PHACE syndrome: Past, Present, Future

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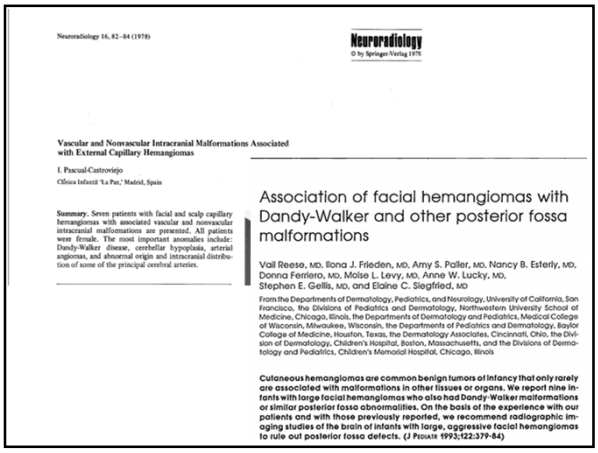
History of PHACE syndrome

- We asked colleagues – had they seen this before?
- We looked carefully in medical literature
- Scattered case reports and 1978 and 1985 series of cases from Spain with intracranial malformations with capillary hemangiomas of the face
- We reported our findings in 1993:

  Case series of facial hemangiomas and Dandy-Walker and other posterior fossa anomalies



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Vascular and Nonvascular Intracranial Malformations Associated with External Capillary Hemangiomas

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Summary. Seven patients with facial and scalp capillary hemangiomas with associated vascular and nonvascular intracranial malformations are presented. All patients were female. The most important anomalies include: Dandy-Walker disease, cerebellar hypoplasia, arterial angiomas, and abnormal origin and intracranial distribution of some of the principal cerebral arteries.

Association of facial hemangiomas with Dandy-Walker and other posterior fossa malformations

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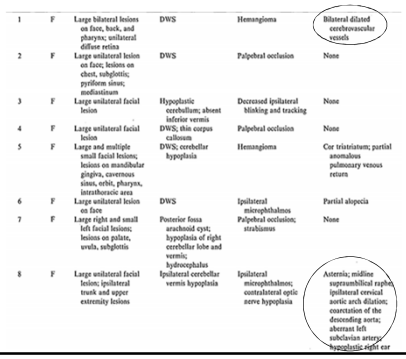
Cutaneous hemangiomas are common benign tumors of infancy that only rarely are associated with malformations in other tissues or organs. We report nine infants with large facial hemangiomas who also had Dandy-Walker malformations or similar posterior fossa abnormalities. On the basis of the experience with our patients and with those previously reported, we recommend radiographic imaging studies of the brain of infants with large, aggressive facial hemangiomas to rule out posterior fossa defects. (J Pediatr 1993;122:379-84)

Hemangiomas & structural anomalies: We had missed something!



1	F	Large bilateral lesions on face, back, and pharynx; unilateral diffuse retina	DWS	Hemangioma	Bilateral dilated cerebrovascular vessels
2	F	Large unilateral lesion on face; lesions on chest, subglottis; pyriform sinus; mediastinum	DWS	Palpebral occlusion	None
3	F	Large unilateral facial lesion	Hypoplastic cerebellum; absent inferior vermis	Decreased ipsilateral blinking and tracking	None
4	F	Large unilateral facial lesion	DWS; thin corpus callosum	Palpebral occlusion	None
5	F	Large and multiple small facial lesions; lesions on mandibular gingiva, cavernous sinus, orbit, pharynx, intrathoracic area	DWS; cerebellar hypoplasia	Hemangioma	Cor triatriatum; partial anomalous pulmonary venous return
6	F	Large unilateral lesion on face	DWS	Ipsilateral microphthalmos	Partial alopecia
7	F	Large right and small left facial lesions; lesions on palate, uvula, subglottis	Posterior fossa arachnoid cyst; hypoplasia of right cerebellar lobe and vermis; hydrocephalus	Palpebral occlusion; strabismus	None
8	F	Large unilateral facial lesion; ipsilateral trunk and upper extremity lesions	Ipsilateral cerebellar vermis hypoplasia	Ipsilateral microphthalmos; contralateral optic nerve hypoplasia	Asternia; midline supraumbilical raphe; ipsilateral cervical aortic arch dilation; coarctation of the descending aorta; aberrant left subclavian artery; hypoplastic right ear

