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Authors

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

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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 craniocervical 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

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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 (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.

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

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Table. Summary of Clinical Variables in PHACE With AIS

Timing of presenting symptoms of stroke
Delayed: 6/22
Acute: 15/22
Unknown: 1/22
Age at time of acute presentation (n=15)
Range, 3 mo to 5 y
Median, 10.5 mo
Mean, 13.6 mo
Gender
Female: 18
Male: 4
Presenting symptoms of acute AIS (n=15)
Seizures only: 3
Hemiparesis only: 5
Both seizures and hemiparesis: 6
Neurologic deterioration and death: 1

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

used to conduct a literature review. Two clinical PHACE registries and a panel of experts at a PHACE Syndrome Research Workshop were queried for unpublished individuals.

Data Extraction and Methodologic Quality

Abstracts were reviewed to identify cases of stroke, and the relevant articles were reviewed in full by 3 authors. A pediatric neurologist (H.J.F.) independently reviewed the selected articles to confirm the stroke diagnosis and data regarding cerebrovascular imaging. For inclusion in this analysis, stroke was defined by (1) clinical symptoms such as sudden onset of focal neurological deficit, headaches, loss of consciousness, or seizure; and (2) CT or MRI documenting a large-territory infarct for arterial ischemic stroke or intracerebral, subarachnoid, and/or intraventricular hemorrhage in a location and of a maturity consistent with the neurological signs and symptoms.[2] We included individuals in whom a remote yet symptomatic infarct was diagnosed in a delayed fashion.[3]

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. Finally, comorbidities and medication exposures were recorded (online-only Data Supplement Table I).

Results

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.[1,4–13] Four unpublished cases were identified through registries and the PHACE research workshop. Of these 22 cases, all had presumed AIS. The age of onset, gender, presenting signs, brain region, or arterial territory are summarized in the Table and online-only Data Supplement Tables I and II.

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 amlodipine, 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 embolisms, 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) cardioembolisms due to structural abnormalities of the heart or proximal aorta. As compared with previously published PHACE case series, this current series of individuals

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.

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