

Rapid Involuting Congenital Hemangioma in the Setting of PHACE Association

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KEY WORDS

hemangioma, PHACE, RICH, infant

ABBREVIATIONS

GLUT-1—glucose transporter-1

IH—infantile hemangioma

NICH—noninvoluting congenital hemangioma

PHACE—posterior fossa anomalies, hemangiomas, arterial anomalies, cardiac anomalies, and eye anomalies

RICH—rapidly involuting congenital hemangioma

Dr Patrick conceptualized the study, drafted the initial manuscript, and reviewed and revised the manuscript; Ms Oh drafted the initial manuscript and reviewed and revised the manuscript; Drs Baumann, Yadav, Guzzetta, Rubin, and Oh conceptualized the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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abstract

Rapidly involuting congenital hemangioma (RICH) is an uncommon vascular tumor that, unlike infantile hemangioma, is largely developed at birth and undergoes rapid postnatal involution. To date, RICH has often been described in the setting of an isolated lesion, whereas infantile hemangioma is a well-known feature of numerous syndromes and associations, including the association of posterior fossa anomalies, hemangioma, arterial anomalies, cardiac anomalies, and eye anomalies. The authors report a unique case of RICH in the setting of this association. *Pediatrics* 2014;133:e1777–e1780

PHACE association, a term first coined by Frieden et al¹ in 1996, describes a constellation of combined findings including posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities or aortic coarctation, and abnormalities of the eye. Hemangiomas described in PHACE are invariably the common infantile lesions, although they are often described as plaque-like and macular, with tendencies toward ulceration.² Importantly, the infantile hemangioma (IH) of PHACE follow the classic pattern of minor to no presentation at birth, with a period of rapid proliferation, followed by plateau and prolonged involutinal phases.

Congenital hemangioma is a distinct entity from IH, with 2 subtypes: rapidly involuting congenital hemangioma (RICH) and noninvoluting congenital hemangioma (NICH). Both types of congenital hemangioma are fully developed at birth, unlike IH, and either quickly involute (RICH) or remain largely unchanged with time (NICH). Although there are several other significant differences between these congenital hemangiomas and IH, one curious finding is that, to date, congenital hemangiomas have not been described in association with other syndromic or systemic features. The authors present an infant with a large facial and scalp RICH, cardiac anomalies, and significant intracranial arteriovenous fistulae consistent with PHACE association.

CASE REPORT

A 1-day-old male infant was transferred to the NICU at our institution for a large congenital right facial vascular anomaly (Fig 1). The mother's pregnancy was complicated by gestational diabetes, which necessitated serial prenatal ultrasonographic studies. During her 34-week prenatal ultrasonographic examination, the mother was informed of "excess skin and tissue over the baby's



FIGURE 1

On day of life 1, a large right facial vascular anomaly is seen obscuring the right eye.

right eye" that was thought to be inconsequential (Fig 2). After birth at 36 weeks' gestational age, the large right facial vascular anomaly was documented. During transfer to our institution, the infant developed respiratory distress, tachypnea, and hypoxemia necessitating supplemental oxygen.

Upon arrival, a chest radiograph revealed cardiomegaly, and subsequent echocardiogram documented pulmonary hypertension. Cranial ultrasonography demonstrated a high-flow solid tumor of the right forehead and



FIGURE 2

Prenatal ultrasound at 34 weeks' gestation. Vascular anomaly is seen over the right eye.

periorbital soft tissue and a cyst in the right posterior cranial fossa. Magnetic resonance studies confirmed the presence of the presumed congenital hemangioma, in addition to a large dural arteriovenous fistula in the posterior cranial fossa with an enlarged right vertebral artery. The patient subsequently developed high-output congestive heart failure that was suspected to be secondary to the dural arteriovenous fistula, necessitating embolization. Repeat echocardiogram demonstrated both atrial septal defect and patent ductus arteriosus.

The congenital hemangioma began to involute rapidly, without active intervention, and the diagnosis of RICH was made; by day of life 43, the lesion had regressed beyond the superior aspect of the right orbit (Fig 3). In follow-up at 4 months of age, there was significant flattening of the lesion, with no functional impairment of the right eye (Fig 4). By 1 year of age, the RICH was completely macular, though hyperemic, and there was no involvement of the right upper eyelid (Fig 5). His overall medical condition was stable, and his family is considering pulsed-dye laser treatment of the residual hyperemia.

DISCUSSION

Congenital hemangioma is an uncommon subtype of hemangioma, with the infantile form being significantly more common. Unlike IH, congenital hemangioma can be documented on prenatal ultrasonography and is fully developed at birth. IH typically presents with a herald lesion a few days to weeks after birth and follows a well-described progression of stages: nascent, proliferative, plateau, and involutinal.³ Congenital hemangiomas, on the other hand, are fully developed at birth and can be classified as RICH or NICH.⁴ After birth, the RICH lesion is stable in size, and involution often begins early in the postnatal period. Time to complete

**FIGURE 3**

At day of life 43, the lesion has regressed beyond the superior aspect of the right orbit.

