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Facing PHACE Twenty-five Years Later

Review and Perspectives on Management

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Abstract

Objectives: To review the key features of PHACE syndrome over the past 25 years, highlighting evaluation, management, current gaps in knowledge, and potential next steps in research and patient-centered care.

Methods: Literature review and synthesis of expert opinion.

Results: PHACE is a congenital neurocutaneous syndrome in which affected patients have posterior fossa abnormalities, hemangiomas, arterial anomalies, cardiac anomalies, and/or eye anomalies. Since its discovery 25 years ago, the scientific and medical communities have made strides in understanding and developing best practice approaches to diagnosis, outcomes, and surveillance. More research will be needed to fully elucidate the pathogenesis of this condition as well as long-term outcomes. We offer suggestions for healthcare maintenance to coordinate and streamline multidisciplinary patient care.

Conclusions: Our understanding of PHACE syndrome has grown immensely since its discovery. As we continue to learn about long-term outcomes and the importance of surveillance into adulthood, a multidisciplinary and patient-centered approach is critical to optimize care for individuals with this disease.

Keywords: PHACE syndrome, PHACES, infantile hemangioma, hemangioma

Introduction

Infantile hemangiomas (IH) are common, and most do not have associated anomalies. However, a small subset, primarily those that are larger and "segmental," that is, involve a territory of skin rather than arising from a singular focus, have associated structural anomalies. In 1991, Burns et al[1] reviewed the existing medical literature and emphasized the few known IH-associated structural anomalies: midline ventral anomalies such as sternal defects and supraumbilical abdominal raphe, right-sided aorta and aortic arch coarctation, and—in the case of lower body IH—sacral and genitourinary anomalies. Two years later, Reese et al[2] published a case series of 9 individuals with facial hemangiomas in association with Dandy–Walker and other posterior fossa brain malformations. Interestingly, one of the cases had midline clefting and aortic arch coarctation. Several others had other anomalies including microphthalmos and dilated cerebrovascular vessels. Twelve years before this, Pascual-Castroviejo, a Spanish neurologist, described a case series of 7 women, with facial and scalp "capillary hemangiomas" and associated anomalies including Dandy–Walker complex, cerebellar hypoplasia, arterial "angiomas," and abnormalities in the cerebrovascular circulation. Arguably, this was the first case series of what later came to be known as PHACE syndrome.[3] Pascual-Castroviejo called these findings "cutaneous hemangioma–vascular complex syndrome," and, in Spain, this was called "Pascual-Castroviejo syndrome II." The association of sternal anomalies and large hemangiomas had additionally been described a few years previously by Hersh et al[4] as "sternal malformations and vascular dysplasias."

Twenty-five years ago, in 1996, Frieden et al[5] reported 2 cases of large segmental IH and structural anomalies including central nervous system (CNS) arterial anomalies, cardiovascular anomalies, and ophthalmologic anomalies, as well as midline clefting. They proposed the acronym PHACE to describe a constellation of findings: Posterior fossa brain malformations, Hemangioma, Arterial lesions, Cardiac abnormalities and aorta Coarctation, and Eye abnormalities.

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The letter "S" was subsequently proposed as an addition to the acronym (ie, PHACES) to denote sternal clefting. Both acronyms are used; for this review, we will use PHACE. In the 25 years since the acronym was first proposed, PHACE has become a well-recognized neurocutaneous disorder with hundreds of citations in the medical literature. It is uncommon but not rare, likely similar in incidence or slightly more common than the better known neurocutaneous disorder, Sturge-Weber syndrome.[6]

In a comprehensive review of PHACE, published in 2001, Metry et al[7] reported 14 additional patients and found 116 additional previously reported cases. These authors emphasized that PHACE represents a *spectrum of anomalies*, with 70% of children having only one extracutaneous manifestation of the syndrome, most commonly CNS arterial anomalies. The skin changes in many previous reports had been mistaken for port-wine stains with some cases misdiagnosed as "atypical Sturge-Weber syndrome." The introduction of PHACE as an acronym, while not describing an entirely novel disorder, did "connect the dots" by linking the features described in previous reports. This ultimately allowed for easier recognition of segmental IH of the head and neck and associated anomalies. In 2001, PHACE became officially listed in Online Mendelian Inheritance in Man (OMIM), a catalog of human genes, genetic disorders, and traits, via identification number 606519.

Publications expanding our knowledge and understanding of PHACE have continued. In 2010, Haggstrom et al[8] conducted a prospective study of large facial IH to determine the risk of PHACE in this setting. Of 108 patients with large facial IH, 33 (31%) were diagnosed with PHACE. The risk for PHACE syndrome was higher in infants with larger hemangiomas and in those with hemangiomas that encompassed >1 facial segment; the most common extracutaneous findings were anomalies in arteries of the cerebrovasculature (91%) and cardiac anomalies (67%).[8] In 2010, Hess et al[9] published a study of the cervical and intracranial arterial anomalies in 70 patients with PHACE. They categorized these anomalies into 5 groups: dysgenesis, narrowing, nonvisualization, primitive embryonic carotid-vertebrobasilar connections, and anomalous arterial course or origin. Another major advance was the establishment of consensus-derived diagnostic criteria,[10] which were subsequently revised in 2016.[11] A PHACE patient registry was established in 2007 and interested physicians or patients can obtain information on the registry at https://childrenswi.org/medical-care/birthmarks-and-vascular-anomalies-center/conditions/phace-syndrome/phace-syndrome-registry/contact-us.

A North-American patient support organization, the PHACE Syndrome Community, (https://www.phacesyndromecommunity.org/) was established in 2013. A PubMed search of PHACE in March 2021 yielded nearly 400 citations.

Clinical features of PHACE

Although the PHACE acronym emphasizes key elements of the syndrome, it was never intended to imply that *all of the elements* of the acronym are present in every individual with this diagnosis. Updated consensus guidelines published in 2016 established major and minor criteria for diagnosis of definite and possible PHACE (Table 1). They emphasize that in addition to facial IH certain additional criteria can establish the diagnosis even in the absence of any other findings.[11] These diagnostic criteria will likely evolve over time with additional clinical observation. Additionally, when the pathogenesis of PHACE is elucidated, diagnostic criteria will likely change. The following sections discuss the clinical features in PHACE in order of prevalence with an emphasis on establishing an approach to screening, surveillance, and patient-centered care.

Infantile hemangioma

Segmental facial IH are a hallmark of PHACE, and their presence is the most frequent finding prompting evaluation for this condition. The hemangiomas of PHACE often present with large (≥5 cm) red plaques with or without a deep component. At birth or early in infancy, they may be flat and resemble a port-wine stain. Other early presentations include areas resembling a bruise or an area of blanched skin often with faint overlying telangiectasias. In some cases, the hemangiomas are clustered papules rather than a contiguous patch or plaque (Figure 1).[5,12,13] Yet, another clinical variation is a segmental vascular patch with negligible to absent proliferative IH (so-called IH with minimal or arrested growth).

Approximately, one-quarter to one-third of infants with segmental facial hemangiomas are found, with further evaluation, to meet diagnostic criteria for PHACE.[6,8] In addition to facial IH, the diagnostic criteria established in 2016 includes segmental IH of the scalp as an at-risk anatomic location.[11] Many examples of IH in patients can be seen at the following links: www.showyourphace.com, https://positiveexposure.org/frame/phace-syndrome/, and https://www.phacesyndromecommunity.org/. Figure 1 is a map of facial patterns of distribution of IH (so-called segments). Segments 1, 3, 4, and the newly defined scalp segment all have a relatively high risk of PHACE, whereas segment 2 has a lower risk of PHACE (A. A. Endicott et al, unpublished data). Periorbital IH without contiguous facial involvement also appears to be a potential at-risk area for PHACE, reflected in the diagram by a dotted line around the left orbit. The orbital structures develop as so-called optic vesicles and thus can arguably be considered a separate segment, making their potential association with PHACE understandable.[14]

Although the presence of a large facial or scalp hemangioma is typically a prominent, even defining, feature of PHACE, it is not an absolute requisite for diagnosis (Table 1). Individuals lacking facial IH can meet diagnostic criteria for definite PHACE if they have an IH of the neck, upper trunk, or trunk and proximal upper extremity (so called PHACE without face) plus 2 other major criteria (Table 1). A diagnosis of possible PHACE can be made even if a patient has no hemangioma at all but 2 other major criteria. At times, an IH is present without overt skin involvement, such as in cases of orbital, throat, or airway hemangiomas.[6,14–19] If there is ever uncertainty about the diagnosis of IH, biopsy of affected skin can be helpful, demonstrating strong GLUT1 positivity in blood vessels.[16,20–22] Discussion of management strategies for PHACE-associated IH are discussed below.

