACE syndrome is not rare and is potentially the most common vascular neurocutaneous disorder.[5] More than 300 cases of PHACE syndrome have been reported, mostly in the form of case reports and small case series.[6] Some cases in the past were erroneously reported as atypical cases of Sturge-Weber syndrome.[7] As with any newly described disease, increased recognition and rigorous screening of at-risk children has broadened the clinical spectrum of PHACE syndrome (Table 1).[8] A large prospective study initiated by the Hemangioma Investigator Group found that among 1096 children with hemangiomas, 25 had extracutaneous anomalies associated with PHACE syndrome. These 25 cases represented 20% of all infants with segmental facial hemangiomas; however, this calculation may have underestimated disease

prevalence, because neuroimaging was not performed on every child. Demographic and perinatal data among PHACE cases compared with the larger hemangioma cohort showed an amplified female preponderance in PHACE syndrome (female-to-male ratio: 9:1) compared with infantile hemangioma in general (ratio 2.8:1.0).[5] In a prospective study of PHACE syndrome, preliminary analysis of 78 infants with large segmental hemangiomas ($\geq$22 cm^2) revealed that 53 (67%) patients had at least 1 associated abnormality.[8]

Cutaneous Anomalies

Hemangiomas are subtle or absent at birth, usually becoming more evident within the first days to weeks of life. Lesions undergo a characteristic proliferative phase during infancy, followed by a period of slow involution, typically over years. Hemangiomas that are associated with PHACE syndrome tend to be large (>5 cm in diameter), with a characteristic appearance and location. The term "segmental" hemangioma was proposed to describe the morphology of hemangiomas that most often are observed in association with PHACE syndrome, covering a territory rather than seeming to arise from a single focal point (Fig 1A).[9] Subsequent studies confirmed that segmental hemangiomas of the face have reproducible patterns associated with developmental segments, which arise from the neuroectoderm and later correspond to a specific region of skin and soft tissues.[10] These hemangiomas can manifest as a solitary, confluent plaque or small individual papules clustered in a patterned distribution.[11] In the newborn period, segmental hemangiomas may have a unique, "telangiectatic" appearance or present as a faintly erythematous patch. It is important to recognize these early patterns, which are often mistaken for capillary malformations or "port-wine stains." When telangiec-

TABLE 1 Anomalies Reported in PHACE Syndrome

Category	Abnormality
Structural brain	Posterior fossa
	Dandy-Walker complex
	Cerebellar hypoplasia/atrophy
	Subependymal and arachnoid cysts
	Hypoplasia or agenesis of
	Cerebrum
	Corpus callosum
	Septum pellucidum
	Vermis
	Polymicrogyria
	Microcephaly
	Heterotopia
	Absent pituitary or partially empty sella turcica
Cerebrovascular	Dysplasia of the large cerebral arteries
	Absence or moderate to severe hypoplasia of the large cerebral arteries
	Aberrant origin or course of the large cerebral arteries
	Saccular aneurysms
	Persistent embryonic arteries (predominantly trigeminal)
	Pial enhancement
	Cerebral sinus malformations
	Sinus pericranii
	Dural arteriovenous malformations/pial malformations
	Intracranial hemangioma
	Arterial stenosis or occlusion with or without moyamoya collaterals
	Absent foramen lacerum
	Acute arterial stroke
Cardiovascular	Coarctation or interrupted aortic arch (most often transverse section)
	Aneurysms of aortic arch
	Right aortic arch
	Double aortic arch
	Congenital valvular aortic stenosis
	Aberrant origin of a subclavian with or without a vascular ring
	Stenosis, occlusion, absence, or moderate to severe hypoplasia of the vertebral arteries
	Subclavian steal syndrome
	Anomalous coronary arteries
	Patent ductus arteriosus
	Anomalous pulmonary veins
	Patent foramen ovale
	Cor triatriatum
	Tricuspid atresia/stenosis
	Dextrocardia
	Persistent left superior vena cava
	Ventricular and atrial septal defects
	Pulmonary stenosis
	Tetralogy of Fallot
Ocular	Retinal vascular abnormalities
	Persistent fetal vasculature
	Iris vessel hypertrophy
	"Morning-glory" disc
	Peripapillary staphyloma
	Optic nerve hypoplasia
	Microphthalmia
	Coloboma
	Congenital cataracts
	Sclerocornea
	Iris hypoplasia
	Exophthalmous
	Congenital third nerve palsy
	Horner syndrome
Ventral developmental	Partial or complete agenesis of sternum
	Sternal cleft or pit

