Title
Stroke in children with posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities (PHACE) syndrome: a systematic review of the literature.

Permalink
https://escholarship.org/uc/item/38h9j0fm

Journal
Stroke, 43(6)

ISSN
0039-2499

Authors
Siegel, Dawn H
Tefft, Kimberly A
Kelly, Teresa
et al.

Publication Date
2012-06-01

DOI
10.1161/strokeaha.112.650952

Peer reviewed
Stroke in Children With Posterior Fossa Brain Malformations, Hemangiomas, Arterial Anomalies, Coarctation of the Aorta and Cardiac Defects, and Eye Abnormalities (PHACE) Syndrome

A Systematic Review of the Literature

Dawn H. Siegel, MD; Kimberly A. Tefft, MD; Teresa Kelly, MD; Craig Johnson, MD; Denise Metry, MD; Patricia Burrows, MD; Elena Pope, MD; Maria Cordisco, MD; Kristen E. Holland, MD; Mohit Maheshwari, MD; Phillip Keith, MD; Maria Garzon, MD; Christopher Hess, MD; Ilona J. Frieden, MD; Heather J. Fullerton, MD; Beth A. Drolet, MD

Background and Purpose—PHACE is an acronym for posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. Several case reports of arterial ischemic stroke (AIS) in individuals with PHACE have been published, but risk factors for AIS in PHACE have not been clearly defined. The objective of this article is to review all cases of stroke in PHACE in children and describe clinical characteristics that may be associated with an increased risk of AIS.

Methods—A literature and registry search was conducted to identify patients with PHACE who had experienced AIS. Data were analyzed to determine age of onset, presenting signs and symptoms, and clinical features among this cohort compared with PHACE without AIS.

Results—Twenty-two individuals with PHACE and AIS were identified. Imaging of the arteries of the head and neck was reported in 20 of 22. Narrowing or nonvisualization of at least 1 great cerebral vessel was present in 19 of 20 and of those, 15 had ≥2 vessels involved. Aortic arch anomalies were reported in 13 of 22 individuals.

Conclusions—Aplasia, hypoplasia, or occlusion of a major cerebral artery appears to be a significant risk factor for AIS in children with PHACE, especially when >1 vessel is involved or if there is coarctation of the aorta. (Stroke. 2012;43:1672-1674.)

Key Words: arterial ischemic syndrome ■ hemangioma ■ Pascual-Castroviejo Type II syndrome ■ PHACE syndrome ■ PHACES association ■ propranolol

Frieden coined the term PHACE syndrome to describe the association of infantile hemangiomas of the head and neck with developmental anomalies.1 PHACE is an acronym for Posterior fossa brain malformations, Hemangiomas, Arterial anomalies, Coarctation of the aorta and cardiac defects, and Eye abnormalities. Approximately 30% of infants with large, facial hemangiomas meet diagnostic criteria for definite PHACE with the most common extracutaneous finding being abnormalities of the craniofacial arteries. The relationship between arteriopathy and arterial ischemic stroke (AIS), a rare but devastating complication affecting a subset of individuals with PHACE, is poorly understood.

In this study we review all known cases of PHACE-related stroke to determine age of onset, presenting symptoms, clinical characteristics, and associated comorbidities to further understand potential risk factors.

Methods

This study was approved by the Institutional Review Board, Children's Hospital of Wisconsin. Scopus, PubMed, and Medline were searched for studies on PHACE and stroke from 1982 to 2011. Any report of stroke in patients with PHACE was included in the study. The Pediatric Stroke Registry was reviewed for children who had experienced an ischemic stroke. The most common extracutaneous finding of PHACE is an arteriopathy with a preference for the large craniofacial arteries, which may be symptomatic or asymptomatic. The relationship between arteriopathy and arterial ischemic stroke (AIS), a rare but devastating complication affecting a subset of individuals with PHACE, is poorly understood.

In this study we review all known cases of PHACE-related stroke to determine age of onset, presenting symptoms, clinical characteristics, and associated comorbidities to further understand potential risk factors.

Received January 24, 2012; accepted February 8, 2012.