Although not the topic of this review, lower body IH can also be associated with structural anomalies (so-called LUMBAR syndrome: Lower body IH and other skin defects, Urogenital anomalies and Ulceration, Myelopathy, Bony deformities, Anorectal malformation and Arterial anomalies, and Renal anomalies).[23] Of note, LUMBAR has also be referred by other acronyms, that is, PELVIS and SACRAL syndromes, though all refer to the same condition. Like those in PHACE, anomalies in LUMBAR tend to correlate with the

Table 1.

Major and Minor Diagnostic Criteria for Definite and Possible PHACE From 2016 Consensus Guidelines[11]

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.
†Kinking, looping, tortuosity, and/or dolichoectasia.
Reproduced from Garzon et al.[11]

region of the cutaneous IH. Many authors have speculated that LUMBAR and PHACE have a similar pathogenesis, with PHACE representing anomalies of the upper body and LUMBAR, the lower body.[23–25] Among the findings seen in both are segmental IH, arterial anomalies, areas of congenital scarring (eg, aplasia cutis congenita), tag-like areas, and an increased propensity for ulceration of the affected area(s).

Extracutaneous IH

There are numerous reports of extracutaneous hemangiomas in PHACE in diverse locations with varying potential morbidities. Cutaneous IH involving the preauricular and mandibular skin (so-called beard distribution; segment 3 on IH map) confer an increased risk of airway IH, with bilateral S3 disease being the highest risk.[26,27] The risk appears to be even higher in PHACE patients than those without PHACE. In 2 studies, with 55 and 23 PHACE patients respectively, 40% and 52% had airway IH.[26,28] Similarly, in a study of 17 infants with beard distribution or already identified airway hemangiomas, 47% eventually were diagnosed with PHACE.[29] Clinical presentation can include stridor, barking cough, or respiratory distress, particularly if the hemangioma is in a location that compromises the airway, most often in a subglottic location. The use of propranolol has resulted in improved outcomes for airway IH, with far fewer patients requiring tracheostomy.[26] Dosage adjustments to higher or prolonged doses of systemic medications may be needed to control airway disease (see "IH management" section).[27,30]

Hemangiomas at visceral sites including the gastrointestinal tract, liver, mediastinum, brain, spine, internal auditory canal (IAC), and other sites have been reported.[31–33] Metry et al[31] reported 4 new cases and reviewed 43 previously reported cases of segmental IH in association with visceral IH. Though not all had PHACE, 40% met diagnostic criteria for PHACE. The most common sites of internal organ involvement were the liver, followed by the gastrointestinal tract, brain, mediastinum, and lung.[31] At least 10 patients with PHACE and GI involvement have been reported, most requiring multiple transfusions due to large segmental hemangiomas of the GI tract.[33] In one case, intussusception was a feature.[34] Multimodal therapies are often required. While we do not advocate routine evaluations to exclude visceral IH, awareness of this potential association is important. For example, GI bleeding in patients with PHACE should be carefully evaluated and not assumed to be due to a more common cause such as cow's milk protein intolerance.

IH of the IAC is a well-documented site of involvement.[9,18] IAC hemangiomas are typically identified on imaging (Figure 2C). They may play a role in hearing deficits found in PHACE, even in infants who passed their neonatal hearing

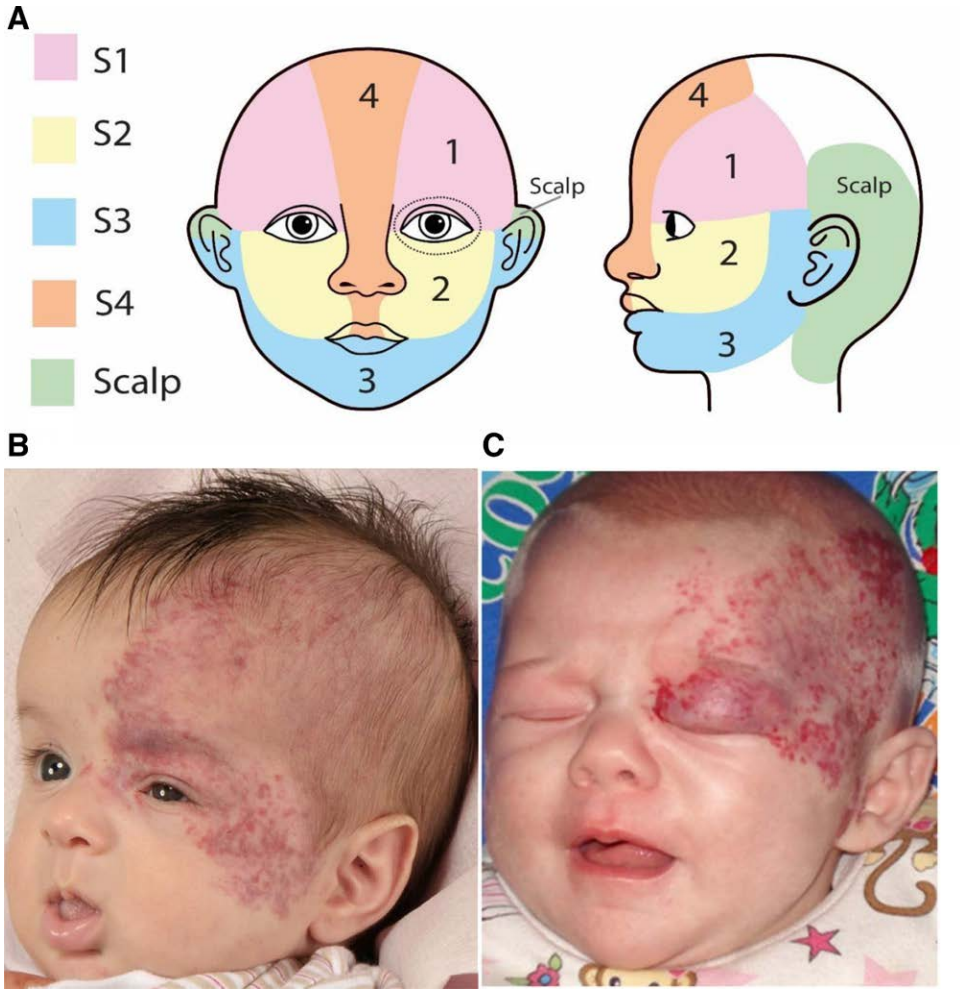

Figure 1. (A) Facial segment distribution as illustrated by Endicott et al, unpublished data (B and C) with images of early S1 hemangiomas taken from Thomson et al[12] (B) and Garzon et al[11] (C). The large flat areas, particularly note in (B) are sometimes mistaken for port wine stains. C, There is soft-tissue swelling involving the upper eyelid, whereas the temple IH is relatively flat, albeit with the multiple, minimally raised papules.

screen (see discussion below under "Hearing loss").[35–37] Viswanathan et al[32] reported on 15 patients from a large vascular anomalies center with IH involving the neuraxis, either brain or intraspinal sites. At least 3 of these had definite PHACE and all had hemangiomas of the head and neck.[32] Intracranial IH noted on MR imaging during PHACE evaluation is not rare. Often brain or IAC IH is found incidentally on imaging, and they rarely cause overt symptoms.[37] They tend to exist in contiguity with cranial nerves, particularly CN VII. Some have suggested that it may be as common or more common than other diagnostic features such as coarctation of the aorta or ventral developmental defects.[37]

