PHACE Syndrome: Consensus-Derived Diagnosis and Care Recommendations

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PHACE syndrome (posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities/coarctation of the aorta, eye anomalies) is characterized by large infantile hemangiomas (IH) of the face, neck, and/or scalp that are associated with developmental defects. The acronym was coined in 1996 to describe a constellation of clinical features. As recognition of these features has improved, the clinical description has evolved. Diagnostic criteria were developed in 2009 and included possible and definite PHACE. There are over 250 case reports/case series detailing the various multisystem features of PHACE. Despite these numerous reports, there are no established clinical guidelines for care.

Although the most apparent feature of PHACE is the infantile hemangioma, abnormalities of the brain, aorta, medium-sized arteries of the chest, neck, and head are common and have the greatest potential to cause long-term morbidity. As patients with PHACE have been followed over time, new age-related comorbidities have been recognized, including headaches, as well as endocrinologic, hearing, and dental anomalies. Evidence-based data for screening and monitoring these potentially progressive morbidities do not exist so clinicians must rely on their individual experiences with a limited number of patients to guide management decisions. As a result, there is significant inconsistency in practice regarding when and how to evaluate for PHACE and surveillance strategies once the diagnosis is established. This multidisciplinary consensus document provides a comprehensive review of the literature and details emerging comorbidities and updates the preexisting diagnostic criteria. This summary also presents care guidelines for both screening at-risk infants and risk-adjusted ongoing health surveillance of those diagnosed with PHACE.

Methods

The development of the content followed the customary consensus methodology based on a comprehensive review of published data and on the experience of a multidisciplinary expert panel. A multi-institutional PHACE syndrome workshop was held in Milwaukee, Wisconsin, in June 2014. Parents and advocates were asked to participate to ensure that the team addressed concerns and outcomes important to patients. The goal of the workshop was to bring together PHACE syndrome experts from various pediatric specialties to address questions about diagnostic guidelines, screening recommendations, and health surveillance. Twenty-eight physicians from 14 institutions attended, representing 9 pediatric specialties, including neuroradiology, neurosurgery, neurology, cardiology, cardiothoracic surgery, dermatology, otolaryngology, hematology-oncology, and plastic surgery.

The evidence was gathered from clinical experience along with a review of published, peer- reviewed medical literature using Medline and PubMed databases. Small, specialty-focused

AIS	Arterial ischemic stroke
IH	Infantile hemangiomas
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PHACE	Posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities/coarctation of the aorta, eye anomalies
QoL	Quality of life

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groups reviewed existing literature on the associated anomalies of PHACE and developed organ-specific content, detailing prevalence, progression, and morbidity. Parents detailed issues relevant to the ongoing care of children with PHACE. The data were summarized, and each small group presented content summaries at the meeting, inviting further discussion. Within specialty-focused groups, expert participants were asked to reach consensus and develop recommendations regarding organ-specific screening protocols and risk-adapted surveillance strategies. These recommendations were then presented to the larger multidisciplinary group, which also refined and edited them until consensus was reached.

The final protocols were then collated into a manuscript that was circulated, edited, finalized, and approved by means of conference calls and electronic communication. Evidence is generally confined to expert opinion, case reports, and observational or descriptive studies. Evidence from randomized controlled studies is lacking. When there was controversy or lack of consensus, a more conservative approach was selected until more evidence-based data are available.

Family-Important Outcomes

Guidelines regarding monitoring and treatment of the abnormalities observed in the aortic arch and the cervical/cerebral arteries observed in PHACE are a priority for families. Currently, there is inconsistency among institutions and providers regarding how patients are evaluated. In addition, families have encountered conflicting information regarding whether the vasculopathy of PHACE is static or progressive. Families express concern and frustration with the lack of information about the potential risk for stroke in persons with PHACE. Cervical and cerebrovascular anomalies are found in the majority of affected individuals; however, these anomalies remain features of PHACE that do not have a predictable course for treatment.

There is also a lack of consensus on imaging protocols and how often to repeat magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA). At some institutions, children undergo MRI/MRA up to every 3 months, whereas other institutions may recommend a repeat scan only every few years. Agreement is needed to help children receive the safest care and to avoid unnecessary procedures. The use of sedation and anesthesia also varies across sites and is of growing concern to families because of data potentially linking repeated anesthesia exposure in young children and an increased risk for learning disabilities.[1]

Improved understanding of the impact of cerebrovascular arteriopathy may also help clarify the risk/benefit profile for medications used in children with PHACE. Beta blockers, previously considered "too risky" for many children with PHACE with cerebrovascular arteriopathy, are now used frequently for extensive IH. Furthermore, although many affected children are prescribed daily aspirin therapy to reduce the risk of stroke, the long-term impact of this treatment remains unknown.

Another primary area of concern for families is the etiology of PHACE. Without an identified cause, families invariably fear that there was an external event or exposure during pregnancy that resulted in PHACE. Studies of the genetics of PHACE are ongoing, and although a specific cause has not been found, families remain engaged and support this line of inquiry for both an explanation and potential therapies. Families recognize that through improved understanding of the cause, whether genetic, environmental, or multifactorial, better treatments can be developed. Most importantly, identification of an etiology, will allow families to cope better with the diagnosis and potentially clarify recurrence risk and prognosis.

