The Cerebral Vasculopathy of PHACES Syndrome

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Background and Purpose—PHACES syndrome is a neurocutaneous disorder of unknown etiology. We studied the spectrum of associated congenital and progressive cerebral vascular anomalies.

Methods—The medical records of 7 patients with PHACES syndrome were reviewed and combined with an additional 108 PHACES cases identified from the literature. We reviewed the clinical characteristics, calculated the relative frequencies of each type of vascular anomaly, and assessed site of vessel involvement relative to hemangioma location.

Results—Among a total of 115 PHACES cases, 89 (77.4%) had congenital and/or progressive cerebral vascular anomalies. The most commonly detected congenital arterial anomalies included dysplasia, aberrant origin or course, hypoplasia, and absence or agenesis. Arterial occlusions and stenoses were detected in 24 (20.9%) and 21 (18.3%) cases, respectively. Twenty (17.4%) had persistent embryonic arteries; 15 (13%) had saccular aneurysms. There appears to be a close relation between the regional distributions of cervicofacial hemangiomas and the locations of intracranial and extracranial vascular (and cardiac) anomalies.

Conclusion—The vasculopathy of PHACES chiefly comprises a spectrum of congenital and progressive large artery lesions. Based on known embryology and the relative frequencies of specific congenital vascular anomalies, we can predict that the initial cerebral vascular changes occur early in embryogenesis, by the fifth gestational week or earlier. There appears to be both a temporal and a regional link between the arterial anomalies of PHACES and the cutaneous infantile hemangioma. (*Stroke*. 2008;39:308-316.)

Key Words: hemangioma ■ moyamoya ■ PHACE ■ PHACES ■ vasculopathy

Cutaneous infantile hemangiomas are common benign vascular tumors affecting 2.5% to 10% of infants. A subgroup of patients with infantile hemangiomas, particularly large facial hemangiomas, exhibits additional associated structural anomalies of the brain, cerebral vasculature, eye, aorta, or heart in a neurocutaneous disorder known as PHACE(S) (OMIM #606519). The PHACE acronym refers to malformations of the *p*osterior fossa, facial *h*emangiomas, *a*rterial cerebral vascular anomalies, *c*ardiovascular anomalies, and abnormalities of the *e*ye.[1] When ventral developmental defects such as *s*ternal clefting or *s*upraumbilical raphe are present, the PHACES acronym is used. The neurologic features of PHACES can be divided into 2 general categories: congenital anomalies, which include structural malformation of the cerebral vasculature, cerebellum, and cerebrum; and progressive stenoses and occlusions of principal cerebral arteries. Stenoocclusive arterial disease leads to arterial ischemic stroke and a moyamoya-like vasculopathy in some affected children.[2–4] Neither the etiology of PHACES nor the pathophysiology of the associated vascular disease has been determined. We report 7 patients with PHACES, all with cerebral vascular anomalies, and review the radiologic findings of an additional 108 patients from 39 published case series and reports. The vasculopathy of PHACES has several distinct features, which may help in elucidating the underlying cause of this neurocutaneous disorder.

Methods

The clinical records and imaging studies of 7 patients with PHACES syndrome, evaluated by the authors between 2002 and 2006, were reviewed. All patients had cervicofacial infantile hemangiomas with associated cerebral vascular anomalies and, thereby, met the fundamental diagnostic criteria for PHACES (hemangioma and at least one extracutaneous feature).[5] Two or more extracutaneous features were identified in 6 of the 7 cases. All patients underwent brain MRI and at least one radiologic evaluation of the cerebral vasculature, including magnetic resonance angiography (MRA; 6 patients) and/or conventional (catheter-based) angiography (4 patients). Transthoracic echocardiography had also been performed in all patients. The facial hemangioma had undergone significant regression in 2 of our patients (patients 3 and 6) before presentation. In both cases, we were able to confirm the hemangioma diagnoses by clinical history and evaluation of early childhood photographs. Patient 1 was included in an earlier prospective study of PHACES syndrome.[6]