TABLE 1 Continued

Category	Abnormality
	Sternal papule
	Lingual ectopic thyroid
	Supraumbilical raphe
	Omphalocele
Miscellaneous	Pituitary insufficiency
	Micrognathia
	Auricular hypoplasia or agenesis/"low-set" ears
	Orofacial clefting
	Spinal dysraphism
	Esophageal diverticulum
	Cervical cyst
	Ipsilateral sensorineural hearing loss

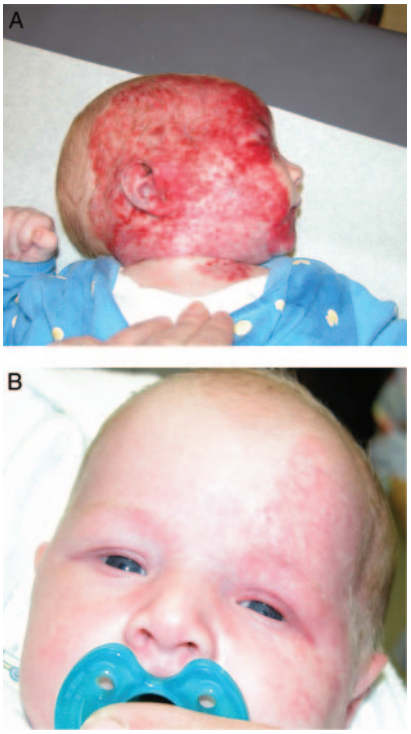

FIGURE 1
A, Segmental hemangioma of the face and scalp in a 4-week-old infant with ipsilateral hearing loss and hypoplasia of the right vertebral artery. B, Reticular hemangioma in a 1-day-old infant with PHACE syndrome and coarctation of aorta as seen in Fig 5.

tatic, the territory of involved skin may be pale (as a result of presumed vasoconstriction) with a prominent capillary pattern (Fig 1B). In some instances, segmental hemangiomas fail to proliferate and maintain this telangiectatic appearance, which has been described by several terms including, "reticular," "abortive," and "minimal growth."[12,13]

Ninety-eight percent of published cases of PHACE report a hemangioma located on the head. Analysis of photographic data from 294 segmental hemangiomas of the face led to the recognition of 4 distinct patterns: segment 1 (frontotemporal), segment 2 (maxillary), segment 3 (mandibular), and segment 4 (frontonasal; Fig 2).[10] Previous reports noted that segment 1 is probably most predictive of cerebrovascular and ocular anomalies, whereas segment 3 seems to predict ventral developmental defects and cardiovascular abnormalities.[3,5,8] Although not yet fully elucidated, similar segmental patterns are observed on the scalp, particularly the posterior auricular region extending to the posterior neck (Fig 3). Although the above observations may

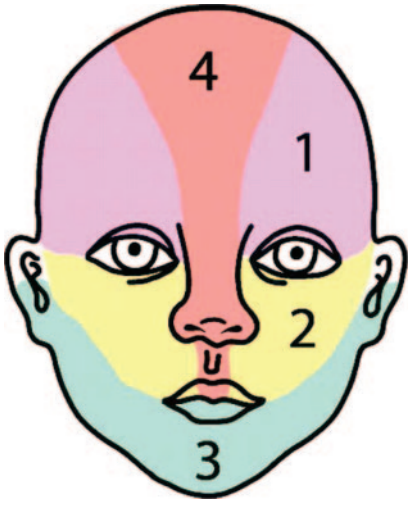

FIGURE 2
Diagram of the proposed facial segments.