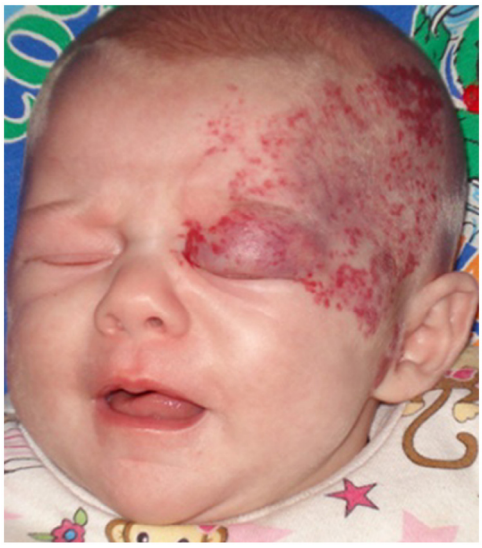

Figure 1. Large segmental infantile hemangioma of the face in a 2-month-old girl with definite PHACE.

Risk for PHACE Syndrome

Children with large, segmental facial IH are well documented to be at risk for PHACE. Segmental IH are defined as lesions that cover an anatomic territory of the face or body. A prospective study supported this finding with 31% of infants with facial IH with a surface area of 22 cm^2 or greater (~5 cm × 4.5 cm) meeting diagnostic criteria (**Figure 1**).[2] However, there has been increased recognition that some patients have major criteria for PHACE but lack the characteristic "facial" location of their large segmental hemangioma.[3,4] Patients with characteristic features of PHACE may have large segmental IH located on the posterior scalp, upper chest, upper proximal extremity, or small, or even absent, hemangiomas on the head.[4,5] Similarly, cases of large intraorbital IH with retroorbital involvement causing proptosis with no extension to the skin surface have been described in association with intracranial arterial anomalies of PHACE.[6] The expert group, therefore, concluded that although these children did not have IH involving the face, the segmental or regional presentation along with classic PHACE anomalies was not coincidental but represented a part of the continuum of IH in patients at risk for the disorder. Accordingly, it was recommended that a screening evaluation be performed in all infants with large segmental IH located on either the face or scalp. A complete screening examination should also be considered for infants with 1 major

Table I. Who should be screened for PHACE syndrome

- Segmental infantile hemangioma of the head
- Infants with infantile hemangioma (smaller or lacking typical morphology or distribution) and characteristic/major anomalies found in PHACE (eg, midline ventral defects, coarctation of the aorta, etc)
- Infants without cutaneous infantile hemangiomas with other characteristic anomalies found in PHACE (major criteria)

criterion of PHACE and a large segmental hemangioma of the neck, upper trunk, or trunk and proximal upper extremity. Infants with 2 major criteria of PHACE (eg, supraumbilical raphe and coarctation of the aorta) but lacking cutaneous IH should undergo complete evaluation for PHACE (**Table I**). The group did not have enough evidenced-based data to define objectively "large" IH, but the only prospective study examining facial hemangioma morphology and risk for PHACE used 22 cm^2.[2]

Reconsideration of Diagnostic Criteria

There was agreement among experts regarding the general reliability of the preexisting diagnostic criteria for PHACE.[7] However, there was also consensus to modify the preexisting diagnostic criteria for definite PHACE. Individuals with IH of the face or scalp >5 cm in diameter and 1 major diagnostic criterion are considered to have definite PHACE. In addition, patients with large segmental IH of the neck, upper trunk, or trunk and proximal upper extremity who also have 2 other major criteria should be considered to have definite PHACE. Increased detail was provided regarding features of the IH in which patients would be designated as having "possible PHACE" (**Table II**).

Update on Clinical Features of PHACE Syndrome

As more patients receive systematic clinical and imaging evaluations for PHACE, the frequency of extracutaneous anomalies can be more accurately estimated (**Table III**). By recognizing all associated abnormalities, and their clinical manifestations and respective morbidity, practitioners can better direct screening and surveillance testing. It is especially important to recognize anomalies that may not manifest clinically during infancy but can later cause morbidity if missed or are untreated.

PHACE Syndrome Associated Arteriopathy and Risk of Acute Ischemic Stroke. Congenital anomalies of the vasculature are the most common extracutaneous finding in PHACE (**Figure 2;** available at www.jpeds.com). Abnormalities of the aorta and the medium-sized arteries of the chest, neck, and head are common and have the greatest potential to cause long-term morbidity. The natural history associated with these arterial abnormalities is poorly understood. Burrows et al were the first to document progressive narrowing in a subset of patients with PHACE with congenital arterial anomalies.[8] Arterial stenoses or occlusions, with or without moyamoya-like vasculopathy, have been further characterized in single case reports and small case series.[9] The presence of blood flow-limiting cerebral vascular lesions confers a risk of arterial ischemic stroke (AIS). Pediatric AIS is often a multifactorial disorder and patients with PHACE have several potential stroke risk factors, including progressive steno-occlusive disease and blood flow-limiting arterial narrowing and thromboembolism related to cardiac and supra-aortic arterial lesions. Several cases of stroke have been reported in patients with PHACE; however, the precise risk of AIS in PHACE is not known.[10] Siegel et al[10] reviewed all 22 published cases of stroke in PHACE; the presenting signs of AIS were seizure and hemiparesis and the average age at time of stroke was 13.6 months. They found that all patients with PHACE with stroke had acute ischemic stroke in the distribution of at least 1 narrow or nonvisualized major cerebral artery, and 79% had 2 or more abnormal arteries. Patients with PHACE and stroke also were more likely to have an incomplete circle of Willis and coexisting cardiac and aortic arch anomalies. Based on this observational study, this multidisciplinary group described 3 risk strata for AIS, based on initial MRA results. All patients with PHACE previously reported to have AIS would be deemed high risk. Recommendations for further health surveillance are based on these risk strata: low risk, intermediate risk, and high risk.