Arterial anomalies

Arterial anomalies are the most common extracutaneous finding in PHACE, seen in as many as 57% of affected individuals.[7] Most anomalies involve medium and large vessels throughout the cardiovascular system with the majority of disease in the head, neck, and chest. Grossly, arterial anomalies can present as dysplasia, stenosis, absence or hypoplasia, tortuosity, or persistence of fetal vasculature.[38] Histopathologic studies have shed insight into the derangement underlying these anomalies. In a study evaluating arterial anomalies in PHACE, 5 of 7 patients whose aorta specimens underwent histological examination after coarctation correction showed marked scarring and necrosis with loss of arterial smooth muscle and elastic fibers in the intima and media. The additional 2 patients had smaller areas of decreased smooth muscle in the tunica media and showed increased adventitial collagen deposition. Compared to control specimens in this study, only 5 of 52 controls displayed similar findings of medial necrosis and these were attributed to suture scar formation in 3.[39] In a postmortem evaluation of a 5-year-old with PHACE whose cause of death was related to bacterial aortitis, sections of the aorta showed extensive degeneration of the medial and adventitial portions. Apart from tortuosity, the other major arteries appeared grossly normal, but microscopic evaluation showed widespread fibrointimal thickening and medial changes including disorganized fibromuscular proliferation, cystic medial degeneration, mucopolysaccharide deposition, and disruption and/or excessive duplication of the internal elastic lamina. Histology of cerebral arteries showed similar findings including thickening and fibrosis of the media and intima as well as variable loss of elastica, distortion of the vessel wall, and surrounding dystrophic collateral vessels.[40] These findings suggest that arterial dysplasia, at least in some patients, may be more extensive than is appreciated clinically, involving many medium to large vessels, even those that appear normal

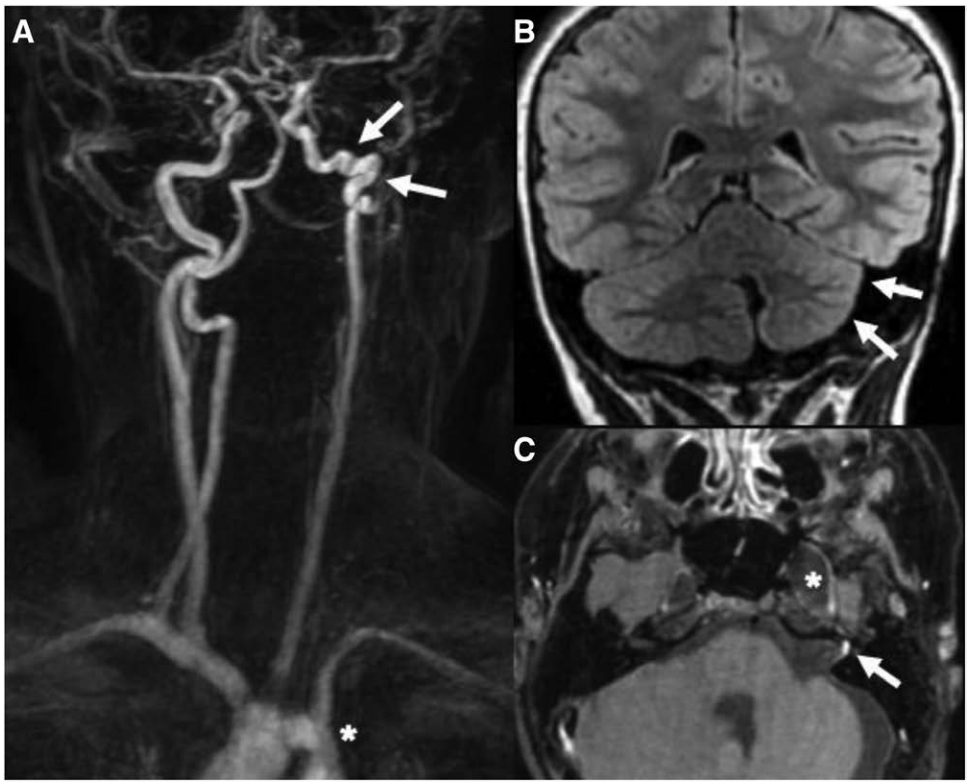

Figure 2. Representative images from a patient with PHACE. (A) MRA of the head and neck, with severe dysplasia of the left internal carotid artery (arrows) and aortic coarctation (*). (B) Coronal T2 FLAIR image showing unilateral left cerebellar hemisphere dysgenesis (arrows). (C) Enlarged left internal auditory canal containing a hemangioma and dural ectasia of the trigeminal cistern (*). MRA, magnetic resonance angiogram; PHACE, posterior fossa brain malformations, hemangioma, arterial lesions, cardiac abnormalities and aorta coarctation, and eye abnormalities.

on imaging modalities. Awareness of arterial anomalies in both the CNS as well as cardiac and systemic vasculature is crucial, as these pose some of the greatest risks to patients, particularly the risk of progressive arteriopathy.[11] In consultation with relevant specialists, serial evaluations including imaging may be required, depending on initial evaluation or emergence of any unsuspected signs or symptoms. Images of representative arterial anomalies can be found in Figure 2.

Arterial anomalies of the CNS

Arterial anomalies of major cerebral or cervical arteries represent one of the major diagnostic criteria for PHACE and include persistent fetal vasculature or dysplasia, stenosis, absence or hypoplasia, and aberrant origin or vascular course. Cerebral artery aneurysms are considered a minor criterion for diagnosis (Table 1).[11] Rarely, complex vascular networks (rete mirabile) have also been reported.[41] A subset of these abnormalities of cerebral or cervical arteries are thought to increase risk for ischemic stroke and have been categorized by severity of the cerebrovascular disease into low-, intermediate-, and high-risk groups (Table 2).[11,42,43] Designation of these groups should be conferred in conjunction with relevant specialists (eg, neuroradiologists and neurologists, ideally those with expertise in neurovascular disease and stroke).

Among the features conferring a higher risk for stroke are aplasia, hypoplasia, or occlusion of a major cerebral artery, multiple vessel involvement, concomitant coarctation of the aorta, or incomplete Circle of Willis.[43] In a series of 15 patients who sustained a stroke, 59% had nonvisualization of a major cerebral artery.[43] Age at stroke onset ranged from 3 months to 5 years in this series, but has also been reported in older children and adults.[38,44–47] Although the benefits of antiplatelet therapy for stroke prevention are uncertain, guidelines based on expert consensus suggest that aspirin (3–5 mg/kg/d up to 81 mg) is reasonable in children with high-risk cerebrovascular abnormalities related to PHACE.[11]

Because some children with PHACE develop progressive arteriopathies, surveillance imaging is important to identify children who might benefit from medical or surgical interventions.[11,48,49] Progressive arteriopathies associated with cervicofacial hemangioma were observed by Burrows et al[50] in 1998 in a series of 8 patients. Four of the children developed progressive arterial stenosis over time and 3 children developed moyamoya vasculopathy. Moyamoya vasculopathy is a chronic, progressive steno-occlusive condition that affects the major cervical and cerebral arteries, resulting in the development of collateral circulation over time to carry blood around narrowed or blocked vessels. In a review of 96 patients with neuroimaging, arterial occlusions and stenoses were identified in 20.9% and 18.3%, respectively, and 8.3% had a unilateral or bilateral moyamoya vasculopathy.[51] Another case series and literature review of moyamoya vasculopathy related to PHACE described 21 patients with mean age of 22.7 months at diagnosis (range of 1 month to 14 years) and mean age of onset of neurological symptoms at 33.6 months.[52] Surgical revascularization may be an option to treat PHACE patients with moyamoya vasculopathy.[51–54] Patients who have intermediate- or high-risk neurovascular anomalies, progressive neurovascular changes or moyamoya

Table 2.