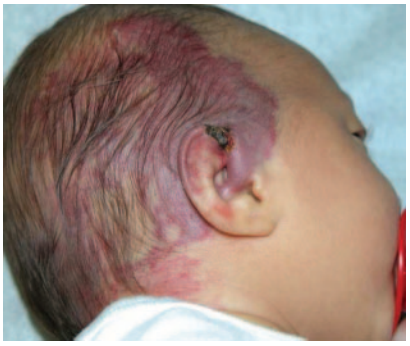

FIGURE 3
Large segmental hemangioma of the posterior auricular region extending down to the neck and into the thorax. The infant had right optic nerve hypoplasia, pituitary hypoplasia, and long segment hypoplasia of the right vertebral artery.

offer insight into pathogenesis, they should not influence anything less than a thorough PHACE evaluation for at-risk infants, which includes MRI and magnetic resonance arteriogram (MRA) brain imaging, imaging of the cardiovasculature, and an ophthalmologic examination. There are also rare reports of infants who demonstrate features of PHACE without the classically described large, facial segmental hemangioma. These include cases with small hemangiomas involving only part of a segment,[14,15] segmental hemangiomas in nonfacial locations,[5] or no obvious cutaneous hemangioma at all.

Cerebral Vascular Anomalies

Cerebral vascular anomalies seem to be the most common extracutaneous manifestation of PHACE syndrome. The rates of detected brain and cerebral vascular anomalies vary among published case series as a consequence of the extent and frequency of neuroimaging and the methods of patient ascertainment. Although there are isolated reports of venous and cerebral sinus anomalies, arterial lesions are detected at far greater frequencies. Predominant involvement of the arterial system is thought to distinguish PHACE from other neurocutaneous

syndromes that involve capillaries and veins, such as Sturge-Weber and cerebrofacial arteriovenous metameric syndrome.[16] The most severe forms of arterial dysplasia observed in PHACE syndrome make this feature of the disease relatively unique, because similar degrees of arterial tortuosity are present in only a few other rare disorders, such as Menkes disease[17] and arterial tortuosity syndrome.[18]

The variety and degree of arterial anomalies in PHACE syndrome are wide ranging but for descriptive purposes can be roughly divided into 4 categories (1): dysplasia (including ectasia, looping, kinking, and/or fusiform dilation); (2) narrowing (including developmental hypoplasia or agenesis and acquired stenosis or occlusion); (3) aberrant course or origin (in which arteries exhibit anomalous origin, elongation, or foreshortening); and (4) persistence of embryonic anastomoses (arterial segments that are present but normally involute during arterial development, such as persistent trigeminal artery). Although the exact prevalence of these different types of anomalies among patients with PHACE syndrome is unknown, relatively large case series suggested that arterial dysplasia is most common (Fig 4), with prevalence estimates as high as 52% among children with documented arterial anomalies, followed by narrowing or occlusion (prevalence 45%–48%) and aberrant course or origin (prevalence 28%–44%).[19–21] Certain anomalies may be visible on routine MRI, although it is necessary to perform magnetic resonance angiography to identify and characterize many of the described anomalies with certainty.

Persistent trigeminal artery occurs with much higher frequency among children with PHACE syndrome (12%–16%) than reports from other large cerebral angiographic series (0.1%–0.2%).[22] The relative frequency with which this otherwise rare anomaly is seen in PHACE syndrome may point to the gestational timing of an error in vasculogenesis. Other persistent embryonic connections, including proatlantal, stapedial, hypoglossal, and otic arteries, are much less common. Saccular aneurysms affect roughly 13% of patients, although the long-term risk for aneurysm rupture and late aneurysm development is not known. Finally, variants within the circle of Willis (absence, hypoplasia, or duplication of the anterior communicating artery, posterior communicating artery, A1 segment of the anterior communicating artery, or P1 segment[s] of the posterior communicating artery) may be more common among children with PHACE syndrome; however, these lack diagnostic specificity because they are also found frequently in the general population, so these variants were excluded from the diagnostic criteria.[20,21]