Table 1.   PHACE Cases

Patient No.	Gender	Age	Posterior Fossa Anomalies	Hemangioma Location	Arterial Anomalies	Cardiovascular Anomalies	Eye Anomalies	Additional Features
1	M	3 years	Vermian and left cerebellar hypoplasia, posterior fossa cystic anomaly, congenital hydrocephalus	Left periorbital and temporal regions with extension into left orbit	Bilateral proatlantal arteries, left trigeminal artery, absent bilateral posterior communicating arteries, tortuous and hypoplastic vertebrobasilar system	Mitral valve prolapse	Left eye exotropia	Mildly delayed myelination on brain MRI, mild hypotonia, and mild developmental delay
2	F	7 months	None	Telangiectatic ("abortive") hemangioma affecting the right temporal, periorbital, neck, and shoulder regions	Hypoplastic right ICA (with subsequent occlusion), hypoplastic right vertebral artery, tortuous basilar artery, abnormal origin of right subclavian artery	Tricuspid atresia, multiple VSDs, distal tapering of the aorta without coarctation	Chorioretinal coloboma, esotropia of the right eye	Necrosis of right ear and digits of the right hand, right MCA distribution stroke, localization-related epilepsy, developmental delays
3	F	4 years	Left cerebellar hypoplasia	Left periorbital and temporal region with extension into left orbit	Absent right ICA, absent right vertebral artery, left ICA stenosis, abnormal origins of the left vertebral and right subclavian arteries, tortuous basilar artery, moyamoya vasculopathy	None	Left eye exotropia	Bilateral centrum semiovale strokes, severe headaches with associated vomiting
4	F	4 years	None	Midfacial with left-sided prominence affecting the forehead, nose, and philtrum	Hypertrophic and tortuous anterior cerebral arteries associated with prominent, abnormal pial vessels at convexities of bilateral frontal lobes, hypoplastic right vertebral artery	None	None	Infantile spasms, cerebral dysgenesis, moderate developmental delay
5	F	10 months	Hypoplasia of the right cerebellar hemisphere and vermis, small posterior fossa cyst	Right temporal region with periorbital involvement, minimal orbital extension	Tortuous right ICA, dysplastic right PCA and SCA with prominent, abnormal pial vessels overlying the right cerebellar hemisphere	None	Right esotropia	Spastic tone and extensor plantar response of left leg, developmental delays
6	F	25 years	Cystic dilatation of posterior fossa with vermian and right cerebellar hypoplasia	Right periorbital and temporal regions	14 × 12 × 10 fusiform aneurysm of right ICA, right persistent trigeminal artery, anomalous origin of right ECA, hypoplasia and tortuosity of the vertebrobasilar system	None	None	Hypoplasia of right lateral cerebral sinus, sigmoid sinus atresia, persistent primitive right occipital sinus
7	F	2 months	Inferior vermian hypoplasia	Left ear, cheek, chin, and lower lip with extension to the trachea and soft tissues of the neck	Ectatic left ICA, hypoplastic right common carotid, internal carotid, and subclavian arteries, hypoplastic vertebrobasilar system with tortuous, looped left vertebral artery	Tetralogy of Fallot, interrupted aortic arch with stenotic segment at level of the renal arteries	None	Polyhydramnios and fetal hydrops, liver hemangiomatosis, prominent bilateral Sylvian fissures and subarachnoid spaces

VSD indicates ventricular septal defect; MCA, middle cerebral artery; PCA, posterior cerebral artery; SCA, superior cerebellar artery; ECA, external carotid artery.

Additionally, we conducted an Ovid Medline literature review of PHACES using keywords "PHACE" and "PHACES." Case inclusion required appropriate clinical description and/or facial photography allowing confirmation of the cervicofacial infantile hemangioma as well as adequate radiologic evaluation of the cerebral vasculature (MRA, CT angiography, catheter-based angiography, or a combination of gadolinium-enhanced MRI with cardiac catheter-

ization). Patients reported in more than one publication, when identified, were counted only once. Our primary search produced 59 English-language references, of which 30 provided case reports that fit search criteria. A secondary (and tertiary) search of the references from these reports produced 9 additional publications. One hundred eight PHACES cases were obtained from the literature. Nineteen of the 25 cases described by Metry and colleagues[6] (and not clearly
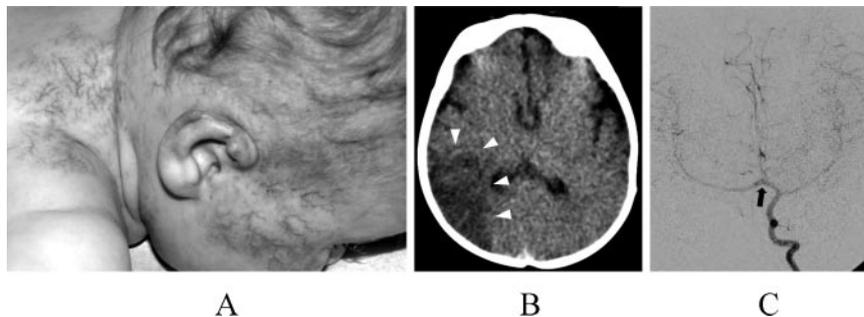
Figure 1. Patient 2. A 7-month-old girl has a telangiectatic right facial hemangioma (A) extending to the right neck, shoulder, and back. Note the deformity of the helix of her right ear secondary to ulceration and necrosis. A head CT (B) performed after onset of focal seizures (4 months of age) reveals a region of hypodensity (triangles) consistent with arterial ischemic stroke in the right middle cerebral artery (MCA) territory. Catheter angiography of the left ICA during the arterial phase (C) demonstrates rapid cross-filling of the right cerebral hemisphere through an enlarged anterior communicating artery (arrow). Although an MRA showed flow-related enhancement of a hypoplastic right ICA 1 month earlier, no right ICA opacification was present on the catheter angiogram.

reported elsewhere) were included. Although imaging details were omitted from the report, specific descriptions of the cerebral vasculature were provided for each patient with PHACES.