**FIGURE 4**

At 4 months of age, there is significant flattening of the lesion, with no impairment of the right eye.

resolution of RICH can vary from 8 to 14 months, often with significant dermal and subcutaneous atrophy.⁴ The mechanism of resolution is unknown, although it is speculated to be accelerated apoptosis.^{5,6}

Pascual-Castroviejo⁷ initially described findings consistent with PHACE in 1978. Both Pascual-Castroviejo⁷ and Frieden et al¹ described cases of large hemangiomas with concurrent Dandy–Walker malformations and other variable defects. The IH in PHACE often has a progressive pattern of growth and

**FIGURE 5**

At 1 year of age, the lesion is completely macular, with no involvement of the right upper eyelid.

regression and is classically raised bright red plaques, although there may be varying patterns of lesion behavior.² The majority of IH in PHACE is in the cervicofacial area and is usually of segmental morphology.^{8,9} Segmental IH has been hypothesized to conform to a unique developmental unit, and there are 4 segments in which they tend to aggregate.⁹ Our patient had an S1 lesion involving the frontotemporal region. The maxillary region is analogous with S2, whereas S3 is mandibular and S4 frontonasal.^{2,9}

IH has been well described in patients with PHACE association, and a prospective study revealed that in infants with large facial hemangiomas, one-third had extracutaneous manifestations consistent with PHACE.¹⁰ The definition of PHACE consists of the characteristic facial IH and at least 1 extracutaneous manifestation.¹¹ The 2009 consensus statement clarified the diagnostic criteria for PHACE: the presence of a hemangioma greater than 5 cm² of the head (face or scalp) plus 1 major criterion or 2 minor criteria.¹² Major criteria include an anomaly of major cerebral arteries, Dandy–Walker complex, aortic arch anomaly, a posterior segment anomaly of the eye, sternal defect, and others.¹² Minor defects include more common congenital cardiac

lesions such as atrial septal defect, ventricular septal defect, patent ductus arteriosus, and others.¹²

Historically, congenital hemangioma and IH have been regarded as separate entities,¹³ although more recent reports have suggested that these lesions may be on a spectrum of vascular tumors.^{4,6} A key basis for the distinction between congenital and infantile hemangiomas is the expression of glucose transporter-1 (GLUT-1). GLUT-1 expression is limited to the microvascular endothelium of blood tissue barriers of the central nervous system, placental trophoblast, and areas of hypoxia and necrosis within other types of vascular tumors.^{2,14} Importantly, GLUT-1 is not present in the vasculature of normal skin and subcutaneous tissue, yet it is highly expressed in the capillary endothelium of IH. This has led to the hypothesis of the possible placental origin of hemangiomas.¹⁴ GLUT-1 expression has also been interpreted to be an indicator of a hypoxic milieu, and it has been theorized that IH develops as a rescue to hypoxic tissue in the setting of PHACE syndrome.^{2,15} To date, RICH and NICH have not been found to express GLUT-1.¹⁴

Although there is some evidence that congenital hemangiomas and infantile hemangiomas are histologically distinct, similarities exist between these 2 types of hemangioma. Insulinlike growth factor 2, which is upregulated in IH and indirectly linked to expression of GLUT-1, is found in RICH and NICH specimens, albeit at very low levels. The level of insulinlike growth factor 2 mRNA expression in congenital hemangiomas was comparable to that of IH in the late involuting and involuted phases.¹⁶ A definitive explanation for such a finding is not yet clear, although it may be extrapolated that congenital hemangiomas are analogous to later-stage infantile hemangiomas. Mulliken and Enjolras⁶ described 2 groups of patients who embody the “missing

links” connecting congenital and infantile hemangiomas: patients who either had RICH or NICH along with IH and patients who were initially diagnosed with RICH but with incomplete involution, persisting as NICH. With the latter it was hypothesized that RICH may be an earlier form of NICH, with the NICH having undergone its involution phase in utero, suggesting a spectrum

of behavior for what were originally deemed to be distinct lesions.¹⁷

Such accounts seem to represent variations on a theme, with the implication that delineations between vascular lesions are more ambiguous than traditionally believed. The cause of diverging behaviors has not been discovered, although the idea of somatic mutations leading to varying

phenotypes has been introduced.^{18,19} Mulliken and colleagues¹⁸ introduced the idea of a unified theory of origin for congenital and common hemangiomas; application of this hypothesis, in the case of our patient, allows a plausible explanation for the development of the rare RICH as the hemangioma within a polymalformative syndrome such as PHACE association.

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