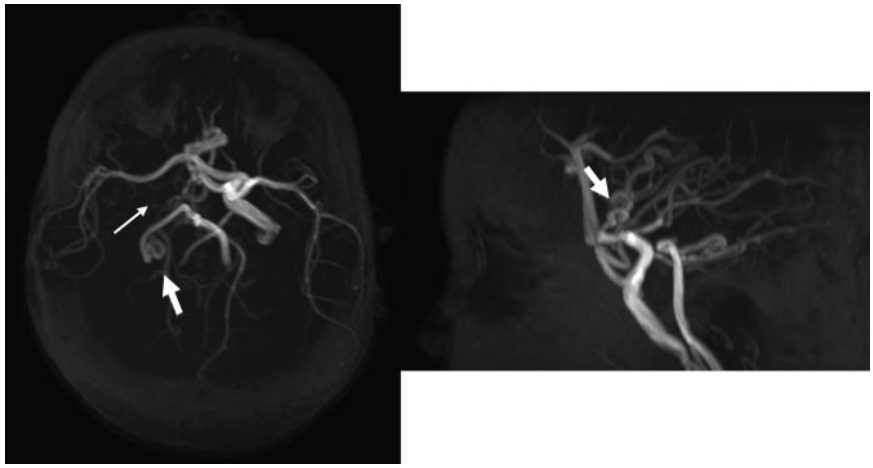

FIGURE 4

Axial A and sagittal (right) maximum intensity projections from time-of-flight intracranial MRA of a child with definite PHACE, demonstrating severe dysplasia of the large cerebral arteries with marked enlargement, tortuosity and looping of the right posterior cerebral artery and right anterior cerebral artery (wide arrows). Nonvisualization of the right internal carotid artery on these images also indicates occlusion or agenesis of this artery (thin arrow).

As first reported by Burrows et al,[19] a subset of patients with PHACE syndrome are at risk for progressive vasculopathy, in which postnatal arterial narrowing and occlusion may result in ischemic stroke.[23] The progressive nature of this rare vasculopathy is underscored by the observation of moyamoya collaterals in some of these patients. The presence of small collateral branches suggests a gradual progression of the stenotic and occlusive arterial disease. It is notable that both the developmental (congenital) and progressive arterial anomalies of PHACE syndrome involve large and medium-sized arteries to a much greater extent than small arteries. Specifically, as reported by Heyer et al,[21,24] the most common arteries affected are the intracranial and extracranial internal carotid artery, the middle cerebral artery, the anterior cerebral artery, the posterior cerebral artery, the basilar artery, and the vertebral arteries. Almost universally, head and neck arterial anomalies in PHACE syndrome occur either ipsilateral to the cutaneous hemangioma or bilaterally.

Structural Brain Anomalies

A spectrum of congenital brain abnormalities have been described among patients with PHACE syndrome, the most commonly observed of which malformations of the cerebellum and

posterior fossa structures are. Specific anomalies reported range from the Dandy-Walker complex to focal dysplasia and/or hypoplasia of the cerebellum. Multiple cerebral (supratentorial) lesions have also been described. In a cohort of patients with 17 PHACE syndrome, Blei et al[25] found that 4 (24%) had supratentorial lesions, including cortical dysplasia, subcortical and subependymal gray matter heterotopias, and agenesis of the corpus callosum. Of note, all patients with cerebral involvement had cerebral vascular anomalies. Regions of cortical dysplasia tend to have associated large- and/or small-vessel abnormalities, often overlying the cortical lesion; however, Poindexter et al[26] described 2 patients with subependymal heterotopic gray matter without adjacent arterial lesions.