From a total of 115 PHACES cases, we assessed the types of vascular lesions present, their relative frequencies, and their intracranial and extracranial locations relative to the cutaneous hemangioma(s). Arterial lesions were subdivided into 8 categories: dysplasia, aberrant origin or course, absence or agenesis, hypoplasia, stenosis, occlusion, persistence of fetal vessels, and presence of saccular aneurysms. The term "dysplasia" encompasses a variety of arterial abnormalities, including looping, coiling, ectasia, dolichoectasia, fusiform aneurysms, and "angiomatous" malformations. Positive and negative predictive values (Table 3) and odds ratios (Tables 3 and 4) were calculated to quantify the relation between hemangioma site and the locations of arterial and cardiac anomalies.

Results

The relevant clinical information and radiologic findings for the 7 patients in our series are listed in Table 1. Data by organ system are summarized as follows.

Demographics and Cutaneous Features

Six of the 7 patients (86%) were female supporting the early and ongoing observations of a female predominance among patients with PHACES.[1,7] All patients had large infantile hemangiomas minimally affecting regions of the head and neck. The hemangiomas localized to facial regions that generally corresponded to the facial segments (segments 1 to 4) described by Haggstrom and colleagues.[8] Patient 2 presented at 2 weeks of age with an atypical telangiectatic ("abortive") infantile hemangioma[9] (Figure 1A) of the right periorbital region with subsequent extension to the right scalp and ear, the neck, and the right shoulder and back. Ulceration

and necrosis of the right ear and the fingertips of the right hand developed 5 weeks later. Conventional angiography revealed an absence of opacification of the second digital terminal tuft of the right hand and multiple foci of contrast puddling along the large arteries of the right arm suggestive of subcutaneous hemangioma. Patient 7 had diffuse hemangiomatosis involving the liver, trachea, and soft tissues of the neck in addition to the cutaneous facial lesion.

Posterior Fossa Anomalies

Five patients had posterior fossa abnormalities. In four of the cases, cerebellar hypoplasia occurred ipsilateral to the cutaneous hemangioma. The fifth patient (patient 7) had mild hypoplasia of the inferior cerebellar vermis and corresponding midline hemangiomas of the trachea and soft tissues of the neck. The brain MRI of patient 5, performed at 10 months of age, revealed enhancement of abnormal pial vessels overlying the cerebellar lesion (Figure 2B) and associated with proximal large vessel anomalies of the basilar, superior cerebellar, and posterior cerebral arteries (Figure 2C). The large artery malformations were predominantly on the right side, adjacent to the right facial hemangioma (Figure 2A).

Eye and Cardiac Anomalies

Four patients in our series had eye abnormalities; 3 had anomalies of the cardiovascular system. Cardiovascular disease was identified in utero in patient 7 in association with polyhydramnios and fetal hydrops. Transthoracic echocardiography followed by cardiac catheterization in infancy revealed multiple malformations including tetralogy of Fallot,
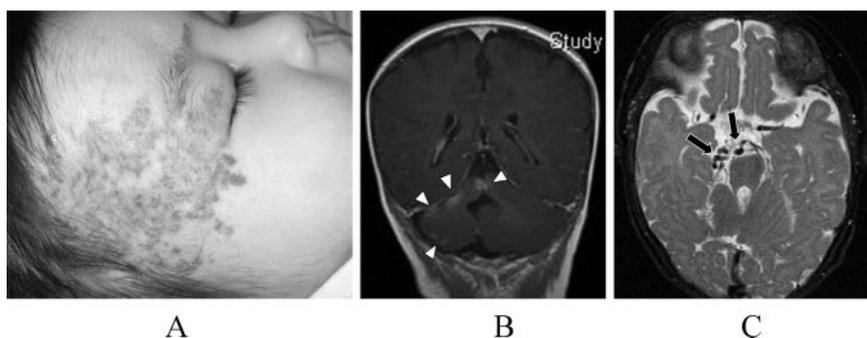