From the Departments of Dermatology and Pediatrics (D.H.S., K.E.H., B.A.D.), Radiology (T.K., C.J., M.M.), and Dermatology (P.K.), Medical College of Wisconsin, Milwaukee, WI; the Department of Dermatology (K.A.T.), University of Kansas Medical Center, Kansas City, KS; the Department of Dermatology (D.M.), Baylor College of Medicine, Houston, TX; the Department of Diagnostic and Interventional Imaging (P.B.), University of Texas Health Sciences Center, Houston, TX; the Department of Dermatology and Pediatrics (E.P.), University of Toronto, Toronto, Canada; the Department of Dermatology (M.C.), Hospital de Pediatria J.P. Garrahan, Buenos Aires, Argentina; the Department of Dermatology and Pediatrics (E.P.), University of Toronto, Toronto, Canada; the Department of Dermatology and Pediatrics (M.G.), Columbia University, New York, NY; and the Departments of Radiology and Biomedical Imaging (C.H.), Dermatology and Pediatrics (I.J.F.), and Neurology and Pediatrics (H.J.F.), University of California–San Francisco, San Francisco, CA.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.112.650952/-/DC1.

Correspondence to Dawn H. Siegel, MD, Department of Dermatology, 8701 Watertown Plank Road, C2010, Milwaukee, WI 53226. E-mail dsiegel@mcw.edu

© 2012 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.112.650952
A total of 148 abstracts were identified in the initial literature review. Thirty of those were selected for detailed review. Using the previously mentioned definition of stroke, 11 of 30 articles (publication years 1998–2011) detailed individuals with PHACE and stroke for a total of 18 cases.4–13 Four articles (publication years 1998–2011) detailed individuals with stroke in the PHACE population. A total of 148 abstracts were identified in the initial literature review. Thirty of those were selected for detailed review. Using the previously mentioned definition of stroke, 11 of 30 articles (publication years 1998–2011) detailed individuals with PHACE and stroke for a total of 18 cases.4–13 Four articles (publication years 1998–2011) detailed individuals with stroke in the PHACE population.

Clinical Variables
Age at presentation of stroke, gender, presenting symptoms, neurological impairment poststroke, infarct distribution, and hemangioma location were noted. Location, type, and severity of arteriopathy were recorded as well as type of stroke. Also noted were the presence of aortic arch anomaly, cardiac or arch surgery, and synthetic graft.

Results

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of acute presentation (n=15)</td>
<td>Range, 3 mo to 5 y</td>
<td>Median, 10.5 mo</td>
<td>Mean, 13.6 mo</td>
</tr>
<tr>
<td>Gender</td>
<td>Female: 18</td>
<td>Male: 4</td>
<td></td>
</tr>
<tr>
<td>Presenting symptoms of acute AIS (n=15)</td>
<td>Seizures only: 3</td>
<td>Hemiparesis only: 5</td>
<td>Both seizures and hemiparesis: 6</td>
</tr>
</tbody>
</table>

PHACE indicates Posterior fossa brain malformations, Hemangiomas, Arterial anomalies, Coarctation of the aorta and cardiac defects, and Eye abnormalities; AIS, arterial ischemic stroke.

Arteriopathy
Of the 22 individuals, 20 underwent imaging of the cervical and intracranial arteries by MR angiography or conventional angiogram. Of those 20, 19 (95%) had either narrowing or nonvisualization of at least 1 great cerebral vessel; 15 of 20 (75%) had narrowing or nonvisualization in ≥2 vessels. Dysgenesis was noted in 15 of 20 (75%), and in 5 of 20 (25%), dysgenesis affected ≥2 vessels. The presence of both anterior and posterior circulation arteriopathy was present in 16 of 20 (80%). Moyamoya phenomenon was noted in 4 of 20 (20%). Four reports noted “progression” of arteriopathy. Four individuals were treated with synangiosis.

Cardiac Anomalies
Cardiovascular findings were reported in 15 of 22 individuals. Aortic anomalies were noted in 13 of 15 with coarctation (7), narrowing (3), interrupted arch (1), right arch (1), and saccular aneurysm (1).

