Genetics Corner:
Genetics Corner: PHACES Syndrome in an Infant with Segmental Facial Hemangiomas and Stridor

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"A 34-day-old female infant was admitted to the Pediatric Intensive Care Unit for hypoxic respiratory insufficiency and worsening biphasic stridor. She was born at 34 weeks gestation but had no problems at birth and was discharged home with her mother."

Case History:

A 34-day-old female infant was admitted to the Pediatric Intensive Care Unit for hypoxic respiratory insufficiency and worsening biphasic stridor. She was born at 34 weeks gestation but had no problems at birth and was discharged home with her mother. Although not present at birth, by a few days of age, the parents noted several small, nonconfluent facial hemangiomas on the lower lip, chin, sublingual area, and preauricular region on the left. Stridor began at about ten days of age, and the baby was diagnosed with laryngomalacia at the first pediatric visit at about two weeks of age. She was admitted to a community hospital for stridor for one day and discharged with oral prednisone. She failed to improve and was admitted to the PICU from the emergency department of another hospital at four weeks of age. Laryngoscopy and bronchoscopy demonstrated a subglottic hemangioma. The infant was initially treated with CPAP in the ED, NIMV in the PICU, and then intubated in the OR on day 2 of her hospital course. She remained intubated and mechanically ventilated for ten days while she was treated with propranolol and decadron. When a supraglottoplasty was performed on day 11, there was an improvement in the subglottic hemangioma, and she was extubated. The sublingual hemangioma had also resolved.

"The consultant diagnosed PHACES syndrome based on the presence of segmental facial hemangiomas in the mandibular distribution with two major criteria affecting the midline chest and abdominal wall."

A genetics consultation was requested on day 13. She had facial hemangiomas as above, a supraumbilical raphe, widely spaced nipples, bifid xiphoid, an area of skin hypoplasia over the midsternum, and a superior sternal cleft, most evident on inspiration, tightly adducted thumbs, fisted hands and moderately increased tone in the lower extremities. The consultant diagnosed PHACES syndrome based on the presence of segmental facial hemangiomas in the mandibular distribution with two major criteria affecting the midline chest and abdominal wall. A chromosome microarray was normal. An echocardiogram revealed a patent foramen ovale. A fundal exam was normal. A brain MRI was considered to be within normal limits: "mild prominence of the bilateral frontotemporal extra-axial spaces, likely related to benign enlargement of the extra-axial spaces in infancy (BESSI)." However, a brain magnetic imaging angiogram revealed neurovascular abnormalities: "markedly decreased caliber/diminutive appearance of the right middle cerebral artery including the distal vessels, which remain patent; subtle caliber change of the right ICA terminus, which may represent possible ectasia/small fusiform aneurysm." In addition, the right A1 segment of the ICA was absent, and the left posterior communicating artery was not visualized. MRA of cervical vessels was considered essentially normal although: "possible diminutive/hypoplastic right brachiocephalic artery versus imaging artifact was documented. Neurosurgical and interventional radiology consultations did not recommend intervention. The infant was discharged on day 21 on propranolol, 1.9 mg/kg/day divided BID.

"In addition, the right A1 segment of the ICA was absent, and the left posterior communicating artery was not visualized. MRA of cervical vessels was considered essentially normal although: "possible diminutive/hypoplastic right brachiocephalic artery versus imaging artifact was documented. "

Discussion:

Infantile hemangiomas are benign, common, isolated, and usually self-limited vascular tumors. However, as this patient illustrates, 2-3% of children with infantile hemangiomas have PHACES syndrome (OMIM #60519), a neurocutaneous disorder characterized by typically large (>5cm) segmental infantile hemangiomas, usually on the face, scalp or cervical region, and extracutaneous anomalies. This disorder of unknown etiology is an acronym for its most common features: ***p***osterior fossa malformation, segmental infantile ***h***emangiomas, ***a***rterial anomalies, ***c***ardiac defects, ***e***ye abnormalities, and ***s***ternal defect or ***s***upraumbilical raphe. (1) In early literature, it was referred to as PHACE syndrome before the sternal elements were recognized as part of the condition. Most patients with PHACES syndrome are female, with a skewed distribution of up to 9F:1M. Segmental facial hemangiomas usually occur shortly after birth in areas that correspond to facial developmental fields: frontotemporal (S1), maxillary (S2), mandibular (S3), and frontonasal (S4). (2) Facial hemangiomas typically re-

spond rapidly to propranolol. (3)

"Airway infantile hemangiomas (AIH) present with hoarseness and stridor from birth to 4 months. Up to 50% of AIH occur in association with PHACES syndrome."