Risk Stratification for Acute Ischemic Stroke in Arterial Anomalies in PHACE with Associated Follow-up and Surveillance Recommendations

Risk Category	Characteristics	Follow-up and Surveillance
Low risk	Anomalies frequently seen in the general screening population (PFO, PDA)	No further imaging is needed after an initial, unless new signs or symptoms emerge as the patient ages
	Embryonic arteries, anomalous arterial origin or course, circle of Willis variants, and other isolated insignificant variants	
Intermediate risk	Non-stenotic dysgenesis including ectatic or segmentally enlarged arteries	Referral to a pediatric neurologist is recommended
	Narrowing or occlusion of arteries proximal to the Circle of Willis with no perceived hemodynamic risk	Elective surveillance imaging may be done as the child grows up—preferably when anesthesia is no longer required
	Requires evaluation of the patency of the circle of Willis	Families should be counseled about the significance of unilateral arterial abnormalities including risk of atherosclerotic disease and trauma (eg, contact sports)
High risk	Significant narrowing >25% or occlusion of principal cerebral vessels within or above the circle of Willis resulting in an "isolated" circulation	Referral to pediatric neurologist is recommended
	Tandem or multiple arterial stenoses that may result in diminished cerebral perfusion or stenosis in the setting of concomitant aortic stenosis	Timing of surveillance imaging should be decided in conjunction with a neurologist
	Imaging findings consistent with chronic or silent ischemia or progressive steno-occlusive disease	Families should be counseled about the significance of unilateral arterial abnormalities including the risk of atherosclerotic disease and trauma (eg, contact sports)
		Aspirin therapy at 3–5 mg/kg/d up to 81 mg should be considered
		If progressive vascular changes such as moyamoya vasculopathy occur patient should be referred to a pediatric neurology and neurosurgery team for evaluation for surgical intervention

Adapted from Garzon et al, 2016 Consensus Guidelines.[11]

vasculopathy should consult with pediatric neurology and neurosurgery.[11]

Children with PHACE may also be at an elevated risk of arterial dissection and ischemic stroke. A small case series described two patients with PHACE who had ICA dissection detected on neurovascular ultrasound, which was thought the likely cause of their ischemic stroke.[46] Both patients were considered high risk for stroke: one had moyamoya collaterals and severe stenosis of the left carotid siphon and the other had a prior stroke. An additional report of a patient with severe headaches identified a dissection of the ICA.[49] It is possible that vasculopathy progression and stroke are underreported in the literature because signs and symptoms of a stroke in a child are sometimes missed, PHACE patients do not always receive serial imaging, and some imaging modalities may miss subtle changes.[43,49]

Cardiac and extra-CNS arterial anomalies

Cardiac anomalies and certain extra-cranial arterial anomalies are important diagnostic features of PHACE (Table 1). The reported prevalence of these anomalies ranges from 21% to 67%.[8,11,39] The largest study to date comes from patients in an international PHACE registry.[39] Of 150 evaluable patients, 62 (41%) had cardiovascular anomalies. Patent foramen ovale and patent ductus arteriosus were excluded (since they are common in the general population). Aberrant origin of a subclavian artery was the most common anomaly, present in 31 (21%) of 150 subjects, with aortic coarctation the next most common, present in 28 (19%). Other arterial anomalies include right-sided aortic arch and vascular rings.[39,55]

In contrast to aortic coarctation from other causes, those found in PHACE more often involve the transverse aorta. In the study above, the majority with coarctation (57%) had both subclavian arteries arise distal to the aortic obstruction, a finding with clinical importance because blood pressure measurements used to screen for coarctation can be normal, leading to missed diagnoses. Other reported aorta anomalies include descending arch abnormalities, long segment obstruction, and segments of aneurysmal dilation.[39,56] Tortuosity of the arch and stenosis of arch branches have also been documented.[39,57,58] Another difference from non-PHACE–associated coarctation is the lack of aortic or mitral valve anomalies in PHACE, which are very common in aortic coarctation from other causes.[39,59]

The most common intracardiac anomalies found in the registry cohort was VSD in 19 patients (84% of those with structural cardiac anomalies). Only 3 had complex heart disease including tetralogy of Fallot and tricuspid atresia.[39] Other reported findings in PHACE have included pulmonary stenosis, atrial septal defect, bicuspid aortic valve, ectopia cordis, and Holmes heart.[19,60,61] These findings taken as a whole highlight the importance of echocardiogram in the diagnostic workup in all cases of suspected PHACE.[11,39] In the PHACE registry, 23 of 62 (45%) subjects required surgical or procedural interventions for their cardiovascular anomalies.[39] The frequency of or need for ongoing care should be based on the recommendations of cardiology or other relevant specialists.[11]

Posterior fossa/structural brain abnormalities

A classic structural brain anomaly in PHACE is the Dandy–Walker Complex, though some have argued that unilateral cerebellar hypoplasia is actually a more characteristic finding.[18] Other brain anomalies, both infratentorial and supratentorial, have been described (Table 1).[5,11,18]

There have been 2 large studies evaluating MRI and CT imaging in PHACE, identifying brain anomalies in the

prevalence of 41% and 35%, respectively.[9,18] Posterior fossa abnormalities were more common than supratentorial abnormalities, an observation supported in case reports and reviews.[7,18,43,62] When supratentorial malformations are present there are often concomitant posterior fossa malformations.[18] Structural abnormalities are commonly ipsilateral to arteriopathies and/or the facial hemangioma. Some have hypothesized that PHACE-associated structural abnormalities, including cerebellar hypoplasia, can be attributed to regional ischemia from adjacent arterial anomalies. However, reports of structural anomalies without adjacent arterial anomalies suggest that other mechanisms, such as abnormal signaling, could be playing a role.[7,9,11,18,63]

Recent studies have highlighted the role of prenatal ultrasound and MRI to predict PHACE in utero.[64–66] With continued research, prenatal imaging of fetal brains may help to identify the likelihood of PHACE before birth.

Eye anomalies

In addition to the impact that the presence of a periorbital IH can have because of its direct impingement on the eye (strabismus, amblyopia, ptosis, and nasolacrimal blockage), several structural anomalies of the eye have been reported in PHACE and contribute to major and minor diagnostic criteria.[11] These can be divided into posterior segment abnormalities (morning glory disk anomaly, persistent fetal vasculature, peripapillary staphyloma, retinal vascular anomalies, optic nerve hypoplasia and atrophy, choroidal hemangioma, and retinal coloboma), and anterior segment anomalies including cataracts, microphthalmia, conjunctival hemangioma, posterior embryotoxon, Mittendorf dots, corneal opacity, sclerocornea and iris coloboma, heterochromia or hypoplasia, or vessel hypertrophy. Other reported ocular abnormalities include congenital glaucoma, cryptophthalmos, proptosis, Horner syndrome, and congenital third or fourth nerve palsies.[67]

Beyond their diagnostic importance, some, but not all, eye anomalies can have a profound impact on vision. Overall the incidence of associated structural eye anomalies in PHACE is 20% or less, and they are most frequent in individuals with IH in the periorbital area or involving the frontotemporal and frontonasal skin (so-called S1 and S4, Figure 1).[10,18,68] Some have questioned the utility of eye exams in *all* patients with suspected or diagnosed PHACE[68]; however, we continue to advocate for this evaluation, except in severely resource-limited settings, to assure that no occult eye disease is present and to potentially aid in diagnosis. Evaluation is imperative when the IH involves the periorbital skin or areas in close proximity because of the additional risks to the ocular axis, including strabismus, astigmatism, and other direct effects of the IH itself.