Other reported brain anomalies in PHACE include pial-enhancing lesions, which, although poorly characterized, are suggestive of small-vessel disease.[21] Reports of absent sella turcica in association with growth hormone deficiency emphasize a known but likely underrecognized association between structural pituitary anomalies, excavated optic disc anomalies (see Table 1), and/or optic nerve hypoplasia and multiple endocrinopathies, including hypopituitarism, hypothyroidism, growth hormone deficiency, and diabetes insipidus.[26–29] Enhancing extra-axial lesions with features consistent with intracranial hemangioma are increasingly detected in patients with PHACE syndrome, likely as a result of improved screening with contrast-enhanced MRI.[30] Although most reports of such lesions are lacking histology and the radiologic characteristics are not entirely specific to infantile hemangioma, the appearance seems to be relatively unique, particularly in the pediatric population. Important, the imaging appearance of intracranial hemangiomas should show the homogeneous enhancement and T2 hyperintensity observed in cutaneous hemangiomas, both before and after contrast administration.

Neurologic Signs and Symptoms

Most patients with PHACE syndrome have normal neurologic examinations in infancy. Screening for congenital lesions by MRI with MRA should not be based on the presence or absence of abnormal neurologic signs. When neurologic features are present in infancy or childhood, they often correspond to congenital lesions of the cerebrum and/or cerebellum or to arterial ischemic stroke. Localization-related epilepsy, developmental delay, and recurrent headaches seem to be the most common neurologic signs and symptoms. Other reported neurologic features of PHACE syndrome include hemiparesis, opisthotonus, temperature instability, apnea, and abnormalities of muscular tone.[3] Neurocognitive impairments are observed in a subset of children with PHACE syndrome, in some cases in the setting of a normal radiographic evaluation.[5] Cranial nerve abnormalities and sensorineural hearing loss are rarely reported.[26,31] Formal study with serial neuroimaging, neurocognitive assessments, and neurologic evaluations is needed for better characterization of long-term outcomes in PHACE syndrome.

Cardiovascular Anomalies

Coarctation of the aorta is the most common cardiac finding reported with PHACE syndrome (14.5% by literature review), and this arch abnormality is critical to recognize because it can be life-threatening if associated with severe obstruction to blood flow. The coarctation observed in PHACE syndrome is often especially unique and complex with long-segment hypoplasia/interruption of the transverse arch and unusual dilation and aneurysm formation of adjacent arch segments (Fig 5A).[3,32–38] In addition, these arch anomalies are often associated with abnormalities of the brachiocephalic vessels (dilation, tortuosity, and aberrant subclavian artery origin) and aortic arch sidedness (right or double aortic arch).[32,38] The incidence of right aortic arch is significantly higher than in the general population (33% of those with PHACE syndrome and arch pathology compared with 0.01% of the general population), so it has been included as a minor criterion for the diagnosis.[32]

The constellation of aortic arch pathology with transverse arch obstruction, dilation/aneurysm formation, and abnormal brachiocephalic vessels/arch sidedness is very rare in children and seems to be specific to PHACE syndrome. In contrast, the typical anatomy of aortic coarctation (without PHACE association) tends to involve the proximal descending thoracic aorta at the isthmus and rarely is associated with other arch or brachiocephalic abnormalities. In "classic" coarctation, mitral and particularly aortic valve abnormalities (50%–80% have bicuspid aortic valve) are common; however, coarctation seen with PHACE syndrome is not usually associated with abnormalities of left ventricular inflow or outflow. The aberrant origin of the subclavian artery observed in PHACE syndrome is important, because if all of the major arm and leg arteries arise below the level of the arch obstruction (as is frequently seen in coarctation with PHACE syndrome), then clinical assessment of coarctation by blood pressure difference between the arms and legs becomes an unreliable indicator (Fig 5B).[35]

Other cardiac anomalies seem to be rarely associated with PHACE syndrome. Although the list and variety of reported cardiac malformations are extensive (Table 1), no clear pattern or

consistent increase in incidence is appreciated for most of the lesions described. The incidence of ventricular septal defect (7.6%) reported in PHACE syndrome is significantly higher than that anticipated in the general population and so has been included as a minor criterion; other cardiac defects do not seem to be specific to PHACE syndrome and have always been associated with more specific findings of the syndrome.[39] Finally, patent foramen ovale is commonly reported in PHACE syndrome. This is a normal finding in at least 25% of the general population (with a higher incidence in infants, when screening echocardiograms are usually done for PHACE syndrome) and so is excluded from the diagnostic criteria.