(1) Low Risk – This category includes arterial anomalies frequently seen in a general screening population. It also includes findings that have either no or very minimal clinical impact on patient outcome, even if rarely seen in the general population. Examples are persistent embryonic arteries, anomalous arterial origin or course, circle of Willis variants, and other isolated hemodynamically insignificant variants.

(2) Intermediate Risk – This category includes patients with nonstenotic dysgenesis, including patients with ectatic or segmentally enlarged arteries. It also includes patients with narrowing or occlusion of arteries proximal to the circle of Willis, with no perceived hemodynamic risk. An example is a patient with stenosis or atresia of a proximal portion of the internal carotid artery, with otherwise normal anatomy and capacious collateral blood flow in the anterior and posterior communicating arteries, and normal distal flow (**Figure 2**). This assessment hinges on an evaluation of the patency of the Circle of Willis.

(3) High Risk – This category includes patients with one or more of the following:
   - Significant narrowing (>25%) or occlusion of principal cerebral vessels within or above the circle of Willis that results in an "isolated" circulation. For example, severe or progressive stenosis of the supraclinoid internal carotid artery in a patient without an ipsilateral anterior or posterior communicating artery would prompt additional risk stratification using catheter angiography

Table II. Diagnostic criteria-revised

Organ systems	Major criteria	Minor criteria
Arterial anomalies	Anomaly of major cerebral or cervical arteries* Dysplasia† of the large cerebral arteries Arterial stenosis or occlusion with or without moyamoya collaterals Absence or moderate-severe hypoplasia of the large cerebral and cervical arteries Aberrant origin or course of the large cerebral or cervical arteries except common arch variants such as bovine arch. Persistent carotid-vertebrobasilar anastomosis (proatlantal segmental, hypoglossal, otic, and/or trigeminal arteries)	Aneurysm of any of the cerebral arteries
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 the subclavian artery with or without a 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 the midline chest and abdomen - Sternal defect - Sternal pit - Sternal cleft - Supraumbilical raphe	Ectopic thyroid hypopituitarism Midline sternal papule/hamartoma

Definite PHACE	
Hemangioma >5 cm in diameter of the head including scalp PLUS 1 major criteria or 2 minor criteria	Hemangioma of the neck, upper trunk or trunk and proximal upper extremity PLUS 2 major criteria

Possible PHACE		
Hemangioma > 5 cm in diameter of the head including scalp PLUS 1 minor criteria	Hemangioma of the neck, upper trunk or trunk and proximal upper extremity PLUS 1 major or 2 minor	No hemangioma PLUS 2 major criteria

*Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system.
†Includes kinking, looping, tortuosity, and/or dolichoectasia.

and other tests to determine whether revascularization might be indicated.

- Tandem or multiple arterial stenoses associated with complex blood flow that may potentially result in diminished cerebral perfusion. Similarly, patients with cerebrovascular stenosis in the setting of coarctation of the aorta are likely at higher risk of transient and permanent neurologic ischemic events.
- Imaging findings in the brain parenchyma suggestive of chronic or silent ischemia, or progressive steno-occlusive disease. These parenchymal brain MRI findings include existing infarction, chronic or border zone ischemic changes, and presence of lenticulostriate collateral dilation or pial collaterals.

The above categorizations were recommended by the expert panel without evidence-based data. A first step to collect empirical or evidence-based data would consist of validating these strata through selection of a group of patients with PHACE and adverse neurologic outcomes and comparing their imaging to a matched group of patients with PHACE without such adverse outcomes.

PHACE Syndrome Associated Structural Brain Abnormalities. Multiple brain lesions affecting the posterior fossa and the cerebrum have been described in PHACE.[7,11-23] The posterior fossa abnormalities range from focal regions of cerebellar dysplasia to various cystic malformations of the posterior fossa including the Dandy-Walker complex. The overall frequency of posterior fossa anomalies in patients with PHACE varies by published report from 30.4% to 81%.[7,14,16] In a study characterizing the neuroimaging features of PHACE, 24 (41%) of 59 patients had structural brain abnormalities detected.[17] All brain lesions that were unilateral had associated cerebral arteriopathy and cutaneous hemangioma on the ipsilateral side. Cerebral anomalies occur less commonly than the posterior fossa lesions. When present, they comprise a variety of abnormalities that include congenital cystic lesions and cerebral dysplasia, diffuse cerebral volume loss, neuronal migration abnormalities (eg, pachygyria, polymicrogyria, and heterotopic