Sternal and other midline defects

Ventral midline anomalies including sternal clefting, absence of the sternum, and as well as supraumbilical raphe are uncommon but well-documented findings in PHACE. Other midline anomalies including lingual or ectopic thyroid and sternal hamartomas have also been described. There are also rare reports of omphaloceles and midline facial anomalies.[11,69] Feigenbaum et al[70] presented a case series of 9 patients with definite or possible PHACE with midline ventral blanching without overt clefting. They suggested that the errors in the midline represent a range of manifestations from ventral blanching without overlying skin changes to raphe to absence of sternum and ectopia cordis at the more extreme end of the spectrum.[58,68] Approaches to surgery for extensive sternal defects in PHACE have been proposed.[71]

Other examples of midline abnormalities include tag-like growths involving the chin, neck and other ventral midline sites. A histopathologic study of elevated midline lesions in PHACE patients showed a variety of findings including rhabdomyomatous mesenchymal hamartomas, verrucous epidermal hyperplasia with vascular proliferation, and folliculosebaceous cystic hamartoma.[72]

Endocrine abnormalities

Although the "E" in PHACE stands for "eye," it could just as easily stand for "endocrine." There are many case reports of endocrine abnormalities in patients with PHACE. These include hypothyroidism, hypopituitarism, growth hormone deficiency, hypogonadotropic hypogonadism, and central adrenal insufficiency.[11,73] Signs and symptoms may be initially missed or attributed to another etiology, resulting in a delay in diagnosis. Thyroid dysfunction and hypopituitarism leading to growth hormone deficiency are the most common endocrinopathies.[11] In a study of 20 PHACE patients with endocrine abnormalities, 55% had hypothalamic-pituitary dysfunction and 50% had primary hypothyroidism due to thyroid dysgenesis.[74] In a radiographic review of 55 patients, 18% had anomalies of the pituitary gland.[18] Of note, although consumptive hypothyroidism from type 3 iodothyronine deiodinase has been reported in patients with hepatic IH, this has not been reported in PHACE.[11,73]

Endocrine abnormalities may not be evident in the newborn period or detected on newborn screening.[74,75] In general, patients with midline structural cranial anomalies should be evaluated for possible hypopituitarism. Any PHACE patient exhibiting poor growth (ie, "falling off growth curve"), failure to thrive, or delayed puberty should be referred for endocrine evaluation for possible endocrinopathy.[11,38,75] Growth hormone deficiency in particular can be erroneously attributed to hypothyroidism or low cortisol levels.[76]

Headaches

Headaches are one of the most common chronic, persistent morbidities of PHACE. The largest study addressing the subject of headaches in PHACE found that of 83 patients in the PHACE registry, 63% reported headaches. They were more common in girls and began at a relatively young age with a mean age of onset of 4 years.[77] The majority had associated migraine symptoms including nausea, photophobia, and phonophobia. The frequency of headaches was weekly in 30% and lasted for more than an hour in 85%. The frequency of headaches may be even more common in adults: 15 of 18 adult patients in the PHACE registry (83%) reported headaches, with triggers including stress, dehydration, and fatigue.[72] Neurology referral should be considered for patients with severe, disabling headaches or those that do not respond to over the counter analgesics.[11] New onset headaches or change in headache quality may warrant neuroimaging.[11,38]

Hearing loss

Hearing loss, while not a diagnostic criterion for PHACE, has emerged as a relatively common association. Importantly,

hearing deficits may be present even if there was a normal neonatal hearing screen.[36] Sensorineural hearing loss is the most common type, but conductive and mixed hearing loss have also been reported, particularly when there is concomitant middle ear and mastoid effusion.[36] Many, but not all, patients with hearing loss have IAC hemangiomas.[35,36] In a series of 12 patients with hearing evaluations and imaging data, 5 of whom had hearing loss, the size of IAC hemangiomas did not seem to impact hearing.[36] Moreover, the hearing loss did not always correct with IAC hemangioma involution nor did propranolol therapy reliably improve hearing. Nonetheless, systemic therapy should be strongly considered to treat IAC hemangiomas, since involution has sometimes reversed sensorineural hearing loss.[78] Ultimately, the hearing loss in PHACE is likely multifactorial and further evaluation will be necessary to fully understand this process.[79]

Because initial newborn hearing screening may be normal, we recommend that all patients with PHACE have repeat audiologic testing. The risk of hearing loss is particularly high with extensive cutaneous hemangiomas involving the ear, pre-auricular skin and if imaging abnormalities of the IAC are present.[11,36] Hearing problems can continue into adulthood, as 33% of adult PHACE patients have reported difficulties with hearing including Meniere's disease ipsilateral to the original facial hemangioma, hearing loss, tinnitus, and a "blood rushing" sound.[72] Further research into mechanisms and the natural history of hearing problems in PHACE should be a priority to help further characterize long-term outcomes.

Neurodevelopment impairment (motor delay, language delay, and cognitive impairment)

Neurologic and cognitive impairments including feeding and swallowing difficulties, language delay, motor delay, hypotonia, and muscle weakness have been reported in case series and case reports, but their true prevalence in PHACE is unclear.[80] In a study evaluating children referred for neurodevelopmental evaluation, either due to structural brain abnormalities or concern for delay by parents, 70% exhibited developmental delay or an abnormal neurologic exam. Gross motor delay was the most common finding followed by language delays, though all patients eventually met milestones.[81] Supratentorial lesions predicted abnormal neurodevelopment while infratentorial lesions did not.[81] In another study, investigators conducted neurodevelopmental and behavioral evaluations in 25 patients 4–18 years of age from the PHACE registry. While mean scores for the cohort did not differ from test norms in most domains and 44% were within the normal range in all scores, 28% had 1 score in the at-risk range, 12% had 2 or more scores in the at-risk range, and 16% had one or more scores in the impaired range (<2 SDs below the mean). The individuals further from the norms tended to have more severe PHACE phenotype although no specific features were found to predict neurodevelopmental deficits. Most participants (79%) had or were receiving early intervention services, suggesting concern for atypical development had already been identified by physicians or parents.[82] Dysphagia, which can be central in origin but also has other possible etiologies, has been reported in association with posterior fossa malformations, but also in infants with lip, oropharynx, or airway IH, and those who required cardiac surgery.[11,80]

The diagnosis of PHACE confers an increased risk of neurodevelopmental lags, particularly in motor and language development. At the same time, it is important to emphasize that most individuals with PHACE will have good neurodevelopmental outcomes. We advocate for pediatric neurology evaluation for all children diagnosed with PHACE as well as close follow-up for potential neurodevelopmental issues. Those who have delays may benefit from early intervention programs. Although reports in adults are limited, Stefanko et al reported on 18 adults from the PHACE registry. The majority (12/18) reported at least one neurodevelopmental abnormality (eg, learning difficulty, coordination/balance issues, difficulty with speech, or swallowing).[72] The study was limited by its small size and the possibility of ascertainment bias since it is likely that milder asymptomatic adults might not be included in this registry. Clinicians need to be aware of the possible neurodevelopmental outcomes of PHACE and assist patients and families to find relevant specialty expertise and resources if concerns arise.

Dental issues

Abnormalities of dentition have emerged as an important manifestation of PHACE. Enamel problems, dental root problems, multiple cavities, nerve pain, missing teeth, premature eruption of permanent teeth, delayed tooth eruption, and malocclusion have all been reported.[72,83–85] In a study of younger children (mean age 4.2 years), only those with intraoral hemangiomas displayed enamel hypoplasia; however, a survey of adults documented enamel hypoplasia in a patient without an intraoral or S3 hemangioma.[72,83] Ochando-Ibernon and Azana-Defez[84] reported a case series of delayed tooth eruption with focal or partial segmental hemangiomas of the lip without oral involvement as well. All patients with PHACE should be evaluated for intraoral hemangiomas and dental evaluations should occur by 1 year of age and regularly thereafter to assess for dental anomalies, particularly enamel defects.[11,83]

Pathogenesis of PHACE

PHACE is a sporadic syndrome with unknown pathogenesis. The combination of IH and structural abnormalities has been hypothesized to be due to a so-called embryologic field defect in which mutations that occur during specific times in gestation impact the growing fetus temporally and spatially, affecting only certain cells in their migration, growth, or differentiation.[4] PHACE does not appear to be hereditary, given the lack of cases with familial recurrence as well as the absence of reports of PHACE in the offspring of adult women with PHACE.[72] Based on the patterns of the IH, cerebral vascular and other structural anomalies the developmental defects leading to PHACE are thought to occur between approximately 6 and 9 weeks gestation.[4] Many authors have hypothesized that PHACE is due to a postzygotic somatic mutation occurring during this time frame. Other possible explanations include de novo genetic variants, copy number variants, epigenetic mechanisms and possible in utero environmental factors or hypoxic events. Several genetic studies have been conducted to examine pathogenic factors contributing to PHACE.[86–90]