Structural Brain Anomalies
Posterior fossa abnormalities were present in 5 of 22 individuals (23%), 2 with Dandy-Walker malformation and 3 with cerebellar hypoplasia.

Hemangioma Location
Hemangiomas were located in the S1 (frontotemporal) segment in 17 of 22 (77%), S3 (mandibular) segment in 14 of 22 (64%), and S4 (frontonasal) segment in 7 of 22 (32%). Extension to the scalp, posterior neck, or torso was noted in 11 of 22 (50%).

Medication Exposure
Medication exposure was reported in 14 individuals, all of whom received corticosteroids. Additional medications included vincristine, interferon, and propranolol. One subject was treated for hypertension with amloidipine, aldactazide, and nadolol.

Comorbidities
Prothrombotic workup was reported in 7 of 22. One was positive for a homozygous C677T mutation of the methylene tetrahydrofolate reductase gene. In 2 cases the stroke occurred after infection, gastrointestinal illness in 1 and Listeria monocytogenes meningitis in another.

Discussion
This literature and registry-based series reports a previously underemphasized cause of AIS in childhood.1,5–14 There are 3 possible mechanisms for AIS with PHACE: (1) artery-to-artery embolism, in which a thrombus forms in a stenotic or dysplastic cervical or cerebral artery, embolizes, then occludes a downstream cerebral artery; (2) ischemia from reduced blood flow and inadequate cerebral perfusion (ie, “watershed infarction”) distal to a flow-limiting arterial stenosis or occlusion with inadequate collateralization (eg, lack of intact circle of Willis and/or poor pial collaterals); or (3) cardioembolism due to structural abnormalities of the heart or proximal aorta.
with PHACE-related stroke has a higher rate of aortic anomalies; 59% versus 36%.14

The majority (21 of 22) had severe underlying arteriopathy. More than 59% had nonvisualization of a major cerebral artery compared with 20% of the Hess cohort of 70 patients with PHACE with arterial anomalies.15 It is possible that the higher proportion of patients with these imaging findings is biased by the inherent pathophysiology of stroke with arterial narrowing or occlusion at the time of symptoms reflecting intravascular thrombus and/or the acute changes in blood flow accompanying infarction. However, the extent of narrowing or nonvisualization, presence of moyamoya collaterals, and the frequent observation of these findings in an arterial territory not directly related to the patient’s acute symptoms mitigate against this possibility. Of those patients with stroke and appropriate imaging of the arteries, none had arterial dysplasia as the sole class of arteriopathy. Long-term cohort studies with baseline imaging before the onset of stroke symptoms are required to establish whether arterial narrowing actually carries an inherently higher risk of developing AIS than other types of arteriopathy in PHACE.

Limitations of this study include its retrospective nature, the lack of access to medical records and radiological images, and the variability in imaging techniques used. Many reported cases reviewed in this series had poststroke imaging only, and as noted previously, nonvisualization of an artery after AIS could represent either a congenitally hypoplastic or absent artery or an acute embolic occlusion.

Conclusions

Children with PHACE have a high incidence of arteriopathy (many with moyamoya phenomenon) that puts them at risk for stroke. The majority of PHACE-related AIS cases with neuroimaging had aplasia, hypoplasia, or occlusion of a major cervical or cerebral artery. There was also a high incidence of aortic arch anomalies. Stroke risk is likely complex due to the potential contribution of the degree of arterial stenosis, absence of an intact circle of Willis, and coexisting aortic arch anomalies. Clinical studies are needed to determine the impact of systemic therapies such as oral corticosteroids and propranolol on the risk of demand-related ischemia in patients with PHACE and severe arteriopathy.

Acknowledgments

We thank Shawna Joachim, Medical College of Wisconsin, for editing and submission assistance.

Source of Funding

This review was funded by the Greater Milwaukee Foundation Grant 2207058.

Disclosures

Dr Frieden was a consultant at Pierre-Fabre Dermatology and the chair of the Data Safety Monitoring Board for the HEMANGIOL study.

References