Table III. Clinical features of PHACE

Organ systems	Common >20% of patients	Less common	Rare/single case report
Arterial	Dysplasia, narrowing, aberrant origin or course of cervical, cerebral, and brachiocephalic arteries	Moyamoya-like arteriopathy Agenesis of cervical, cerebral, and brachiocephalic arteries Aneurysms of cervical, cerebral or brachiocephalic arteries Persistent carotid-vertebrobasilar anastomosis (proatlantal segmental, hypoglossal, otic, and/or trigeminal arteries	Arteriovenous dural fistulae/malformation
Structural Brain	Posterior fossa brain anomalies Dandy-Walker complex Other hypoplasia/dysplasia of the mid- and/or hind brain	Malformations of cortical development - Polymicrogyria - Heterotopia - Cortical dysplasia Midline brain anomaly - Hypoplasia/ agenesis of the corpus callosum - Hypoplasia/agenesis of the septum pellucidum Absent pituitary or partially empty sella turcica Intracranial hemangioma - Internal auditory canal - Cerebellopontine angle cistern	
Cardiovascular	Anomalies of the aorta - Coarctation of the aorta - Dysplasia of the aortic arch Aberrant origin of a subclavian artery	Right aortic arch (double aortic arch) Interrupted aortic arch Structural anomalies of heart - Ventral septal defect Vascular ring Systemic venous anomalies - Retroaortic innominate vein - Bilateral vena cava with a left superior vena cava draining to the coronary sinus	Tetralogy of Fallot Ectopic cordis Pulmonary stenosis Atrial septal defect
Ocular		Posterior segment anomaly - Persistent fetal vasculature (Persistent hyperplastic primary vitreous) - Retinal vascular anomalies - Morning glory disc anomaly - Optic nerve hypoplasia - Peripapillary staphyloma - Coloboma Microphthalmia	Cataract Anterior segment abnormality Sclerocornea
Midline		Anomaly of the midline chest and abdomen - Sternal defect - Sternal pit - Sternal cleft - Supraumbilical raphe	Omphalocele Midline facial anomaly
Neurologic signs and symptoms	Migraine-like headaches	Seizures Cyclic vomiting Developmental delays - Speech/language delay - Gross motor delay - Fine motor delay Hypotonia Tremor Dysphagia Opisthotonus Hearing loss - Conductive hearing loss - Sensorineural hearing loss Mixed hearing loss Facial nerve palsy - Horner/ptosis/heterochromia - Third nerve palsy - Optic nerve hypoplasia	
Endocrine		Hypopituitarism Hypogonadism Hypothyroidism Ectopic thyroid gland Growth hormone deficiency	Diabetes insipidus
Hemangioma-related complications		Impairment of visual axis Stridor related to subglottic hemangioma Ulceration of hemangioma	GI bleeding from GI hemangioma
Miscellaneous		Dental abnormalities Feeding disorders Dysphagia	Spinal dysraphism Micrognathia Orofacial clefting Auricular hypoplasia

gray matter), midline and pituitary defects, and acquired AIS.[13,17-23] Much like the regions of cerebellar dysplasia, when a focal cerebral lesion is present, it tends to occur on the same side as the facial hemangioma.

PHACE Syndrome Associated Congenital Heart Disease, and Aortic Arch and Brachiocephalic Abnormalities. In a comprehensive review of the literature, the prevalence of congenital heart disease in patients with PHACE ranges from 41%-67% with coarctation of the aorta in 19%-30%.[2,24] This is significantly higher than the general population and those with many other syndromes well known to be associated with congenital heart disease.[2,24] Aortic arch anomalies observed in PHACE are unusually complex, with involvement of the transverse and descending aorta arch (**Figure 3**; available at www.jpeds.com). The arch obstruction is most often long-segment, rather than the typical discrete juxtaductal narrowing seen in coarctations of patients without PHACE. The obstruction is frequently characterized by regions of arch narrowing or interruption with adjacent segments of marked aneurysmal dilatation. In addition, the obstruction may be difficult to assess clinically in those with PHACE because of the commonly associated aberrant subclavian origin where both subclavian arteries arise distal to the obstruction. This makes 4-extremity blood pressure assessment of gradient between upper and lower extremities inaccurate for identifying the arch obstruction. Consequently, ongoing imaging evaluation of children with congenital aortic arch abnormalities is recommended, even if they are asymptomatic.

Thirty-seven percent of those with arch anomalies will require surgical intervention, and extensive arch reconstruction is commonly required.[24] Careful preoperative assessment is necessary to characterize fully the aortic, and cerebrovascular arterial and venous abnormalities.[25] Recurrent obstruction is common because of the nonnative tissue techniques (ie, interposition graft or patch angioplasty) needed to relieve the arch anomaly.[25] Standard intraoperative monitoring for patients with PHACE should include advanced neurophysiologic monitoring given the increased risk for ischemic brain injury and need for cardiopulmonary bypass. As noted above, aberrant origin of a subclavian artery, with or without a vascular ring, is also commonly found in patients with PHACE with heart disease (50%).[24] In addition, a right or double aortic arch, a ventricular septal defect, and systemic venous anomalies are other cardiac abnormalities associated with PHACE.[24]