Figure 2. Patient 5. A 10-month-old girl has a right temporal infantile hemangioma (A) with periorbital involvement and minimal extension into the orbit. A coronal T1-weighted MRI with gadolinium (B) shows pial enhancement (triangles) of a hypoplastic left cerebellar hemisphere. Axial T2-weighted MRI (C) shows effacement of the right pons in association with dysplasia of the right-sided posterior cerebral and superior cerebellar arteries (arrows).
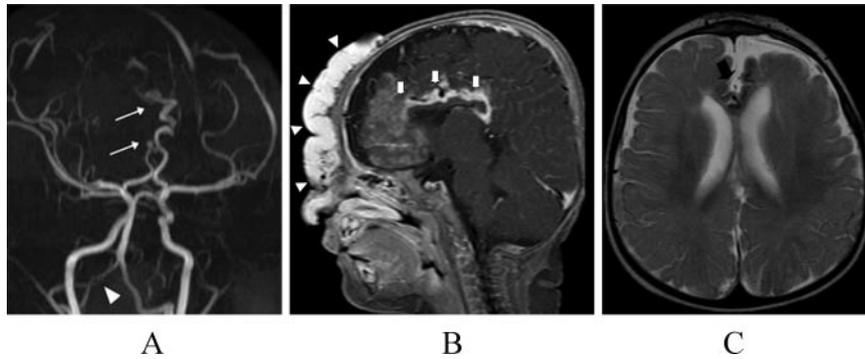
Figure 3. Patient 4. A 4-year-old girl has a midfacial infantile hemangioma affecting the forehead, nose, and philtrum. MRA (A) reveals enlarged and tortuous anterior cerebral arteries (ACA) bilaterally (arrows) and a hypoplastic right vertebral artery (triangle). Sagittal T1-weighted MRI with gadolinium (B) performed at 5 months of age shows diffuse enhancement of the cutaneous hemangioma (triangles) and concomitant pial enhancement overlying the medial left frontal lobe and pericallosal region (arrows). Left-greater-than-right cerebral atrophy and dysgenesis are also present. Axial T2-weighted MRI (C) performed at 14 months of age better demonstrates the associated cerebral dysgenesis. Tortuous ACA flow voids (black arrow) are directly related to the cerebral lesion.

an interrupted right aortic arch, right subclavian artery atresia, and a long segment of high-grade stenosis affecting the distal, descending aorta. Notably, the thoracic and cerebral vascular lesions occurred in association with diffuse hemangiomatosis involving the liver, head, and neck.

Neurologic Features

Abnormal neurologic signs and/or symptoms were present in 5 of 7 patients. Four patients showed evidence of mild to moderate developmental delay. Patient 5 exhibited focal pyramidal signs, including increased tone in the left leg, brisk left patellar deep tendon reflexes, and an extensor–plantar response of the left toe. Her MRI demonstrated moderate effacement of the right pons (Figure 2C) and cerebral peduncle with corresponding vascular anomalies of the pre-pontine and ambient cisterns. Two children (patients 2 and 3) had arterial ischemic strokes, which are described in detail subsequently. Patient 2 had localization-related epilepsy after her right middle cerebral artery distribution stroke. Patient 4 developed infantile spasms at 5 months of age. An electro-encephalogram showed a modified hypsarrhythmia pattern in combination with spike and slow-wave complexes emanating

primarily from the left frontal cortex, a finding consistent with the left-greater-than-right frontal atrophy and dysplasia seen on brain MRI (Figure 3C). To our knowledge, this is the first report of infantile spasms associated with PHACES syndrome. Her seizures responded well to valproic acid and subsided completely at 20 months of age.

Cerebral Vascular Anomalies

All patients in our series had cerebral vascular anomalies. Patient 6 had hypoplasia of the transverse sinus, atresia of the sigmoid sinus, and persistence of a primitive occipital sinus, all ipsilateral with the right-sided facial hemangioma. Other-wise, all vascular anomalies were arterial in origin. The locations of arterial lesions tended to correspond roughly with the regional distributions of the cutaneous hemangiomas. Patients with hemangiomas affecting the periorbital, orbital, and lateral scalp regions (5 patients) either had arterial abnormalities located exclusively in the adjacent cerebral hemisphere or had bilateral cerebral vascular disease. Patient 4 had a midfacial hemangioma with left-sided prominence affecting the forehead, nose, and philtrum. Brain MRI with MRA revealed corresponding bilateral anterior cerebral ar-
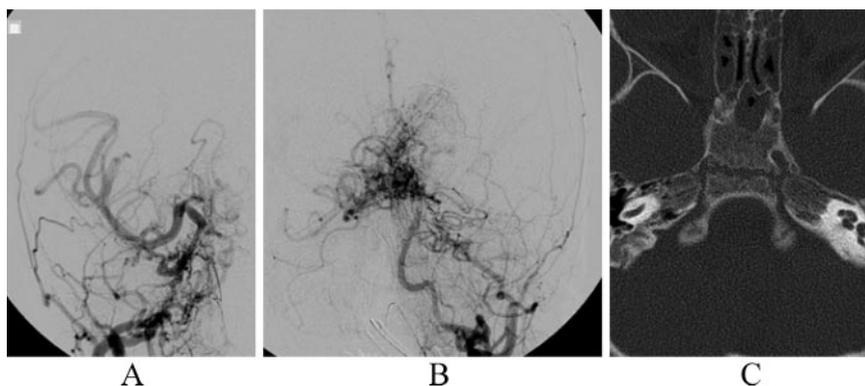