PHACE Syndrome

Posterior fossa
Hemangioma
Arterial
Cardiac
Eye

Frieden IJ, Reese V, Cohen D.
PHACE syndrome. The association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities.
Arch Dermatol. 1996;132:307-11

Last 2 decades
More than 120 published articles

- Increased appreciation hemangioma and lower body anomalies
- Defining hemangioma patterns on the face
- Determining risk and incidence of PHACE in setting of large facial hemangiomas
- Understanding more about complications and outcomes
- Hunting for the cause

The many Faces of PHACE syndrome

- Comprehensive review of 116 previously reported cases and 14 new cases
- Emphasized PHACE as a *spectrum* of anomalies with most children having 1-2 extracutaneous manifestations
- Probably as common as Sturge-Weber syndrome

Metry et al. J Pediatr 2001;139:117-23

AMERICAN JOURNAL OF NEURORADIOLOGY

ORIGINAL RESEARCH

Cervical and Intracranial Arterial Anomalies in 70 Patients with PHACE Syndrome

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BACKGROUND AND PURPOSE: Cerebral and cervical arterial abnormalities are the most common non-cutaneous anomaly in PHACE syndrome, but the location and type of arterial lesions that occur have not been systematically assessed in a large cohort. Our aim was to characterize the phenotypic spectrum of arteriopathy, assess the frequency with which different arteries are involved, and evaluate spatial relationships between arteriopathy, brain structural lesions, and hemangiomas in PHACE syndrome.

MATERIALS AND METHODS: Intracranial MRA and/or CTA images from 70 children and accompanying brain MR images in 59 patients with arteriopathy and PHACE syndrome were reviewed to identify the type and location of arterial lesions and brain abnormalities. Five categories of arteriopathy were identified and used for classification: dysgenesis, narrowing, nonvisualization, primitive embryonic carotid-vertebrobasilar connections, and anomalous arterial course or origin. Univariate logistic regression analyses were performed to test for associations between arteriopathy location, hemangiomas, and brain abnormalities.

RESULTS: By study design, all patients had arterial abnormalities, and 57% had >1 form of arteriopathy. Dysgenesis was the most common abnormality (56%), followed by anomalous course and/or origin (47%), narrowing (39%), and nonvisualization (20%). Primitive embryonic carotid-vertebrobasilar connections were present in 20% of children. Hemangiomas were ipsilateral to arteriopathy in all but 1 case. The frontotemporal and/or mandibular facial segments were involved in 97% of cases, but no other specific associations between arteriopathy location and hemangioma sites were detected. All cases with posterior fossa anomalies had either ICA anomalies or persistent embryonic carotid-basilar connections.

CONCLUSIONS: The arteriopathy of PHACE syndrome commonly involves the ICA and its embryonic branches, ipsilateral to the cutaneous hemangioma, with dysgenesis and abnormal arterial course the most commonly noted abnormalities. Brain abnormalities are also typically ipsilateral.

AJNR Am J Neuroradiol. November 2010;31:1980-6.

Consensus Diagnostic Criteria

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Consensus Statement on Diagnostic Criteria for PHACE Syndrome

Denise Metry, Geoffrey Heyer, Christopher Hess, Maria Garzon, Anita Haggstrom, Peter Frommelt, Denise Adams, Dawn Siegel, Karla Hall, Julie Powell, Ilona Frieden and Beth Drolet

Pediatrics 2009;124;1447; originally published online October 26, 2009;
DOI: 10.1542/peds.2009-0082

Consensus Diagnostic Criteria: Don't need add 5 letters

PHACE	Possible PHACE
Facial hemangioma 5 cm or greater PLUS 1 major or 2 minor criteria	Facial hemangioma plus 1 minor criteria
	Hemangioma neck or torso plus 1 major or 2 minor criteria
	No hemangioma plus 2 major criteria

