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Infantile and congenital hemangiomas

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ABSTRACT

Infantile hemangiomas (IHs) are the most common benign vascular tumors of infancy. Since they predominantly involute without significant residua, the majority do not require treatment. Indications for intervention include ulceration, prevention of disfigurement, and impairment of function or vital structures. Some IHs have associated structural anomalies. When and which IH to treat requires knowledge of the natural history and clinical findings of increased risk. Congenital hemangiomas (CHs) are fully formed at birth. They also differ from IHs in their histological and immunohistochemical findings and thus represent a distinct clinical entity. Their clinical characteristics and management are also discussed.

Introduction

The term "hemangioma" has been used both correctly and incorrectly in the literature for a variety of vascular lesions. Infantile hemangiomas (IHs) are vascular tumors, usually absent at birth or present as a premonitory mark with rapid post-natal growth followed by slow involution. IHs are the most common tumor of infancy and childhood, occurring in ~4% of children.[1] While many clues have emerged regarding pathogenesis, many questions still remain. Therapy has changed dramatically in the past 5 years, and early treatment is critical for those requiring systemic medications as many interventions limit proliferation.

Infantile hemangioma

Pathogenesis

The pathogenesis of IH is not completely understood and is likely multifactorial. Several reviews have summarized recent advances.[2] IHs are more common in females, supporting the hypothesis that estradiol increases endothelial cell proliferation.[3] Vascular endothelial growth factor (VEGF), more than estradiol, invoked hemangioma-derived endothelial cell (HemEC) proliferation, but the combination of VEGF and estradiol was synergistic.[4]

Stromal cells isolated from proliferating IHs release VEGF.[5] VEGF can bind receptors, such as vascular endothelial growth factor receptor (VEGFR)-2, which are expressed on proliferating IHs and HemECs and then can stimulate growth.[6]

There is increasing evidence that IHs arise due to an intrinsic defect in an endothelial or progenitor cell, through either a somatic (post-zygotic) mutation or a germline mutation.[6] Twin studies showed no differences in concordance between monozygotic and dizygotic twins; however, there is a report of 3 families with autosomal-dominant inheritance of IH and linkage to 5q.[7] Some evidence suggests that IHs are clonal tumors; HemECs from proliferating IHs in female infants display a nonrandom pattern of X-chromosomal inactivation.[8] In contrast, non-endothelial cells showed a mixed inactivation pattern. Walter et al.[9] also found clonality from cells in hemangioma tissue sections. Clonality in both tissue sections and in isolated HemECs supports the theory that genetic alterations, possibly somatic mutations, cause IH. In addition, IH can be associated with structural malformations, also suggesting early post-zygotic somatic mutation.

Jinnin et al.[6] identified mutations in the integrin-like receptor tumor endothelial marker 8 (TEM8) and in VEGFR-2 in a subset of HemECs and corresponding blood samples from patients with IHs. These "risk-factor" germline mutations may contribute to IH.

Clinical

IHs are the most common tumor of infancy and childhood, with approximately 4% incidence in Caucasian infants. Many have a premonitory mark at birth (e.g., pale macule with telangiectasias,

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mottled vascular stain, or bruise-like area). Most superficial IHs are evident by 1–4 weeks of age while deep IHs often present at 2–3 months of age. Dependent on location, tumors may be brightly erythematous macules, papules, or plaques (superficial) or blue nodules (deep) or exhibit a combination of these features. Ulceration is the most common complication, is more common in perioral and perineal sites, and may even be the presenting finding before the development of an obvious IH.

Epidemiology and natural history

Increased risk factors for IH include Caucasian race, female gender, prematurity, low birth weight, and being the product of multiple gestations. The female predominance is even higher in patients with PHACE association, 7:1.[10]

IHs classically grow in early infancy followed by spontaneous involution. IHs reach 80% of their final size by a mean age of 3 months[11]; however, many superficial IHs have an accelerated growth phase between 4 and 7 weeks, and many have completed the majority of growth by 2 months.[12] Deep IHs typically appear 1 month later and proliferate for longer than superficial IHs. Rarely, some IHs have minimal proliferation, termed IHs with minimal or arrested growth (Figure 1). Based on these growth characteristics, initiation of systemic therapies—if needed—should ideally be initiated prior to 3 months of age. Involution gradually occurs over several years but in most cases is nearly complete by the age of 4 years.[13]

Risk stratification

Because IHs are so heterogeneous in size, location, and growth characteristics, an approach to stratifying their risk of potential complications is needed (Table 1). Regional (also known as "segmental") IHs are much more likely to develop complications, including ulceration, bleeding, visual compromise, auditory compromise, cardiac compromise, or airway obstruction, than localized IHs.[14] Ulceration is the most common complication of IHs, occurring in approximately 10–15% of patients, usually developing by 4 months of age. Pain, bleeding, rarely profuse, and occasionally infection may complicate ulceration. Liver and airway are the most common extracutaneous sites. In general, patients with 5 or more IHs are screened for liver IHs by abdominal ultrasound. Other complications related to syndromic associations are discussed below.