Protocols to Screen for Associated Abnormalities in at Risk Children

These screening recommendations are designed to obtain the critical clinical information required to make a diagnosis and assign risk in PHACE, while minimizing patient exposure to both anesthesia and contrast agents (eg, gadolinium) and finally, to reduce unnecessary cost. A complete physical examination should be performed at presentation with special attention to ocular abnormalities and midline fusion defects such as sternal pits, clefting, and abdominal raphe (**Figure 4**; available at www.jpeds.com). A screening echocardiogram should be performed in all at-risk children. If abnormalities are identified, a cardiac MRI/MRA is recommended to better delineate the arch and brachiocephalic anatomy. A screening MRI with and without gadolinium and MRA of the head, neck, and aortic arch should be performed as part of the baseline diagnostic evaluation for PHACE. (**Table IV**; available at www.jpeds.com) MRI is not sufficient for delineating arterial abnormalities. If renal function is normal, gadolinium contrast should be used to demonstrate fully the extent of the cutaneous hemangioma and to detect subglottic, periorbital, and intracranial hemangioma(s). Other imaging modalities, such as computed tomography (CT) angiography and catheter-based angiography, may provide better resolution of the vascular anatomy, but are not recommended as initial diagnostic tests because of the potential risks. The invasive nature of catheter angiography and significant radiation exposure outweigh the potential diagnostic benefits, except for evaluation prior to surgical intervention. In institutions with appropriate expertise, a feed-and-wrap technique can be attempted for MRI/MRA in young infants, to avoid sedation or anesthesia.

Risk-Adjusted Health Surveillance Protocol to Facilitate Early Identification and Treatment of PHACE-Related Morbidities

There is significant phenotypic variation in PHACE, affecting both disease severity and risk for progressive morbidity. The results of the initial screening examinations should guide clinical care and future monitoring (**Figure 5**). The following guidelines represent current knowledge; it is understood that clinical guidelines may evolve as new research findings emerge.

Physical Examination. A significant sternal defect and/or abdominal raphe may require a referral to pediatric surgical specialists for evaluation and potential intervention.

Echocardiogram. Intracardiac and aortic arch anomalies identified by screening echocardiogram require urgent evaluation by a pediatric cardiologist. If arch abnormalities are suspected, a cardiac MRI/MRA is recommended to delineate better the arch and brachiocephalic anatomy. Arch obstruction is common and complex in PHACE and may be difficult to appreciate clinically because of the associated aberrant subclavian origin.

Detailed multimodality preoperative imaging is needed to characterize fully the aortic and cerebrovascular arterial anomalies. If nonobstructive aortic arch anomalies are identified, ongoing pediatric cardiology evaluation with yearly echocardiography is recommended as progressive narrowing of coarctation and/or progressive aneurysmal dilation have rarely been observed in children with PHACE with congenital abnormalities of the aortic arch.[24,25]

MRI of Head and Neck. The presence of baseline structural brain abnormalities and the emergence of neurologic signs or symptoms will guide health surveillance. The presence of a Dandy-Walker complex with or without hydrocephalus,

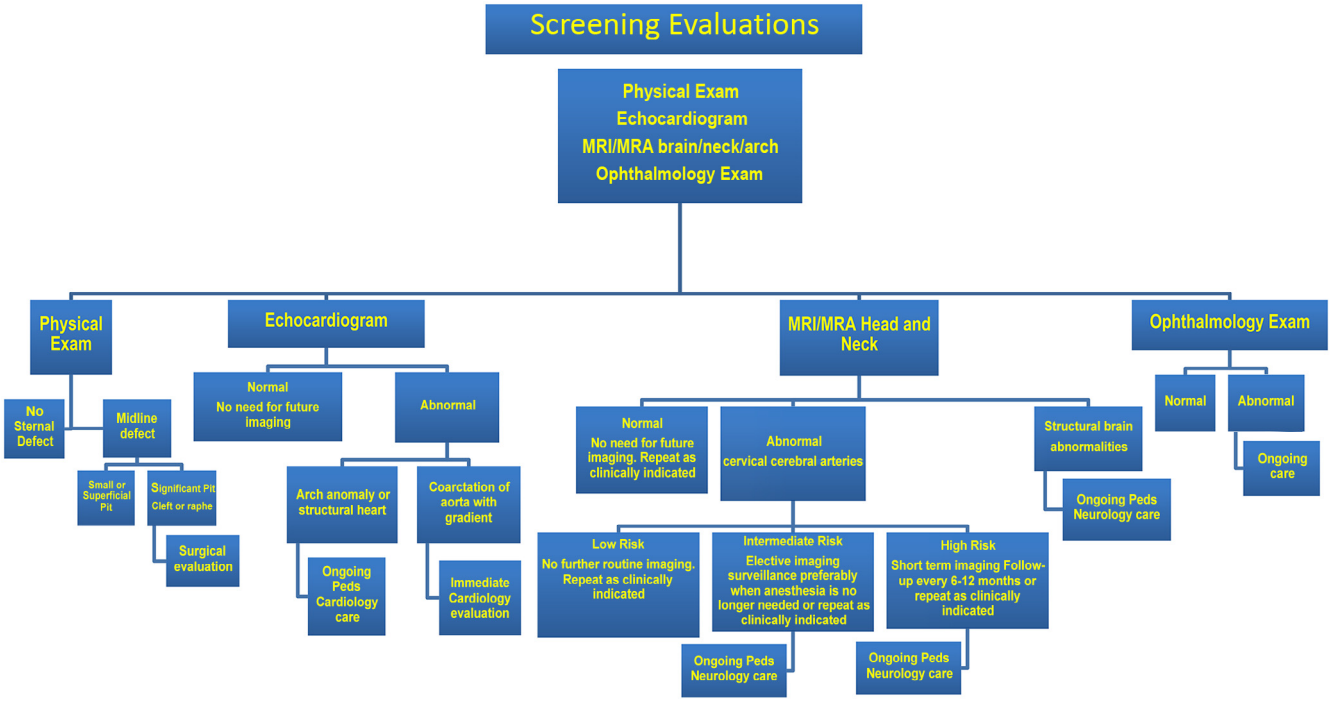

Figure 5. Recommended health surveillance of patients with PHACE based on results of initial screening examinations.