PHACE syndrome affects females at a greater rate than males, with a female-to-male ratio of 4:1,[91] yet the reason for this gender predilection remains poorly understood. Although there has not been evidence of heritability this female predominance has led some to hypothesize that skewed X-inactivation may contribute to the pathogenesis of PHACE, and that perhaps skewing toward the unaffected X may confer a survival

benefit, with mothers potentially being asymptomatic carriers.[86] However a study of X-inactivation patterns in 29 female PHACE patients and their mothers did not support that hypothesis.[87] There are no known prenatal exposures such as medications or illnesses associated with the risk of PHACE, but mothers of children with PHACE do report a higher incidence of pre-eclampsia and placenta previa.[91]

Copy number variants (CNVs) are deletions and duplications in the human genome, which may contribute to disease. CNV in PHACE was investigated in 98 individuals using the Affymetrix Gene Chip 6.0 single nucleotide polymorphism (SNP) array.[88] This study did not reveal any large (>130 kb), rare CNV regions shared across multiple individuals. Large, rare copy gains, and copy losses in single individuals were reported at 1q32.1, 3q26, 3p11.1, 10q24.32, 12q24.13, 17q11.2, and 18p11.31. Genes of interest in these regions based on their roles in development, angiogenesis, and matricellular signaling include *PIK3CA* (3q26), *EPHA3* (3p11.1) and *EMILIN2* (18p11.31).

Deep whole exome sequencing of hemangioma and aorta tissue has been conducted to analyze for somatic tissue (unpublished data). These studies screened for somatic variants that were simultaneously present in low levels in the tissue, considered low (5%) allele frequency in population databases, absent in germline or parental samples, and predicted deleterious by sequence-based predictive algorithms. A rare, shared, somatic variant has yet to be identified using this analysis strategy. Whole genome sequencing (WGS) on 100 affected individuals from the PHACE Syndrome International Clinical Registry and Genetic Repository and their unaffected parents has been completed through an NIH Gabriella Miller Kids First X01 (https://kidsfirstdrc.org/). Although a single causative gene has not emerged, rare variants in matricellular signaling genes have been identified in a subset of patients (unpublished data).

There is evidence to support the hypothesis that genetic variants are associated with progressive arteriopathy, including moyamoya vasculopathy, in PHACE as well.[89] Whole exome sequencing analysis in 38 individuals with PHACE identified variants in *RNF213* in 2 patients with moyamoya vasculopathy.[90] *RNF213* variants were identified in an additional three patients who were in early childhood and may be at risk for progression of moyamoya vasculopathy over time. Genetic variants may be useful biomarkers to predict which individuals with PHACE are more likely to experience neurovascular complications.

Neuroimaging

Structural brain and cerebrovascular anomalies are common extracutaneous features of PHACE, and imaging of the brain and cerebrovascular system is critical to both diagnosis and surveillance. Imaging protocols vary by institution; but generally, magnetic resonance angiogram (MRA) with conventional anatomic MRI of the brain and neck including T1-, T2-, and gadolinium-enhanced T1-weighted sequences are sufficient to identify and characterize arteriopathy, infarcts, and structural brain lesions.[9,92] Gadolinium (Gd)-based contrast agents can also be useful to detect and characterize intracranial hemangiomas, improve the quality of MRA, and in some cases identify abnormal pial enhancement.[37,38] CT and CT angiography (CTA) have also been used, although they generally carry too high of a radiation dose to be used for screening examinations.

Five imaging categories of arteriopathy have been established (Table 3).[9,38] The large majority of patients exhibit anomalies ipsilateral to segmental facial hemangioma, and those with bilateral hemangiomas are more likely to have bilateral brain involvement.[9,38]

Arteriopathy in the brain, neck, and chest may be identified using MRI, CT, or catheter angiography. The optimal technique depends on the age of the patient. Serial imaging with either or both MRI and CT can sometimes identify subtle or dynamically evolving arteriopathy that may not be evident when imaging children as neonates. Newer techniques are being considered as adjunctive tools. For example, recent use of 4D flow and vessel wall MRI were recently used in a 7-year-old patient to identify vessel wall enhancement, altered blood flow and progressive luminal narrowing, as well as a focal dissection otherwise not seen on conventional imaging.[49] Arterial spin-labeled perfusion (ASL), a perfusion sequence that does not require exogeneous contrast, has been suggested to identify cerebral blood flow (CBF) abnormalities. Mamlouk et al[93] showed that ASL revealed decreased CBF in 24% of 41 PHACE patients while traditional MR showed no evidence of acute or chronic infarcts. It is possible that ASL may serve as a further assessment for AIS in high-risk individuals (Table 2). An additional smaller study of three patients used $H_2{}^{15}O$-PET scan with acetazolamide challenge to assess for cerebral perfusion.[94]

Several structural brain anomalies have been attributed to PHACE and are now used as identifying features in diagnosis (Table 1). Recently, asymmetric Meckel's cave enlargement (trigeminal nerve cistern) was found on neuroimaging in 19 of 25 patients with PHACE (76%). Of note, 60 other patients in the study who had imaging but were not ultimately diagnosed with PHACE all lacked Meckel's cave enlargement suggesting that this finding may be specific to PHACE.[92] Steiner et al,[18] in a review of 55 PHACE patients with MR imaging, also observed dural ectasia of Meckel's cave as the second most common anomaly, after cerebellar hypoplasia. As more individuals with PHACE receive neuroimaging, it is likely that additional findings may emerge.

Not all those diagnosed with PHACE require specialized or serial imaging. For those who are low risk for ischemic stroke after initial diagnostic imaging, it is reasonable to forgo surveillance in the absence of new symptoms, for example, the development of new headaches.[11,38] In those with vascular anomalies deemed intermediate and high risk on initial imaging screening, serial imaging should be considered (Table 2). Lack of progression by 1 year of age may lower risk of later progression in narrowed vessels, but defects such as saccular aneurysm or arterial stenosis should be followed longer term.[38,43] Additional imaging should be obtained outside of normal surveillance in intermediate- and high-risk patients if new symptoms or signs develop.[11,38]

The "feed and bundle technique" (also termed "feed and wrap," "feed and sleep," or "feed and swaddle") in which infants (usually <3 months of age) are fed, kept warm, and swaddled to promote natural sleep and limit motion is often used to try to avoid the need for general anesthesia in very young infants during imaging studies.[95] In a retrospective investigation into 308 "feed and bundle" scans at Columbia University, nearly 25% had motion artifact, but of note, only 11% required repeat imaging due to poor image quality.[95] Although this study did not indicate worse artifacts with contrast, in our experience the use of gadolinium as a contrast agent can make this technique more challenging, both

Table 3.

Five Classification Categories of PHACE Arteriopathy Described in by Heyer[38]

Dysplasia	Arterial coiling, looping, kinking, elongation, ectasia, and focal or fusiform aneurysm
Hypoplasia	Abnormal narrowing of an arterial segment
Aberrant origin or course	Differences in expected branching or course of a principal cervical or cerebral artery
Absence or agenesis	Lack of normal embryonic development or abnormal embryonic involution of a principal cervical or cerebral artery
Persistent embryonic artery	Persistence of an embryonic anastomosis between anterior and posterior circulations (eg, trigeminal, otic, hypoglossal, and proatlantal arteries)
Stenosis or occlusion	Arterial narrowing or closure that is progressive; requires serial imaging studies for proper assessment

Adapted from Hess et al.[9]

because it adds to the length of the study and anecdotally some infants appear to wake during contrast administration. As previously noted, Gd is not needed for delineating intracerebral arterial anomalies which can usually be done with time-of-flight techniques without contrast. However, contrast with Gd is useful in demonstrating the anatomic extent of head and neck hemangiomas as well as any intracranial hemangiomas (which are very common with PHACE). Additionally, it is helpful in delineating arterial anomalies involving the neck and chest. Thus, the decision whether to try to use "feed and bundle" techniques, particularly without contrast, depends on the age of the infant (younger is easier), how high risk the patient is for PHACE itself including distribution of the IH as well as any other anomalies which have been detected, and local radiology department preferences.