Figure 4. Patient 3. Catheter-based angiography revealed bilateral moyamoya-like vasculopathy. Right external carotid arteriogra-phy (A) shows extensive skull base, transdural collaterals reconstituting a right ophthalmic artery with retrograde opacification of the intracranial right ICA and branch vessels. Right common carotid injection fails to demonstrate opacification of the right ICA. The left ICA origin is markedly hypoplastic. Left external carotid arteriography (B) reveals moderate transdural collaterals supply-ing the left intracranial ICA and ophthalmic arteries. Skull base CT scanning (C) demonstrates an absent right carotid canal. Canal remnants are present at other levels suggesting right ICA aplasia (rather than agenesis).
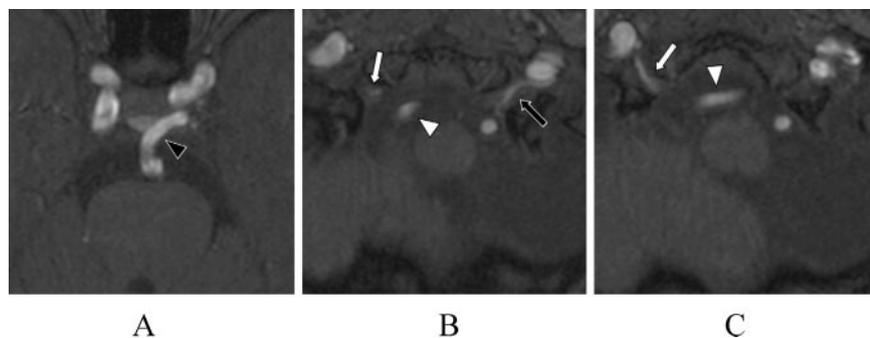
Figure 5. Patient 1. Axial MRA (3-dimensional time of flight) performed at 6 months of age (A) reveals a left persistent trigeminal artery (black triangle). Bilateral proatlantal arteries were identified on repeat MRA performed 3 years later. B, A left proatlantal artery (black arrow), a short segment of the right proatlantal artery (white arrow), and a tortuous right vertebral artery (triangle). C, The anterior portion of the right proatlantal artery (white arrow) and further tortuosity of the right vertebral artery (triangle). Notice absence of the left cerebellar hemisphere (B–C).

tery tortuosity and bilateral enhancement of the pial vessels over the frontal convexities (Figure 3A–B). The left frontal lobe was more severely affected than the right.

Serial neuroimaging revealed progressive, stenoocclusive arterial disease in 2 patients. At 3 months of age, patient 2 had flow-related enhancement of a hypoplastic right internal carotid artery (ICA) identified by MRA. One month later, she developed seizures and left arm paresis. A brain CT scan revealed a new right middle cerebral artery distribution stroke (Figure 1B). Conventional angiography performed soon after failed to demonstrate right ICA opacification either by way of aortic injection or through a left ICA injection (Figure 1C) through an enlarged anterior communicating artery. The cause of her stroke remains unclear. Both middle cerebral arteries filled rapidly from the left ICA injection. Transthoracic echocardiography did not detect cardiac thrombi, and a laboratory investigation of prothrombotic disorders was normal. In the clinical setting of severe congenital heart disease, we presumed a thromboembolic etiology and began low-molecular-weight heparin therapy. Patient 3 presented at 4 years of age with headaches and vomiting. However, symptom onset began at 7 months with prolonged episodes of irritability, vomiting, and lethargy. Conventional angiography done at the referring hospital revealed multiple congenital vascular abnormalities (Table 1), including absence of the right ICA, left ICA stenosis, and bilateral posterior cerebral artery stenoses, and extensive transdural and leptomeningeal collaterals consistent with moyamoya syndrome. On repeat angiogram, the large artery stenoses were essentially unchanged. However, the multiple collateral vessels appeared larger and more numerous (Figure 4A–B). MRI revealed chronic, bilateral corona radiata strokes. Skull base CT scanning (Figure 4C) confirmed right-sided carotid canal aplasia with remnants of the canal present on some images. We determined that she was not a candidate for a pial synangiosis procedure because the primary blood supply to her brain already derived from collaterals of the external carotid arteries bilaterally and the numerous transcranial branches increased her risk of potential surgical complications, specifically bleeding.

Two patients had primitive fetal anastomoses. Conventional angiography revealed multiple arterial and cerebral sinus anomalies in patient 6, including a right-sided persistent trigeminal artery (PTA). Patient 1 had an extremely rare combination of persistent fetal vessels: a left trigeminal artery and bilateral proatlantal arteries. MRA, performed at 6 months of age, demonstrated a left PTA (Figure 5A) associated with a tortuous and hypoplastic vertebrobasilar system and bilateral absence of the posterior communicating arteries. The bilateral proatlantal arteries were not appreciated until a repeat MRA was performed 3 years later (Figure 5B–C).