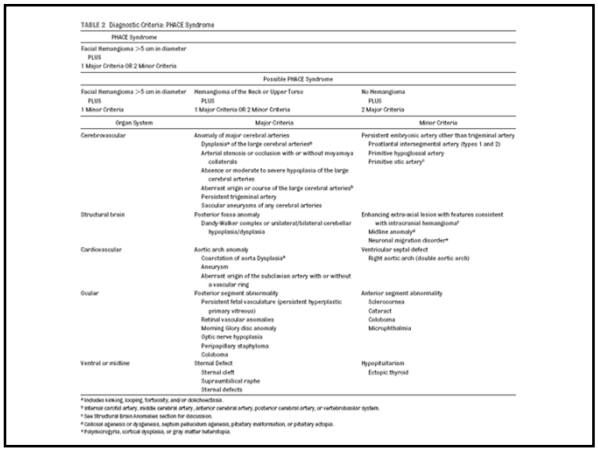


TABLE 2 Diagnostic Criteria: PHACE Syndrome

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

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

Diagnostic criteria: Best assessment *at the time*

- Once we find the cause of PHACE, will need to reasses the disease spectrum
- Also need to reassess over time
- Criteria could be overly restrictive
  - Questionable if you really need a facial hemangioma
- With better treatment hemangiomas of PHACE may be less prominent feature in some cases

How Common is PHACE?

- Not common but not rare
- No good population-based data exist for how many people have PHACE syndrome
- Estimates of incidence of another vascular syndrome, Sturge-Weber, range between one in 20–50,000 live births.
- PHACE is more common than SWS
- *At least* 1/20,000 is "good guess"

Comi AM Lymph ResBiol. 2007, 5: 257-264

Metry D et al. Am J Med Genet A. 2006;140:975-86.

What are the Key Clinical Findings?

PHACE Syndrome Acronym: Take 2

Posterior fossa

Hemangioma of the Face

Arterial + Aorta

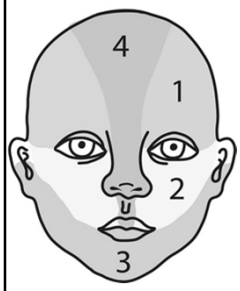
Cardiac

Eye

Other important findings

- S: Sternal and Supraumbilical raphe
- E: Endocrine: Growth, thyroid, pituitary
- E: Ear – hearing loss
- H: Headaches
- A: Airway hemangiomas
- U: Ulcerations

Patterns of facial segmentals correspond to embryololgic patterns



Haggstrom et al.
2006;117:698-703

Prospective study of facial hemangiomas for risk of PHACE risk

We included any facial hemangioma ≥ 22 cm2

33/108 (31%) had PHACE

Mean size with PHACE 86 cm2

Frontotemporal (Seg 1)	28/33
Maxillary (Seg 2) only	1/33
Mandibular (Seg 3)	24/33
2 or more segments	15/33

Haggstrom et al. Pediatrics. 2010;126:e418-26

Cerebrovascular Anomalies

Major	Minor
▪ Abnormal course, width, development of arteries ▪ narrowing ▪ absence ▪ dilated ▪ aneurysm ▪ Moya-Moya ▪ Trigeminal artery	▪ Persistent embryonic arteries(other than trigeminal artery)

Imaging and Clinical Features and Stroke Risk in PHACE Syndrome

Risk Category	Cerebrovascular Anomalies
High[a]	• Multiple vessels with severe narrowing or non-visualization without adequate collateral circulation and Moyamoya disease and Cardiac or Aortic arch anomalies • Severe narrowing/stenosis[b] or non-visualization of 1 major vessel[c] without adequate collateral circulation and Moyamoya disease and Cardiac or Aortic arch anomalies • Severe narrowing/stenosis[b] or non-visualization of 1 major vessel[c] without adequate collateral circulation and Moyamoya disease • Severe narrowing/stenosis[b] or non-visualization of 1 major vessel[c] without adequate collateral circulation and Cardiac or Aortic arch anomalies • Severe narrowing/stenosis[b] or non-visualization of 1 major vessel[c] without adequate collateral circulation
Standard	• Severe narrowing/stenosis[b] of major vessels[c] with adequate collateral circulation • Mild narrowing/stenosis[d] of major vessels[c] with adequate collateral circulation • Hypoplasia, dysplasia, aberrant origin or course of major vessels[c, e] • Persistent embryonic arteries • Aberrant subclavian artery

[a] risk further increased if coexistent cardiac or aortic arch anomalies.
[b] defined as vessel narrowing >75%.
[c] internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, basilar artery, vertebral artery.
[d] defined as vessel narrowing <75%, and categorized as standard risk given known frequency of overdiagnosis with MRA.
[e] any degree of severity.