warrants neurosurgical evaluation. Structural pituitary abnormalities or symptoms suggesting endocrine abnormalities should prompt an endocrine assessment. Most structural brain abnormalities are static lesions (eg, unilateral cerebellar hypoplasia and malformations of cortical development) that do not require surveillance neuroimaging. In rare cases, patients with posterior fossa cystic abnormalities, such as Dandy-Walker malformation or arachnoid cyst can develop cyst enlargement or hydrocephalus. The presence of structural brain lesions warrants evaluation and monitoring by pediatric neurologists and/or neurosurgeons for potential symptoms, including developmental delays, seizures, and headaches. Additional neurodiagnostic testing, such as electroencephalography (EEG) for seizures is not recommended as part of routine PHACE screening, but should be performed when clinically indicated.

MRA Head, Neck, and Arch. MRA is an adequate imaging modality to screen for the common cerebral vascular anomalies of PHACE. Other imaging modalities, including magnetic resonance perfusion, may be indicated based on the MRA results. Patients with vascular abnormalities that are associated with an increased stroke risk should be evaluated and managed by clinicians with expertise in pediatric stroke. The initial imaging of the cervical and cerebral arteries can help to categorize patients into one of the risk strata detailed above.

(1) Low Risk – No further surveillance imaging is needed after the baseline scan. Repeat imaging should be done as indicated by the emergence of new signs or symptoms.

(2) Intermediate Risk – Referral to a pediatric neurologist is recommended for risk evaluation and clinical monitoring of neurologic signs and symptoms. Elective imaging surveillance may be done later, preferably when anesthesia is no longer required. If there is narrowing or occlusion of a single artery, the redundancies in the cerebral vasculature will allow for the occlusion of a cerebral artery without consequent stroke and without substantial effects on neurologic outcomes. However, families should be counseled about the significance of unilateral arterial abnormalities as risk factors in later life. Examples include the onset of atherosclerotic disease or in the setting of a traumatic or sports-related vascular injury to the uninvolved side. We recommend that patients avoid contact sports and activities that involve extreme neck positions (eg, wrestling). When an individual is reliant on a single anterior artery, care should be taken to minimize potential traumatic injury to that blood vessel. Patients with marked vessel tortuosity and turbulent blood flow may be at increased risk for thrombus formation or aneurysm in adulthood.

(3) High Risk – Pediatric neurologist referral and short-term imaging surveillance at 6 months and 1 year is recommended. For patients in this category, we believe that the potential risk of progressive vascular changes and stroke outweigh the potential risks of anesthesia for repeat imaging. Specific intervals for repeat imaging and continued surveillance beyond 1 year should be determined on a case-by-case basis by the managing specialists. The use of contrast agents and the specific MRI sequences or use of other imaging techniques used for surveillance

should be determined by the type(s) of abnormalities present. Avoidance of contact sports as described above for the intermediate risk group is also recommended. Although evidenced-based data are lacking, prophylactic aspirin therapy at a dose of 4-5 mg/kg/d up to 81 mg should be considered for high-risk patients. If progressive vascular changes, such as a moyamoya-type vasculopathy, are present, the patient should be referred to a pediatric neurology and neurosurgery team at a tertiary center with expertise in vascular neurology.

Other Long-Term Morbidities Associated with PHACE Syndrome

Treatment of Hemangiomas. Propranolol is the only US Food and Drug Administration (FDA) approved agent for the management of problematic IH and is considered first line therapy in patients with IH requiring systemic treatment. However, controversy exists for its use in patients with PHACE with arterial disease who are at risk for stroke. Siegel et al[10] reported acute ischemic stroke in 2 patients with PHACE on an oral beta-blocker. Both patients were also treated simultaneously with oral corticosteroids, and had severe arteriopathy. Metry et al[26] reported treatment in a group of 32 infants with PHACE and arterial anomalies including 7 patients at high stroke risk. The majority of patients tolerated treatment well. For patients with life-threatening or function-threatening hemangiomas, such as obstruction of the visual axis or airway involvement, treatment with oral propranolol may be considered before imaging data are obtained. Parents should be counseled regarding theoretical increased risks should the child prove to have abnormalities of the cerebrovascular and/or great arteries on subsequent imaging. Lower target doses than the standard 2 mg/kg/d and/or a slower escalating schedule should be considered, and patients should be monitored. The total daily dose should be divided into 3 doses to minimize fluctuations in peak blood levels. The dose may be increased as clinically indicated with appropriate reassessments and monitoring.