Literature Review

We combined the radiological findings from our 7 patients with those of the 108 PHACES cases identified from the literature. The radiologic evaluation was described in 96 of the 115 patients (see "Methods"); 41 underwent MRA only, 30 underwent catheter angiography only, 19 had both MRA and catheter angiography, 5 had various imaging combinations including MRI and cardiac catheterization, and one patient underwent CT angiography. Only 12 patients had serial neuroimaging reported. Autopsy evaluation was performed in a single case.[10]

Eighty-nine patients (77.4%) had congenital and/or progressive vascular lesions (Table 2).* The most commonly detected congenital anomalies included arterial dysplasia, aberrant origin or course of principal cerebral arteries, hypoplasia, and vessel absence or agenesis. Progressive arterial

Table 2.   Cerebral Vascular Anomalies

Dysplasia: 37 (32.2%)	Occlusions: 24 (20.9%)
Aberrant origin or course: 32 (27.8%)	ICA: 8
ICA: 6	Multiple/other arteries: 16
Ophthalmic: 3	Stenoses: 21 (18.3%)
Multiple/other arteries: 23	ICA: 9
Hypoplasia: 26 (22.6%)	MCA: 6
ICA: 12	Multiple/other arteries: 6
Multiple/other arteries: 14	Persistent embryonic arteries: 20 (17.4%)
Absence or agenesis: 25 (21.7%)	
ICA: 10	Trigeminal artery: 14
VA: 5	Proatlantal artery: 2
Multiple/other arteries: 10	Cervical intersegmental: 2
	Multiple/other: 2
	Saccular aneurysms: 15 (13%)

Cerebral vascular anomalies are summarized from 115 patients with PHACES described in 39 published case series and reports in addition to our own. Eighty-nine patients (77.4%) had cerebral vascular anomalies. A single patient from our series (patient 1) was included in a prospective study by Metry and colleagues.

VA indicates vertebral artery; MCA, middle cerebral artery.

*1–4, 6, 10–14, 20, 21, 26–52.

Table 3. Relation Between Cutaneous Hemangioma Location and Arterial and Cardiac Anomalies

.	Cardiac, Aortic, and/or Supraaortic Anomalies			
	Present	Absent	Total	
Mandibular (S3), neck, shoulder, and/or chest hemangioma(s)				
Present	39	21	60	PPV
				0.65
Absent	9	38	47	NPV
				0.81
Total	48	59	107	OR [CI$_{95}$]
				7.8 [3.2–19.2]

Involvement of the mandibular region (segment 3), neck, shoulder, and/or chest by infantile hemangioma is associated with anomalies of the heart, aorta, and origins of the supraaortic arteries. Cases without adequate descriptions of hemangioma location were excluded.

PPV indicates positive predictive value; NPV, negative predictive value; OR, odds ratio; CI$_{95}$, 95% confidence interval.

Table 4. Relation Between Laterality of Cutaneous Hemangioma and Laterality of Cerebral Vascular Anomalies

	Laterality of Cerebral Vascular Anomalies			
	Ipsilateral	Bilateral	Total	
Laterality of cervicofacial hemangioma(s)				
Unilateral	27	16	43	
Bilateral	7	24	31	
Total	34	40	74	OR [CI$_{95}$]
				5.8 [2–16.4]

The association between laterality of the cutaneous hemangioma(s) and corresponding cerebral vascular anomalies is demonstrated. Cases with normal cerebral vasculature and those without adequate descriptions of hemangioma laterality were excluded.

OR indicates odds ratio; CI$_{95}$, 95% confidence interval.

occlusions and stenoses occurred in 24 (20.9%) and 21 (18.3%) cases, respectively. Eight patients had a unilateral or bilateral moyamoya-like vasculopathy.[2–4,11] Persistent embryonic arteries were identified in over 17% of reported patients with PHACES with the PTA identified most commonly. Fifteen patients (13%) had saccular aneurysms. None of these cases had clinical evidence of aneurysmal bleeding.

Cardiac anomalies and the specific intracranial and extracranial arterial lesions correlated with hemangioma location (Table 3). Hemangiomas involving the mandibular region (facial segment 3) and/or the neck, shoulder, or chest were more likely to coincide with cardiac, aortic, and/or supraaortic vascular anomalies at an odds ratio of 7.8. In this context, "supraaortic" anomalies are restricted to dysplasia of the brachiocephalic, subclavian, or common carotid arteries or absence of the vertebral arteries. The presence of mandibular, neck, shoulder, and/or chest hemangiomas was 65% predictive of associated cardiac, aortic, or supraaortic anomalies (ie, the positive predictive value equals 0.65). Conversely, the negative predictive value equals 0.81. When hemangiomas were restricted to the temporal, periorbital, and maxillary locations, these cardiac and basal–arterial anomalies occurred in only 19% of cases. A similar regional correlation can be demonstrated based on hemangioma laterality (Table 4). Patients with unilateral facial hemangiomas tended to have ipsilateral cerebral vascular anomalies, whereas bilateral facial lesions were associated with bilateral vascular lesions at an odds ratio of 5.8. More importantly, we are unaware of any patient with PHACES and cerebral vascular anomalies exclusively contralateral to the cervicofacial hemangioma. A single case report describes prominent tortuosity of the ICA contralateral to facial hemangioma with deep orbital extension and with "questionable" ipsilateral ICA involvement.[12]