Ocular Anomalies

Ocular anomalies are relative rare in PHACE syndrome; however, specific posterior segmental anomalies, when observed in conjunction with an ipsilateral segmental hemangioma, seem to be very specific. Microphthalmia, optic nerve hypoplasia, persistent fetal vasculature, and morning glory disc anomalies are reported most frequently (Table 1).

Midline Anomalies

Numerous reports of ventral developmental defects—sternal clefting and/or supraumbilical abdominal raphe—have been described in association with PHACE syndrome. These malformations can manifest as a nonunion involving only the manubrium or extend the entire length of the sternal plates and into the abdomen. Subtle cutaneous changes such as a sternal pit, dimple, or papule are also commonly seen. Endocrine abnormalities have also recently been described in this patient population, involving both the thyroid and the pituitary glands. Lingual thyroid with subsequent hypothyroidism was reported previously[2] as was congenital hypothyroidism as-

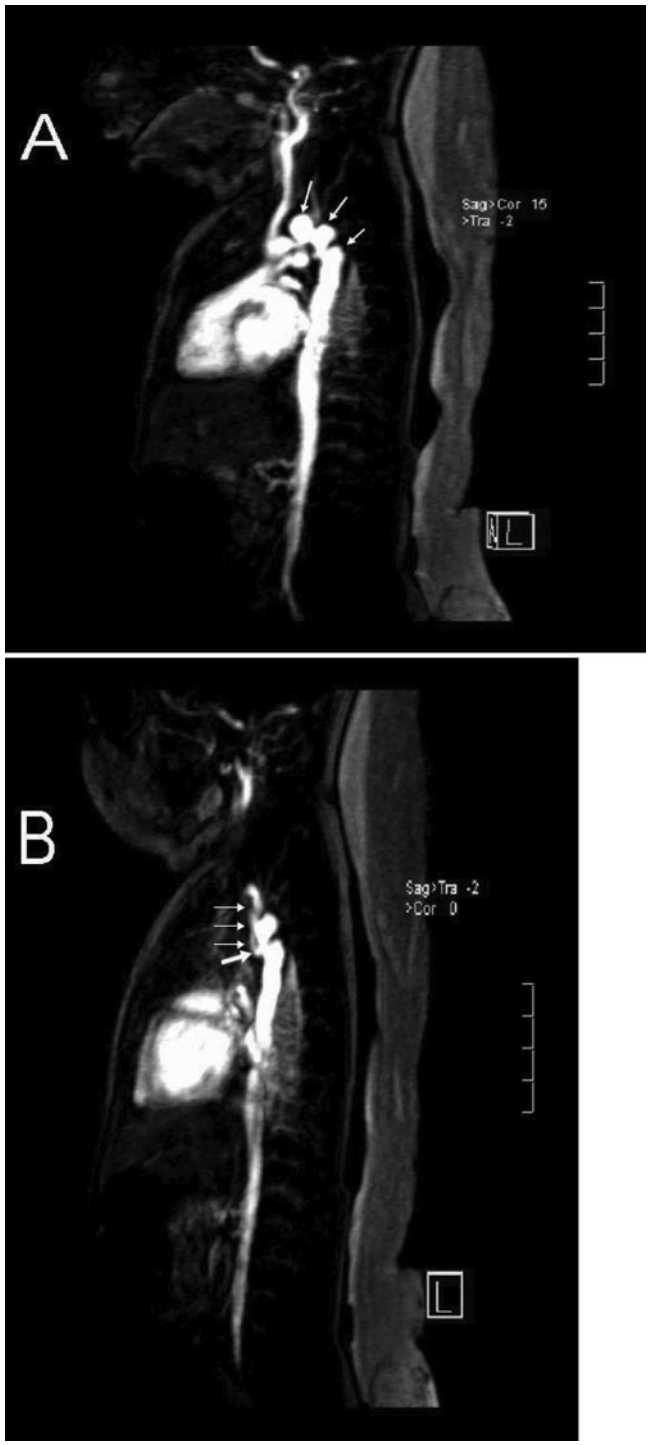

FIGURE 5
A, Two-dimensional MRI aortic imaging on this patient with a left aortic arch and coarctation shows multiple areas of significant transverse aortic arch narrowing and aneurysmal dilation (arrows) that resulted in severe obstruction to blood flow, necessitating surgical arch reconstruction with a tubular graft to bypass the long segment of abnormal aorta. B, Also an aberrant right subclavian artery arose from the descending aorta below the area of arch narrowing (large arrow) and coursed toward the right arm (small arrows); because all the subclavian arteries originated distal to the transverse arch obstruction, the coarctation was not suspected by blood pressure assessment in the arms and legs.

TABLE 2 Diagnostic Criteria: PHACE Syndrome

PHACE Syndrome		
Facial Hemangioma >5 cm in diameter PLUS 1 Major Criteria OR 2 Minor Criteria		
Possible PHACE Syndrome		
Facial Hemangioma >5 cm in diameter PLUS 1 Minor Criteria	Hemangioma of the Neck or Upper Torso PLUS 1 Major Criteria OR 2 Minor Criteria	No Hemangioma PLUS 2 Major Criteria