Disfigurement

Permanent scarring and disfigurement are the most common adverse sequelae of IHs. Large facial IHs frequently distort normal anatomy and disfigure with fibrofatty residua, anetoderma, atrophy, erythema, hypopigmentation, and telangiectasias. Ulceration almost always causes scarring. Nasal tip lesions may splay the underlying cartilage, and revision is often necessary to correct the deformity. Ulceration of the columella and helix may also destroy the cartilage of the nasal septum and helix, respectively.

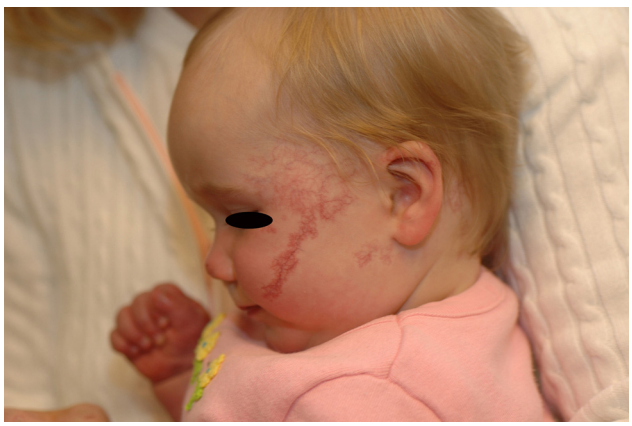

Fig. 1. Arrested IH in an infant with PHACE. (Color version of figure is available online.)

Impairment of function

Periorbital IHs may cause visual impairment most commonly by deformation of the cornea causing astigmatism. Other rarer ocular complications include visual axis obstruction, proptosis, and strabismus. Perioral IHs, particularly when ulcerated, may impair feeding. Patients with regional IHs in a lower facial, "beard" distribution are at risk for upper airway and subglottic involvement. Infants present within the first few weeks of life with noisy breathing, stridor, hoarse cry, and difficulty feeding. Ulcerated IHs of the perianal area may damage the anal sphincter and cause incontinence. Other severe complications include congestive heart failure with liver IH, visceral hemorrhage, abdominal compartment syndrome, gastrointestinal bleeding, and hypothyroidism.

Syndromes associated with infantile hemangiomas

Although most infantile hemangiomas occur solely as a cutaneous disease or—less frequently—with hepatic hemangiomas, a subset of these have associated structural abnormalities, several of which are highly relevant to surgical practice. These occur primarily in association with segmental IHs, which involve an anatomic territory, rather than arising from a single spatially confined focus (i.e., localized IH).[14] Conceptually, these associations can be divided into 2 major malformation groupings: PHACE association (OMIM 606519), where IHs primarily involve the face and to a less extent the ventral torso and extremities, and LUMBAR association, a constellation of anomalies with IHs involving the lower body.

PHACE association

The acronym PHACE refers to posterior fossa brain malformations, hemangiomas of the face (typically large and segmental), arterial anomalies, cardiac anomalies, and coarctation of the aorta, and eye abnormalities.[15] The association is referred to as "PHACES" when ventral developmental defects, such as sternal clefting or supraumbilical raphe, are present. Surgeons will often be called upon to manage the ventral developmental defects in PHACE, which are typically identified at birth. These ventral anomalies have also been called "sternal malformation/vascular dysplasia association."[16]

The cause of PHACE remains unknown. For unclear reasons, PHACES has a stronger female predominance (between 5:1 and 9:1) relative to the 3:1 as seen in IH in general.[17] Unlike IH, prematurity is not a specific risk factor, though it is also not per se protective against PHACE. The distribution of cutaneous hemangiomas and ventral developmental defects point to a so-called developmental field defect occurring between 4 and 6 weeks of gestational age as the likely explanation for this association.[14]

While the precise incidence of PHACE is not known, in a prospective study of 108 patients with facial hemangiomas larger than 22 cm^2, all of whom had systematic investigation with MRI/MRA of the head and neck, echocardiogram, and eye examination, 31% met diagnostic criteria.[17]

Consensus diagnostic criteria for PHACE have been proposed[18] (Table 2). Approximately 90% of patients with PHACE have more than 1 extracutaneous manifestation; however, most do not have all of the findings indicated by the acronym PHACE.[17] Other key features of PHACE of relevance to surgeons include an unexpectedly