Discussion

PHACES syndrome is a neurocutaneous disorder of unknown etiology defined by the association of a characteristic infan-

tile hemangioma with one or more anomalies of the brain, arteries, heart, eyes, or sternum. Our patients with PHACES and those identified from the literature exhibit a spectrum of extracutaneous manifestations associated with cervicofacial infantile hemangiomas. Anomalies of the cerebral vasculature, comprising both congenital and progressive arterial lesions, were detected in nearly 77.4% of the cases we reviewed. However, potential publication and referral biases limit our estimates of the "true" prevalence.

One of the patients in our cohort (patient 6) had cerebral sinus malformations: hypoplasia of the transverse sinus, sigmoid sinus atresia, and persistence of a primitive right occipital sinus. Venous and/or cerebral sinus anomalies are rarely reported in patients with PHACES. Although 49 of 96 cases (51%) underwent catheter-based angiography, the lack of dedicated venous imaging (magnetic resonance venography or CT venography) may have led to an underestimation of venous lesions. Among the cases reported with venous or cerebral sinus anomalies, Smith and colleagues identified a persistent left superior vena cava in a patient during surgical repair of an aortic coarctation and aneurysm,[13] and baseline MRI demonstrated the rare finding of sinus pericranii in the case described by Drosou et al.[14] It remains unclear if such lesions broaden the PHACES phenotype or merely represent incidental findings.

The cerebral vasculopathy of PHACES chiefly comprises arterial anomalies with the principal arteries of the circle of Willis most commonly involved. The increased frequency of certain congenital lesions suggests that the arterial pathogenesis begins during early embryonic development. Two specific arterial anomalies, persistence of fetal anastomoses and absence of the ICA with corresponding aplasia of the carotid canal, help us to determine the latest possible embryonic period affected. The embryology of each is briefly described subsequently.

Over 17% of patients with PHACES have persistent embryonic anastomoses with trigeminal arteries detected most commonly. Although this frequency likely reflects a publication bias, it remains approximately 100-fold higher than the overall angiographic PTA prevalence, estimated at 0.1% to 0.2%.[15] Patient 1 had an unusual arterial configuration comprising bilateral proatlantal arteries and a left trigem-

inal artery, whereas patient 6 had a right-sided PTA. Both patients had associated vertebrobasilar and/or posterior communicating artery anomalies. In the early embryo (4-mm crown-to-rump-length stage, 27 to 29 days gestation), the internal carotid system supplies the paired longitudinal neural arteries, anlagen of the adult basilar artery, through 4 transitory vessels.[16] These temporary anastomoses (referred to as presegmental arteries in the embryonic period) include the trigeminal, the otic (acoustic), the hypoglossal, and the proatlantal arteries. As the adult configuration of the circle of Willis develops, the presegmental vessels regress. The posterior communicating arteries emerge in the 5- to 6-mm embryo (28 to 30 days). Formation of the basilar (5 to 8 mm, 28 to 33 days) and vertebral (7 to 14 mm, 31 to 36 days) arteries follow through consolidation of the longitudinal neural arteries and the cervical intersegmental arteries, respectively. The horizontal portion of the vertebral artery derives, in part, from a proatlantal segment. During the normal course of embryogenesis, the transitory presegmental arteries exist for a brief period of only 7 to 10 days.[15] Padget was unable to find any definite, uninterrupted presegmental arteries beyond the 14-mm stage (36 days gestation).[16] Regression of these primitive vessels appears to depend on adequate communication through the posterior communicating arteries and/or patency of the vertebrobasilar system. Accordingly, presegmental arteries such as the trigeminal are more likely to persist when disruption of normal vascular development occurs. Indeed, the three Saltzman types of PTA can be distinguished, in part, by hypoplasia or absence of the corresponding posterior communicating, basilar, or vertebral arteries.[15,17]

Absence of the ICA relates to an insult occurring during a similar, overlapping period in embryogenesis. Often one can distinguish between primary ICA agenesis and secondary regression after initial ICA development based on the absence or presence of the infraorbital and alveolar arteries. These vessels, however, are rarely mentioned in PHACES reports. Instead, we estimate the embryonic period affected by assessing absence or aplasia of the corresponding carotid canal. The basal mesenchyme begins consolidating to form the sphenoid cartilage, primordium of the skull base, in the 12- to 14-mm embryo (35 to 36 days).[16,18] If the ICA is not present when the skull base develops, the carotid canal does not form. If only remnants of the vessel are present, a small aplastic canal results as seen in our case (patient 3) and several published reports. Although ICA "agenesis" has been reported,[19–21] our review of PHACES cases suggests that ICA aplasia occurs more commonly. The primitive ICA develops and then, due to some putative insult, subsequently regresses.