Organ System	Major Criteria	Minor Criteria
Cerebrovascular	Anomaly of major cerebral arteries Dysplasia[a] of the large cerebral arteries[b] Arterial stenosis or occlusion with or without moyamoya collaterals Absence or moderate to severe hypoplasia of the large cerebral arteries Aberrant origin or course of the large cerebral arteries[b] Persistent trigeminal artery Saccular aneurysms of any cerebral arteries	Persistent embryonic artery other than trigeminal artery Proatlantal intersegmental artery (types 1 and 2) Primitive hypoglossal artery Primitive otic artery[c]
Structural brain	Posterior fossa anomaly Dandy-Walker complex or unilateral/bilateral cerebellar hypoplasia/dysplasia	Enhancing extra-axial lesion with features consistent with intracranial hemangioma[c] Midline anomaly[d] Neuronal migration disorder[e]
Cardiovascular	Aortic arch anomaly Coarctation of aorta Dysplasia[a] Aneurysm Aberrant origin of the subclavian artery with or without a vascular ring	Ventricular septal defect Right aortic arch (double aortic arch)
Ocular	Posterior segment abnormality Persistent fetal vasculature (persistent hyperplastic primary vitreous) Retinal vascular anomalies Morning Glory disc anomaly Optic nerve hypoplasia Peripapillary staphyloma Coloboma	Anterior segment abnormality Sclerocornea Cataract Coloboma Microphthalmia
Ventral or midline	Sternal Defect Sternal cleft Supraumbilical raphe Sternal defects	Hypopituitarism Ectopic thyroid

[a] Includes kinking, looping, tortuosity, and/or dolichoectasia.
[b] Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system.
[c] See Structural Brain Anomalies section for discussion.
[d] Callosal agenesis or dysgenesis, septum pellucidum agenesis, pituitary malformation, or pituitary ectopia.
[e] Polymicrogyria, cortical dysplasia, or gray matter heterotopia.

sociated with large facial hemangioma.[15,25,26,40] These findings differ from the acquired hypothyroidism associated with liver hemangiomas, which is attributed to peripheral destruction of thyroid hormone by type 3 iodothyronine deiodinase.[41]