Drolet B A et al. Pediatrics 2013;131:128-140

Brain Anomalies

Major	Minor
▪ Dandy-Walker complex ▪ Unilateral or bilateral cerebellar hypoplasia/dysplasia	▪ Intracranial hemangioma ▪ Midline anomaly e.g. corpus callosum, septum pellucidum, pituitary malformation, ▪ Neuromigrational disorder (e.g. polymicrogyria, cortical dysplasia, heterotopia)

Cardiovascular

Major	Minor

■ Aortic arch anomaly
  ■ Coarctation aorta
  ■ Abnormal formation such as kinking, looping, tortuosity
■ Aortic arch aneurysm
	■ Aberrant subclavian with/without vascular ring
	■ Right-sided arch
	■ Ventricular septal defect

E= Eye (Ophthalmologic)

Major	Minor
■ Persistent fetal vasculature ■ Morning glory anomaly/Peripapillary excavation ■ Optic nerve hypoplasia	■ Sclerocornea ■ Cataract ■ Coloboma ■ Microphthalmia

Ventral Developmental Defects

Major	Minor
■ Sternal cleft or other defects ■ Suprumbilical raphe	■ Small sternal pits or tags ■ Hypopituitarism ■ Ectopic thyroid

Vascular abnormalities and clinical findings as clues to cause of PHACE

- Looking at cerebrovascular anomalies:
  - Those with **structural brain anomalies** typically have **arterial anomalies** which could explain them
- Eye anomalies also likely due to impaired vasculature as reactive process
- Blanching as clinical finding before development and surrounding hemangiomas

Drolet BA, Frieden IJ. Characteristics of infantile hemangiomas as clues to pathogenesis: does hypoxia connect the dots? Arch Dermatol. 2010 ;146:1295-9

Timing of PHACE embryonic "hit"

- Defects associated with PHACE are early embryologic events, occurring between 4 and 8 weeks gestation
- Hemangiomas may not be evident at birth, but are true birth defects
- At least some have very early embryologic origins

PHACE W/U based on hemangioma risk

Full

- Careful Physical exam
- Eye exam
- Cardiac echo
- MRI/A with contrast

"Lite"

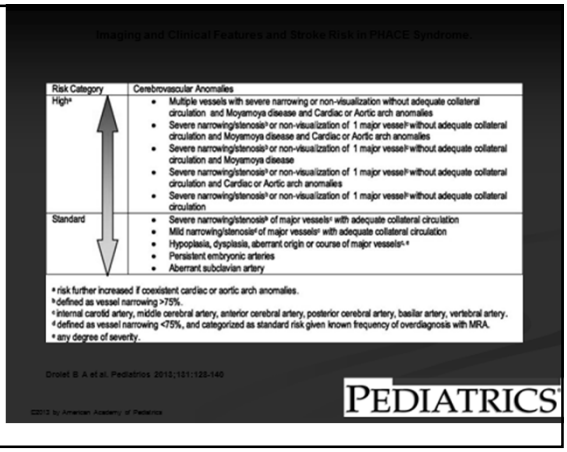
- Careful Physical exam
- Eye exam
- Cardiac echo
- Defer MRI/A unless signs/symptoms

If PHACE is diagnosed, then what?

- Formal pediatric neurology exam (ideally pediatric stroke specialist)
- Other organ-specific care (e.g. eye, ENT)
- Anticipatory guidance
  - Headaches – early onset
  - Motor delays
  - Language/speech delays
  - Airway disease
- If "mild" without symptoms, reevaluation at age 3 to 4 or as needed

Paying extra attention

- Hearing
- Growth velocity
- Hearing testing
- Dental issues
- Hemangioma rebound growth
- **Parents will help us figure this out!**



New and Future Directions

- More defining "severe" vs "mild" PHACE
- Interactions of various anomalies e.g. coarctation aorta and cerebrovascular
- Prognosis – neurologic and neurocognitive
  - Hypotonia and speech delay
  - Identifying risk-factors for stroke
  - Scope and magnitude of headaches
- Propranolol – usage in PHACE patients
- Genetic and molecular studies

Thank you