Accordingly, based on these observations, we can predict that the initial vascular changes in PHACES begin during the fifth week of embryogenesis or earlier. This finding is compatible with the proposed embryonic origin of infantile hemangiomas.[22,23] The large, plaque-like hemangiomas characteristically associated with PHACES syndrome exhibit nonrandom growth patterns that correspond to early embryonic facial segments, a surprising observation considering the tumors themselves often are not apparent at birth.[8,23] Although precise timing of the cutaneous lesion has not yet been established, the infantile hemangioma and the cerebral vasculopathy of PHACES appear to be temporally linked by an insult occurring in early embryogenesis.

We hypothesize that the progressive stenoocclusive arterial disease of PHACES, observed in infancy and early childhood, derives from the same (or similar) pathogenic insult. Although congenital anomalies seem to correlate with the embryonic establishment of an infantile hemangioma, the progressive cerebral vasculopathy corresponds with the proliferative phase of hemangioma growth. Excluding those arterial ischemic strokes in the PHACES literature related to presumed surgical complications, the average age of stroke among patients with PHACES is 8.8 months.[4] The progressive arterial stenoses and occlusions occur earlier. Patient 3 had advanced moyamoya disease at 4 years of age, yet symptom onset began much earlier at 7 months. Although the large vessel stenoses were stable on serial angiograms, exuberant collateral formation continued. We are not aware of any arterial stenoses or occlusions having occurred in patients with PHACES after hemangioma involution.

In addition to the temporal link, the data from our review suggest that a regional link between cutaneous hemangioma and cerebral vascular lesion exists as well. The congenital and progressive arterial anomalies of PHACES tend to occur on the same side as the unilateral facial hemangiomas and in some cases bilaterally, whereas bilateral facial lesions are more likely to associate with bilateral arterial disease. In no case did one occur exclusively contralateral to the other. The most conspicuous vascular malformations are often nearest to the facial hemangioma itself or stand in direct relation to the intracranial "feeder" vessels. Additionally, nonfacial hemangiomas appear to cause local vasculopathy. Patient 2 had hemangioma involvement of the shoulder and arm with related occlusion of the small arteries of the hand and fingertip necrosis. Metry and colleagues report a patient with PHACES with a similar shoulder hemangioma and diminished ipsilateral radial and ulnar pulses.[5] Severe stenosis of the thoracic aorta observed in patient 7 corresponds with diffuse hemangiomatosis involving the liver as well as the head and neck.

Understanding the pathophysiological link between cutaneous infantile hemangiomas and the cerebral vasculopathy of PHACES may help to elucidate the underlying cause of the neurocutaneous disorder. Originally hypothesized by Burrows and colleagues,[2] vascular growth factors or other vascular modulators elaborated by the hemangioma itself may constitute the putative insult leading to cerebral arteriopathy. A differential expression of certain vascular growth factors at different stages of hemangioma growth has been well documented.[24,25] Congenital vascular anomalies could result from a diffusible factor(s) produced during the embryonic period of hemangioma formation, whereas the same (or similar) vascular modulator(s) elaborated during the proliferative phase of hemangioma growth could lead to stenoocclusive arterial disease. A "growth-factor" hypothesis is not inconsistent with the observation by Baccin et al that affected cerebral arteries demonstrate "segmental vulnerability."[26] The disproportionate segmental involvement of the cerebral arteries, aorta, and heart corresponds with the embryonic

location of the facial infantile hemangioma. Those arterial segments nearest the hemangioma in the early embryo are most conspicuously affected. Our data confirm that hemangiomas localizing to the mandibular facial segment (S3) or lower are more likely to coincide with cardiac, aortic, and/or supraaortic defects than those restricted to the periorbital, maxillary, and/or temporal regions (S1, S2, and S4). Regrettably, the "growth factor" hypothesis fails to explain the primary origin of the hemangioma itself. Alternative potential etiologies include defective expression of a developmental gene or (less likely) early in utero exposure to some teratogen. A genetic insult, particularly a somatic mutation, affecting vascular development could lead to parallel cutaneous and cerebral vascular manifestations. Notably, familiarity has never been reported with this neurocutaneous disorder.

In conclusion, the cerebral vasculopathy of PHACES comprises a spectrum of congenital and progressive arterial lesions. Venous and cerebral sinus anomalies occur much less frequently. Although the cause of vasculopathy has not been determined, we can establish that an early embryonic period is affected: the fifth gestational week or earlier. The data from our review demonstrate a regional and a temporal link between the cutaneous hemangioma of PHACES and the associated cerebral vascular anomalies, both of which potentially can be explained by the elaboration of small molecule vascular modulators produced during different phases of hemangioma establishment and growth. A better understanding of the arteriopathy of PHACES may lead to improvements in predicting which patients will develop progressive arterial disease and greatly impact future treatments and stroke prevention in affected children.

Disclosures
None.

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