Diagnostic Criteria

The expert panel designed the diagnostic criteria to be relatively inclusive by stratifying patients into 2 categories: (1) PHACE syndrome or (2) possible PHACE syndrome. The diagnosis of PHACE syndrome requires the presence of a segmental hemangioma or hemangioma >5 cm^2 of the head (face or scalp) plus 1 major criterion or 2 minor criteria listed in Table 2. We recognize that it may be possible to have PHACE syndrome with a hemangioma affecting the neck, chest, or arm only or no cutaneous hemangioma at all. In these cases, fulfilling the following criteria would lead to a possible PHACE diagnosis: Facial hemangioma >5 cm in diameter plus 1 minor criterion; hemangioma of the neck or upper torso plus 1 major criterion or 2 minor criteria; or no hemangioma plus 2 major criteria. Important, ≥1 anomaly listed within a given organ system category counts for only 1 criterion.

The term "arterial hypoplasia" can be subjective when interpreting magnetic resonance angiography. Accordingly,

TABLE 3 Relative Frequencies of Major and Minor Criteria in the Published Literature and PHACE Syndrome Registries

Parameter	Published ($N = 317$), %	Texas Children's Registry ($N = 46$), %	Genetic Analysis of PHACE OHSU ($N = 65$), %
Major			
Segmental infantile hemangioma of head	92.4	95.7	100.0
Infantile hemangioma of head >5 cm^2	92.4	95.7	100.0
Dysplasia of large cerebral artery[a]	15.4	30.5	13.9
Stenosis, occlusion, absence, or hypoplasia of larger cerebral artery[b]	18.3	52.2	60.4
Aberrant origin or course of the large cerebral arteries	4.4	10.9	2.0
Persistent trigeminal artery	4.7	13.0	2.0
Posterior fossa anomaly	32.2	30.4	34.5
Coarctation of the aorta	14.5	6.5	28.3
Anomalous subclavian	6.3	15.2	13.9
Posterior segment anomalies of the eye	5.7	8.7	7.7
Sternal defect	19.50	10.90	21.58
Umbilical raphe	9.1	4.3	9.2
Minor			
Segmental infantile hemangioma of neck or chest only	0.3	4.3	0.0
Persistent embryonic arteries other than trigeminal artery	1.6	8.7	6.9
Midline anomalies[c]	6.3	6.5	1.5
Disorders of migration[d]	2.8	4.3	6.2
Ventricular septal defect	7.6	8.7	13.2
Anterior segment defect of the eye	6.6	8.7	7.7
Sternal papule	1.6	2.2	1.5

[a] Includes kinking, looping, fusiform aneurysms, and/or dolichoectasia.
[b] Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system.
[c] Callosal agenesis or dysgenesis, septum pellucidum agenesis, pituitary malformation, or pituitary ectopia.
[d] Polymicrogyria, cortical dysplasia, or gray matter heterotopia.

TABLE 4 Recommended Minimal Neuroimaging for Infants at Risk for PHACE Syndrome

Structural brain imaging
Axial spin-echo T2
Volumetric gradient-echo T1 (preferred) or axial spin-echo T1
Axial diffusion-weighted imaging (this includes ADC mapping)
Gadolinium-enhanced T1 in 2 planes (we do axial and coronal), preferably with fat suppression
Intracranial and cervical angiography
Intracranial axial TOF MRA
Contrast-enhanced MRA (preferred) or TOF MRA of the cervical vessels

ADC indicates apparent diffusion coefficient; TOF, time-of-flight.

we have added the qualifier "moderate to severe" to improve diagnostic specificity among radiologists. In contrast, even subtle narrowing of the aorta seems to be specific for PHACE syndrome, so no qualifier was used in that instance.

While creating the major and minor criteria, members of the expert panel determined the relative frequencies of each criterion in the literature and existing registries (Table 3). Although these data are useful, it must be tempered with the knowledge that most reported patients have not undergone standardized imaging for all of the potentially associated anomalies of PHACE syndrome. Furthermore, many publications do not provide details of cardiac and central nervous system imaging (Table 4). It is understood that these diagnostic criteria are likely to be modified over time to incorporate new clinical and research findings.

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Consensus Statement on Diagnostic Criteria for PHACE Syndrome

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