Extracutaneous IH arise in children with PHACE and include intraorbital/ periorbital IH resulting in vision impairment, intracranial hemangiomas, segmental IH of the intestinal tract leading to gastrointestinal bleeding, and airway IH causing respiratory compromise. Forty-seven percent of children with classic "beard area" IH and associated airway involvement met the diagnostic criteria for PHACE.[27] Intracranial hemangiomas are generally rare but may be seen with increased frequency in PHACE. They are typically found within the auditory canal or cavernous sinus ipsilateral to other central nervous system anomalies and to the skin IH.[17]

Headache. Headache is more prevalent and severe and may present at an earlier age among persons with PHACE compared with other children.[28] If a patient develops new headaches, an evaluation for secondary headache causes including vasculopathy and cerebral ischemia should be conducted regardless of the presence or absence of abnormalities on the initial MRI. Age-appropriate neurology referral should be considered for any patient with severe headaches, headaches that cause functional disability, headaches that do not respond to simple analgesics, or headaches with suspected secondary etiologies. The presence of arterial abnormalities in PHACE is a relative contraindication for vasoconstrictive headache medicines including triptans, dihydroergotamine, and ergotamine tartrate.

Hearing Abnormalities. Hearing loss and speech-language delays are reported in patients with PHACE. Speech-language delays may be a consequence of hearing deficits, prolonged hospitalizations, or may occur as a result of other neurodevelopmental anomalies. Sensorineural hearing loss is the most common type and is usually ipsilateral to the IH which may involve the ipsilateral cranial nerve VIII.[29] The IH may also lead to conductive hearing loss with eustachian tube compression with otitis media or tympanic membrane involvement.[29,30] Early detection is crucial as some hearing loss is difficult to reverse, but can be managed with amplification or restorative hearing surgery. All patients with PHACE should undergo hearing screening in the newborn period or at the time of diagnosis if not done previously. Individuals with higher risk for hearing impairment should have at least 1 follow-up hearing test even if initial screening is normal.

Dysphagia, Speech, and Language Abnormalities. A subset of individuals with PHACE experience dysphagia, feeding disorders, speech disorders, and/or language delay. This risk seems to be increased in patients with posterior fossa malformations, lip/oropharynx or airway hemangiomas, hearing loss, and those with history of cardiac surgery.[30] Children with these risk factors should undergo initial speech-language evaluation with a pediatric speech-language pathologist no later than 24 months of age and/or referred to the local early intervention program for ongoing monitoring. Earlier evaluation may be indicated if there is evidence of delayed milestones. Children displaying feeding difficulties, failure to advance to solid foods, or possible aspiration, should be referred for evaluation by a pediatric speech-language pathologist at any age. Dysphagia may be secondary to the disease location (lip, oral cavity, and pharynx) or oral motor coordination.

Endocrine Abnormalities. The association of PHACE with endocrine abnormalities is well recognized. Although thyroid dysfunction and hypopituitarism resulting in growth hormone deficiency are the most frequently reported abnormalities, other manifestations of hypopituitarism including hypogonadotropic hypogonadism and adrenal insufficiency have been described.[14,22,31-33] Hypothyroidism may be caused by abnormalities in the hypothalamus, pituitary, or thyroid gland. Ectopic thyroid tissue, and dysgenesis or malformations of the thyroid may also occur. Pituitary dysgenesis can present as an empty sella turcica noted on MRI.[14,31-36] Consumptive hypothyroidism caused by the abnormal production of type 3 iodothyronine deiodinase by large hepatic IH has been rarely reported. Although some infants with PHACE and hepatic hemangiomas have been reported, consumptive hypothyroidism has not to date been reported in patients with PHACE.[37,38] Normal levels

of thyroid stimulating hormone and T4 have been reported in the newborn period in children with PHACE who are subsequently found to have hypothyroidism. Although neonatal screening is diagnostic in some cases, it may miss cases with later onset. Repeat studies are indicated if symptoms related to endocrine abnormalities arise.[31]

Growth hormone deficiency is increasingly recognized in association with PHACE. The majority of reported cases are associated with hypopituitarism with empty or partially empty sella turcica noted on MRI but may also occur without evident central nervous system malformations.[39] Neonatal hypoglycemia can be a sign of hypopituitarism and should prompt additional endocrinologic evaluation in patients with PHACE. Other consequences of pituitary dysfunction include hypogonadotropic hypogonadism manifesting with delayed pubertal onset and late-onset adrenal insufficiency. These findings emphasize the importance of focused assessment of height, weight, and developmental milestones in the care of children with PHACE.

Dental Anomalies. Enamel hypoplasia is a newly recognized association with PHACE. A study of 18 children with PHACE or possible PHACE revealed that 28% had enamel hypoplasia. All of the affected children had intraoral hemangiomas; 5 of 11 (45%) with intraoral hemangiomas had enamel defects. Children with enamel hypoplasia are at increased risk for developing caries. We recommend that children with PHACE be examined for the presence of intraoral hemangiomas and if present should be referred to a pediatric dentist by 1 year of age for early screening and management with intraoral hemangioma.[40]

Psychological Impact and Quality of Life. Although the medical complications and morbidity have been well described in PHACE, little qualitative or quantitative data about the psychological and social implications and quality of life (QoL) in patients with PHACE have been reported. However, the psychosocial impact of IH has been investigated.[41]