Airway infantile hemangiomas (AIH) present with hoarseness and stridor from birth to 4 months. Up to 50% of AIH occur in association with PHACES syndrome. Although AIH can occur without cutaneous manifestations, most are associated with facial hemangiomas in the mandibular or "beard" (S3) distribution that, as in the patient described above, includes the lower lip, chin, mandible, and preauricular area. Biphasic stridor is typical of subglottic AIH. Steroids are ineffective, but most AIH responds rapidly to propranolol, 1-3 mg/kg/d. In a retrospective review of 36 patients with AIH successfully treated with oral propranolol, the median length of propranolol treatment was 15 months. Relapses occurred in 15% of this cohort. (4)

"Revised diagnostic criteria for PHACES syndrome allows a definite diagnosis of the syndrome when a segmental hemangioma of 5 cm or greater occurs with one major or two minor criteria or a hemangioma of less than 5 cm occurs with two major criteria. (5)"

Revised diagnostic criteria for PHACES syndrome allows a definite diagnosis of the syndrome when a segmental hemangioma of 5 cm or greater occurs with one major or two minor criteria or a hemangioma of less than 5 cm occurs with two major criteria. (5) Airway infantile hemangiomas (AIH) present with hoarseness and stridor from birth to 4 months. Up to 50% of AIH occur in association with PHACES syndrome. The brain and cervical arteriopathy of PHACES syndrome commonly involve the internal carotid artery and its embryonic branches, ipsilateral to the cutaneous hemangioma. In one study, dysgenesis was the most common intracranial vascular anomaly, seen in 39/70 cases of PHACES syndrome. Aneurysms were frequently encountered within the dysplastic segments. Three of the 70 patients had remote infarcts on imaging. Among those with conventional brain MR imaging, structural abnormalities were present in 41% (24/59). (6)

LUMBAR syndrome is a similar disorder with a different distribution of anomalies. This acronym is for ***l***ower body hemangiomas, ***u***rogenital anomalies, ***m***yelopathy, ***b***one deformities, ***a***norectal malformations/***a***rterial anomalies, and ***r***enal anomalies. There is speculation that, as yet, uncharacterized somatic gene mutations cause both PHACES and LUMBAR syndromes. (7)

The evaluation of an infant with suspected PHACES syndrome should include an echocardiogram, ophthalmologic exam, brain MRI and MRA. In a retrospective review of infantile segmental or periorbital hemangiomas, the hemangioma size (>5 mc or not) did not correlate with extracutaneous anomalies. (8) The authors concluded that infants with small, <5 cm segmental hemangiomas should be evaluated for other anomalies, a conclusion that this case also supports.

Figure 1: (A, B): Facial hemangiomas of the lower lip, chin (Figure 1A), and preauricular area (Figure 1B) are within the mandibular or S3 distribution, but they are small and discontiguous, measuring less than 5 cm.

Practical applications:

1. Consider the diagnosis of PHACES syndrome in infants with segmental facial infantile hemangiomas, especially when accompanied by cardiac, brain, ocular, and sternal defects or a supraumbilical raphe.

2. When PHACES syndrome is suspected, regardless of the hemangioma size, evaluate for extracutaneous anomalies of the heart, eyes, and brain by ordering an echocardiogram, ophthalmology consult, and brain MRI and MRA. Appreci-

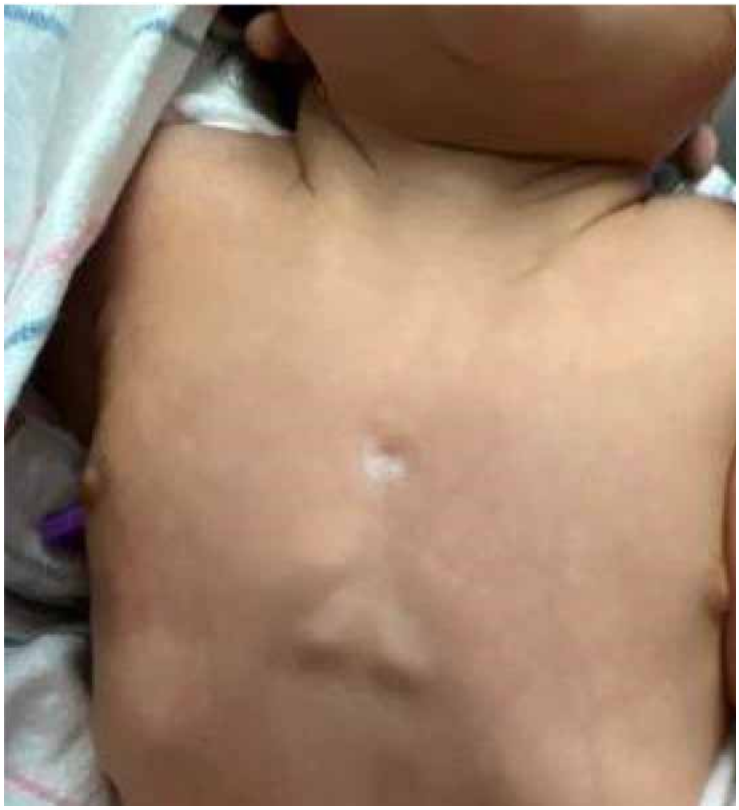

Figure 2: (A, B)These two views of the chest illustrate the supra-umbilical raphe (Figure 2A), widely spaced nipples, bifid xiphoid process (Figure 2B), and midline region of dermal hypoplasia over the sternum. There is a subtle cleft of the superior sternum, more evident on inspiration (Figure 2A).

ate that neurovascular anomalies increase the risk for infantile stroke.

3. Appreciate that airway hemangiomas are more frequent in the presence of segmental facial infantile hemangiomas in the S3, mandibular, or "beard" distribution. Specifically, understand that biphasic stridor is a sign of subglottic infantile hemangioma.

4. Recall that propranolol is the treatment of choice in infantile hemangiomas, and that relapse can occur after treatment is discontinued.

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