An additional question raised is whether individuals with PHACE syndrome are at higher risk for anesthetic complications given possible arterial, brain, and cardiac anomalies. To our knowledge, there are no studies indicating worse anesthetic outcomes in PHACE. A recent, small retrospective cohort of 18 patients who underwent a total of 60 anesthetic procedures/imaging studies did not show any major intraoperative or postoperative complications; however, minor intraoperative and postoperative complications including intraoperative hypotension, oxygen desaturations, laryngospasm, and postintubation croup were noted.[96] Radiologists and anesthesiologists should be aware of the potential for anesthetic events, particularly since many with PHACE have airway hemangiomas and their structural anomalies carry at least a theoretical risk of complications.[96]

IH management

Beta-blocker therapy

For many with PHACE, the large facial IH is the first manifestation of disease, and one that often requires treatment. Based on recently published American Academy of Pediatrics clinical practice guidelines, most infants with PHACE have IH which are categorized as very high risk both because of the underlying risk for PHACE, as well as the important risk of vital structures involvement (airway, eye, lip, nose, and ear) and the risk of scarring, ulceration, or permanent distortion of anatomic landmarks.[97] Oral propranolol is the only FDA/EMEA-approved treatment for those IH which need systemic therapy.[97–99] Although approved for this indication in 2013, PHACE patients were excluded from the original clinical trials. There is an—at least theoretical—concern regarding possible risks of propranolol in PHACE syndrome, particularly in those with narrow CNS arteries with less than robust collaterals that could lead to stroke if cardiac output or blood pressure decreases.

The collective experience to date, however, suggests that propranolol can be safely used in people with PHACE. A retrospective study of 32 infants, where 22% were categorized as high-risk for ischemic stroke, showed that the medication was well tolerated. One patient developed a mild hemiparesis during the course of treatment, but this resolved without intervention or cessation of propranolol.[42] A larger retrospective study of 76 patients with PHACE receiving propranolol therapy, where 59% had high or intermediate risk for stroke, did not have cases of stroke, TIA, or serious cardiovascular events. There was a slight increase in other adverse events (eg, sleep disturbance, GI tract symptoms, respiratory tract symptoms, cold extremities, hypotension, bradycardia, and hypoglycemia) compared to patients without PHACE, but none of these were severe enough to require discontinuation of propranolol.[100] To our knowledge, there have been no published cases of stroke associated with propranolol use in patients with PHACE; however, this is a rare enough event that it may not be captured in case series of the sizes reported.[100]

Although these studies are reassuring, the theoretical risk of stroke or hemodynamic instability remains, and published guidelines recommend that individuals with PHACE have a pretreatment assessment of the presence and severity of cerebrovascular or cardiac anomalies or coarctation of the aorta before propranolol initiation. This evaluation should include echocardiogram and MRI/MRA of the head and neck. It may not always be possible to obtain MRI/MRA before initiating propranolol and in such cases, one might consider low doses, unlikely to cause major changes in blood pressure or heart rate, while arranging for imaging studies to be done. In patients with high risk cerebrovascular or cardiac abnormalities or coarctation of the aorta the management team should include a pediatric cardiologist and neurologist. Propranolol should be dosed to avoid critical changes in blood pressure by using the lowest effective dose (eg, starting at 0.5 mg/kg/d) divided 3 times a day.[11,97–100] The setting of propranolol initiation (inpatient versus outpatient) depends on patient characteristics (age, gestational age, severity of cerebrovascular, and cardiac anomalies) and local practice patterns and constraints.

There are rare patients with contraindications to or lack of response to propranolol therapy who may still require systemic therapy. One relevant contraindication is very severe aortic coarctation. Having cardiology examination and ideally echocardiogram is useful in excluding this. Other beta-blockers such as atenolol and nadolol are also effective in treating IH and may have a lower risk of adverse effects such as sleep disturbance. However, their safety and efficacy have not been as well studied as propranolol.[101] Prednisone, sirolimus, and vincristine have all been used with varying degrees of success for patients with complicated IH that do not respond or have contraindications to propranolol.[102–104]

Laser and surgical therapies

Lasers targeting the blood vessels of cutaneous IH (most commonly pulsed dye laser) are used for two indications: to

lighten residual erythema and telangiectasias and improve ulcerations. Most physicians do not use laser to treat large segmental proliferative lesions early in infancy because beta blockers are a more effective treatment.[97] Our experience is that facial segmental IH associated with PHACE often leave residua that are effectively addressed with several pulsed dye laser treatments after the proliferative phase is over.[105] The use of ablative resurfacing for residual hemangiomas has also been reported.[106] Surgery may be needed to reconstruct key facial features such as nasal tip, lip, and eyelid, especially where tissue distortion leads to functional impairment. Surgery is most often performed in the involutional phase.[107]

Natural history of cutaneous hemangiomas in PHACE

The natural history of IH is one of rapid growth followed by spontaneous involution. While this remains true for many cutaneous IH in the setting of PHACE, the medium- and long-term outcomes in PHACE may be somewhat different. Because they have more complicated cutaneous IH and a higher risk of rebound growth, patients with PHACE often need a longer propranolol treatment course than those without PHACE and have a higher risk of rebound growth after discontinuation of propranolol.[108] Late growth after 3 years of age is also more common in PHACE than infants without PHACE, but the causes of this are unknown.[109] Knowledge of the possibility of late growth or persistence of IH is important for anticipatory guidance of families and worthy of further study.

Multidisciplinary surveillance and health maintenance for patients with PHACE

The multiple potential morbidities in PHACE emphasize the need for a close relationship with a primary care provider and multidisciplinary care. Consensus-derived diagnosis and care recommendations have been proposed by Garzon et al.[11] Using these and other information, we propose recommendations for healthcare maintenance in patients with PHACE based on their age at the time of evaluation (Table 4). These recommendations are not formal consensus guidelines. Physicians will need to consider many factors, including access to relevant specialists and local medical practices in their implementation. Often care can be streamlined in centers with vascular anomalies teams. Close communication with the patient's primary care provider throughout care is essential.

Key specialists to consider and recommendations for each include:

Neurology

1. Monitor patients with intermediate- and high-risk cerebrovascular anomalies for progression of arteriopathy, counseling about the possibility of arterial dissection and signs/symptoms of stroke, and consideration of aspirin or strategies for stroke prevention.
2. Monitor patients with structural brain abnormalities for developmental delays, weakness, coordination, and speech difficulties.
3. Help evaluate and treat headaches, complex migraines, developmental delay, learning difficulties, and attention deficit and hyperactivity disorder.
4. Special consideration should be given before anesthesia for children with high grade stenosis of cervical or cerebral arteries.

Cardiology

1. Determine the type and frequency of monitoring for those patients with a history of cardiac repair, aortic stenosis, structural heart anomalies, or arch anomalies.

Ophthalmology

1. Monitor any patient with PHACE who has an abnormal ophthalmologic exam and provide treatment such as corrective lenses or surgery.

Dermatology

1. Address the sequelae of the segmental, facial IH which can be significant and may require propranolol or other medical therapy for several years.
2. Monitor for rebound or late growth, residual telangiectasia, anetoderma, scar, and functional impairment associated with the IH.
3. Consider laser therapy and reconstructive surgery for residual IH or destructive sequelae. Early referrals to appropriate specialists are important so that families are aware of the optimal timing for procedures.

Otorhinolaryngology (ENT)

1. Assess for difficulties with hearing, tinnitus, airway, speech, and swallow and provide surgical treatment as needed. Audiology, speech therapy, and occupational therapy should be involved if needed.

Surgical specialties (eg, plastics, ENT, oculoplastics)

1. Debulking or reconstructive surgery may be needed for very large IH or those leaving significant residual skin changes or other sequalae such as distortion of anatomic landmarks.

Endocrinology

1. Monitor growth and sexual development and evaluate and treat thyroid or pituitary abnormalities if present.

Dental

1. Coordinate regular dental care and assessment for enamel abnormalities and caries.

Mental health

1. All providers should assess for health-related quality of life, self-esteem, social integration, bullying, and success at school or work. Referral to mental health providers, social work, peer-support groups, and camps for people with facial differences and complex medical needs can be particularly powerful.

