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PHACE Syndrome: A Retrospective Review of 23 Patients

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Abstract

We present 23 patients with PHACE syndrome showing similarities in our population with data that already exist while highlighting neurodevelopmental occurrences arising in a subset of these patients.

We present a retrospective review of 23 patients with PHACE syndrome (Metry 2009 criteria) (1) from 2003 to 2012 from records of the Children's Hospital of Philadelphia. Demographic characteristics, hemangioma distribution (Haggstrom segment map) (2) and extracutaneous manifestations mirror data that exist for PHACE syndrome. Nevertheless, although there were no recorded acute ischemic strokes, several of our patients displayed seizures, developmental delay, late-onset childhood headaches, and sensorineural hearing loss.

INFANT DEMOGRAPHICS

Nineteen (83%) of the patients were girls. Parents self-reported 13 (57%) as white, 6 as Hispanic or Latino (26%), 2 as black (9%), 1 as Asian (4%), and 1 as Middle Eastern (4%). Four (19%) were born preterm.

HEMANGIOMA DISTRIBUTION

Segment 1 was most common, occurring in 17 patients (74%), followed by segment 2 in 8 (35%), segment 3 in 14 (61%), and segment 4 in 8 (35%). Eleven (48%) had involvement of multiple segments. Hemangiomas were right-sided in nine patients (39%), left-sided in seven (30%), and bilateral in seven (30%).

EXTRACUTANEOUS MANIFESTATIONS

Cerebrovascular anomalies were most common, occurring in 21 patients (91%), followed by structural brain malformations in 16 (70%), cardiac anomalies in 10 (45%), sternal

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malformations in 8 (35%), and eye anomalies in 3 (14%). All 17 patients with segment 1 involvement and all 7 with bilateral involvement of any segment had cerebrovascular anomalies, brain anomalies, or both. Segment 3 involvement was noted in 80% (8/10) with cardiac anomalies, all 7 with sternal malformations or defects, and all 3 with airway hemangiomas.

TREATMENT

Nineteen patients (83%) were treated with systemic therapies, including oral prednisolone (58%, 11/19), oral prednisolone plus intravenous vincristine (5%, 1/19), oral prednisolone plus propranolol (11%, 2/19), and propranolol monotherapy (26%, 5/19). Additional therapies consisted of interferon alfa (1/19), aspirin (2/19), pulse dye laser (10/19), intralesional steroids (1/19), and topical timolol (1/19).

COMPLICATIONS OF TREATMENT

Bleeding with ulceration was the most common complication (oral prednisone [21%] and propranolol [29%]). Other reported side effects while taking oral prednisolone were hypertension (2/14); adrenal suppression (1/14); upper gastrointestinal bleeding (1/14); reflux, vomiting, and abdominal pain (1/14); and thrush (1/14). A side effect from propranolol was asymptomatic hypotension (1/9). Propranolol-induced hypoglycemia was not reported. Other reported side effects noted in both groups included growth delay (3/23) and seizures with normal electroencephalograms (EEGs) (3/23).

NEUROLOGIC OUTCOMES

Clinical or radiologic evidence of postnatal stroke was not observed. One patient demonstrated a prenatal cerebellar insult noted on fetal magnetic resonance imaging (Table 1).

Seizure activity was described in three patients (13%), with central nervous system findings significant for intracranial hamartomas ($n = 1$), Dandy Walker malformation ($n = 1$), and cerebrovascular anomalies ($n = 3$).

Late-childhood headaches were described in three patients (13%) with neurologic histories notable for structural brain anomalies ($n = 2$), cerebrovascular malformations ($n = 2$), and reported seizures ($n = 1$).

Neurodevelopmental delays were present in four patients (17%) and included gross and fine motor delay ($n = 3$) and expressive language delay ($n = 2$). These patients had cerebrovascular malformations ($n = 4$), structural brain anomalies ($n = 3$), attention deficit hyperactivity disorder ($n = 1$), autism spectrum disorder ($n = 1$), and sensorineural hearing loss ($n = 3$).

This report introduces 23 new patients to the literature and further supports many of the demographic features, clinical findings, and complications seen in this population (3). Our report highlights that, despite concern for a risk of stroke (4), children with PHACE may be

at risk for other neurologic problems, including developmental delay (5). In our patients with these other neurologic problems, EEGs and repeat imaging suggested no relationship between central nervous system anomalies and no evidence of acute ischemic stroke.

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TABLE 1

Neurologic Outcomes

Patient	Neurologic outcomes reported	Age at onset of headache or seizure	Imaging after onset of headache or seizure	Most recent follow-up
1	Left frontal headaches	6 years	MRI stable	7 years: continued headaches
	Mild low-frequency hearing loss			
	Attention deficit hyperactivity disorder			
2	Simple childhood motor tics autism spectrum disorder	9 years	EEG c/w tics, MRI/MRA stable	9 years: tics, annual surveillance MRI/MRA stable
3	Chronic headaches	4 years	MRI stable	5.5 years: continued headaches
4	Cerebellar ischemic insult	Prenatal	MRI/MRA stable	3 years: stable
	Mild decreased tone and motor delay in lower extremities			
	Hearing loss			
5	Seizures	4 months	EEG wnl	2.5 years: continued seizure activity and new-onset headaches
	Headaches	2.5 years	MRI data unavailable	
	Musculoskeletal developmental delays			
6	Seizures (3 episodes)	2 years	EEG wnl, MRI stable	3.5 years: seizures resolved
	Mild fine motor delay			
	Expressive language delay			
	Hearing loss			
7	Expressive language delay			2 years: stable

MRI, magnetic resonance imaging; MRA, magnetic resonance angiogram; EEG, electroencephalography; c/w, consistent with; wnl, within normal limits.