Notably, Tanner et al[42] interviewed the parents of 25 children with IH and reported parent's feelings of disbelief, guilt, sadness, panic, or fear related to their child's hemangioma. Social interactions were described as stressful by most parents and accusations of child abuse were reported by 36% of interviewees. When generic QoL instruments and hemangioma-specific questions were administered to Dutch children age 1-15 years with a history of IH, panic and disbelief among parents were reported. In addition, the parents related that public reactions made them and their children more aware of the hemangioma.[43] Moreover, the Infantile Hemangioma QoL Scale, a validated QoL scale in children under the age of 18 months with hemangiomas, supports a significantly larger effect on QoL with increasing hemangioma size and facial location.[44] Physicians caring for children with PHACE should address parental concerns regarding their child's hemangioma, including the psychosocial ramifications, and make appropriate referrals for support. Patient support groups such as the PHACE Family Community can be invaluable in helping families navigate the medical and emotional complexities that can arise both with initial diagnosis and over time. ■

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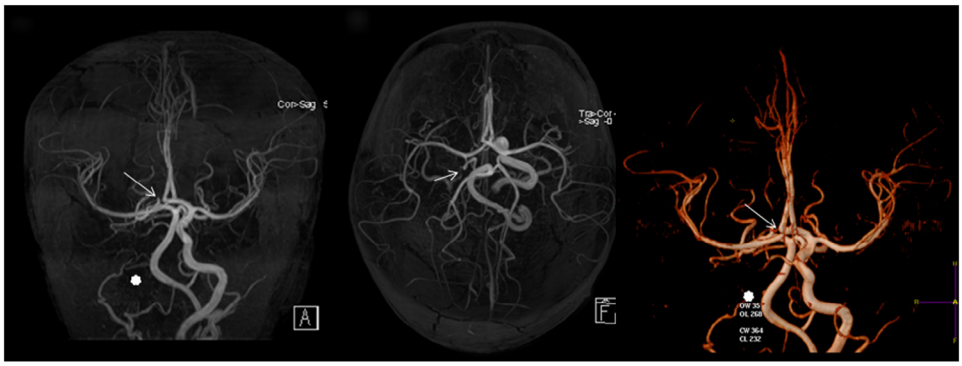

Figure 2. MRA of the brain (maximum intensity projection and three dimensional reformatted images obtained by time of flight Multiple Overlapping Thin Slab Acquisition technique) in a female child with definite PHACE demonstrating absence of the right internal carotid artery with reformation of the right middle and anterior cerebral arteries via circle of Willis collaterals (anterior and posterior communicating arteries).

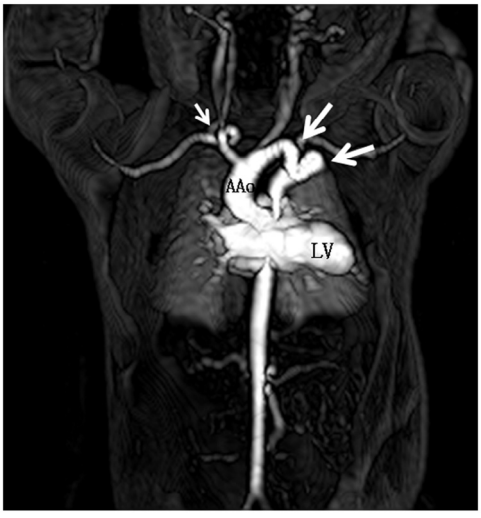

Figure 3. Cardiac MRI of the aortic arch and brachiocephalic vessels in a patient with PHACE with coarctation of the aorta and long segment bizarrely twisted areas of narrowing in the transverse arch (*large arrows*). The right subclavian artery also has a "corkscrew" twist in the proximal segment (*small arrow*). The left ventricle (LV) and ascending aorta (AAo) are normal.

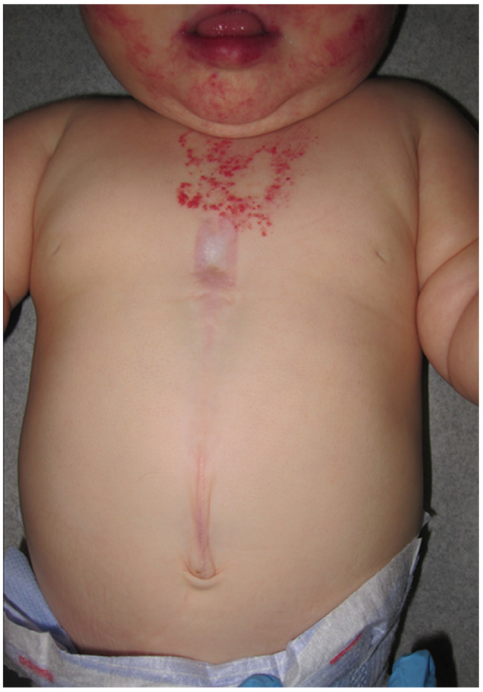

Figure 4. Example of 3-month-old female with midline defect of sternal cleft and abdominal raphe and definite PHACE.

Table IV. Magnetic resonance technical specifications for screening at risk children

- Magnet strength adequate to detect arterial anomalies in young children
- MRI of brain and neck
- Gadolinium contrast
- MRA of brain, neck, and aortic arch
- MRA parameters appropriate to the patient's age
- Exclusion of common artifacts
- The examination should be performed at a center familiar with imaging children, and with expertise in the interpretation of brain structural and vascular lesions, preferably with neuroradiology training