Controversies and future directions

The past 25 years have been a time of defining PHACE morbidities and associations and establishing diagnostic criteria,

Table 4.

Suggested Healthcare Maintenance in PHACE Patients by Age

Newborn/Infant Evaluation
Complete PHACE evaluations for those at-risk (See discussion of risk in "Infantile Hemangioma" section) • Echocardiogram • MRI/MRA brain/neck/arch • Dilated eye exam with an ophthalmologist with expertise in pediatrics

Healthcare Maintenance in Patients with Possible or Definite PHACE	
Patient Age	**Healthcare Maintenance Suggestions**
Newborns and infants	• Referral to pediatric neurology if one or more of the following: ◦ Structural brain anomalies ◦ Hypotonia or other abnormalities on neurologic exam ◦ Delayed development/other neurodevelopmental issues ◦ Intermediate or high-risk neurovascular anomalies Neurologists should decide upon the frequency and timing of repeat surveillance imaging for progressive arteriopathy and safety considerations for anesthesia. • Management of infantile hemangioma and any potential complications • Awareness of risk of airway IH • Routine well-child healthcare maintenance with particularly close attention to somatic growth (growth curves) and developmental milestones (especially dysphagia, feeding difficulties, hypotonia, and language or gross motor delays). Physical examination should include evaluation for sternal defects and supraumbilical raphe • Repeat hearing screen (even if normal as newborn) • Specialty-driven referral and follow-up visits (specialists with pediatric expertise): ◦ Dermatology or other specialists for cutaneous hemangioma care (eg, propranolol dosing, tapering, pulsed dye laser treatment, etc.) ◦ Neurology if structural brain abnormalities or intermediate or high-risk neurovascular anomalies, hypotonia, developmental delays or other abnormalities on neurologic examination ◦ Cardiology if congenital heart defects, aortic anomalies or cervical or subclavian arterial anomalies ◦ ENT for airway or hearing issues ◦ Endocrinology if growth issues ◦ Ophthalmology if periocular IH or structural/developmental eye anomalies ◦ Other specialists as relevant
Toddler	• Routine well-child healthcare maintenance with particularly close attention to somatic growth (growth curves) and developmental milestones (especially dysphagia, feeding difficulties, hypotonia, language or gross motor delays) • Dental evaluation including evaluation for enamel defects or dental root anomalies • Screen for presence of migraine headache or migraine equivalents (eg, cyclic vomiting, phonophobia, and photophobia) • Provide counseling about stroke signs and symptoms in a child • Consider repeat imaging on a case-by-case basis (eg, depending on severity of anomalies, signs and symptoms, and previous MR findings) • Refer to PHACE registry and PHACE Syndrome Community or other relevant support network (if outside of the United States) • If significant residual IH, scarring, or distortion of anatomic landmarks, consider consultation with/referral to surgical specialists in anticipation of need for reconstructive procedures (typically at age 3–5 years, an age by which completion of IH involution would be expected) • Follow-up with relevant specialists (see in Newborn/Infant section above)
School-aged	• Routine well-child health care maintenance with particularly close attention to somatic growth (growth curves) and developmental milestones ◦ High index of suspicion for growth hormone deficiency and refer to endocrinology as needed ◦ Review school performance to assess for learning differences, consider neuropsychiatric testing ◦ Screen for the presence of headaches or migraine equivalent • Consider repeat MRI/MRA of the brain and neck (in conjunction with neurology): ◦ Low risk: repeat if symptoms develop ◦ Intermediate risk: repeat when able to obtain without sedation ◦ High risk: ▪ Timing and modality of surveillance to be determined in consultation with neurology, neuroradiology and/or neurosurgery ▪ Consider daily aspirin for stroke prevention ▪ Discuss safety considerations for procedures requiring anesthesia • If clinical signs or imaging findings suggestive of ischemia or moyamoya vasculopathy, referral to neurosurgery in conjunction with neurology for further management • Provide counseling about stroke signs and symptoms in a child • Dental evaluation including evaluation for enamel defects or dental root anomalies • Follow-up with relevant specialists (examples below): ◦ If residual cutaneous IH present consider treatment options to diminish these, if bothersome to child ◦ Depending on which structural anomalies are present (eg, CNS, cardiac, etc.) make sure there is follow-up with relevant specialists who can consider whether repeat imaging studies are needed to monitor for progression • If not already connected consider referral to PHACE registry and PHACE Syndrome Community or other relevant support network (if outside of the United States)
Adolescents and adults	• Routine healthcare maintenance • Identify relevant adult specialist(s) and if needed educate re: PHACE care to help in transition of care • Review school or work performance for any developmental concerns • Screen for presence of headaches or migraine equivalent • If residual cutaneous IH present consider treatment options to diminish these, if symptomatic or bothersome to patient • Follow-up with relevant specialists for structural anomalies (eg, neurology, cardiology, and ophthalmology). Consider whether repeat imaging studies are needed to monitor for progression • For female patients: consider whether combined estrogen-progesterone contraception should be avoided (eg, in a smoker who has migraines with aura or if history of stroke). Provide counseling for alternative effective forms of contraception when appropriate • For women considering pregnancy or who are pregnant: if cerebrovascular or cardiac anomalies are present, consider referral for high-risk obstetrical consultation • Monitor for depression and anxiety • Provide counseling about stroke signs and symptoms • Consider referral to PHACE registry and PHACE Syndrome Community or other relevant support network as part of adolescent transition of care of for adults who are not yet connected with a support network

Abbreviation: MRA, magnetic resonance angiogram.

all with the goal of improving care for affected individuals. Despite attempts to find a genetic basis for PHACE, the underlying pathogenesis remains frustratingly elusive. Beyond determining the actual etiology, many questions remain. We still do not understand the strong female predominance of PHACE. We do not understand why beyond their actual patterns of distribution, the hemangiomas in PHACE patients seems to have a higher risk of persistent IH tissue and more prolonged duration of growth. We do not yet have good natural history studies to accurately predict which patients with PHACE will have progressive disease (eg, progressive changes in cerebral arteriopathy or aortic dilation) versus a more stable or indolent course. These questions have practical implications in terms of whether children with PHACE need follow-up imaging to assess disease progression. Again, a multidisciplinary approach is advised: those with headaches, neurocognitive abnormalities, or other medical issues require communication among specialists to address the needs of an individual patient.

An important ongoing controversy is to further define *which patients* with IH are at greatest risk for PHACE. Both prospective and retrospective studies have shown that certain anatomic areas of the face have a higher risk of PHACE than others, leading to questions about whether all patients with large, segmental IH (eg, >5 cm) should have a PHACE work-up. This question has real implications for infants and families since MRI and MRA in young infants typically requires general anesthesia, with its attendant expenses and potential medical risks. For those with lower risk for PHACE (eg, parotid IH and S2 distribution), is there a role for more limited PHACE evaluations, deferring or omitting the MRI and MRA until a child is older? We do not know the answer to this question with certainty. For now, we favor shared decision-making with families to decide whether to proceed with MRI and MRA. In younger infants, if local practices allow, feed-and-wrap MRI/MRA can be attempted, and when successful, can eliminate the need for general anesthesia. Even if MRI and MRA are not performed early in infancy, those at-risk for PHACE should have careful evaluation of organ systems which do not require general anesthesia (eg, cardiac exam including echocardiogram and ophthalmologic examination). Using guidelines summarized in Table 4 can be helpful in looking for possible signs and symptoms of PHACE, for example, hearing loss, abnormal dentition, abnormal somatic growth, lags in neurocognitive development, and early-onset headaches.

Finally, all families and clinicians caring for children with PHACE face the issue of "transitions of care" as children with PHACE become adults. Education about PHACE for relevant specialists who see adults is critical to the ongoing health of affected individuals. This is an appropriate coda to our look at the 25 years since PHACE was first described. The syndrome is a quarter of a century old, and many of those recognized as having PHACE are adults. Much has been learned in those 25 years, but there is still much to learn, all with the goal of improving our understanding of PHACE, its morbidities, natural history, and management strategies.

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