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Hemangiomas and the eye☆

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Abstract Infantile hemangiomas are a common vascular birthmark with heterogeneous presentations and unique growth characteristics with early rapid growth and eventual self-involution. Hemangiomas that develop around the eye have the potential for inducing amblyopia by several mechanisms and may eventually result in permanent visual impairment in otherwise healthy infants. Segmental periocular hemangiomas carry the additional risk of associated structural anomalies and PHACE syndrome. In recent years, the treatment of periocular hemangiomas has been revolutionized by the serendipitous discovery of the effectiveness of beta-blockers (systemic and topical), with most experts viewing these as first-line therapies. The management of periocular hemangiomas should involve a close partnership between an ophthalmologist and dermatologist or other relevant specialists familiar with the unique clinical features, differential diagnosis, treatment approaches, and potential complications.

Introduction

Infantile hemangiomas (IH) are a common birthmark occurring in 4-5% of all infants, with female gender, prematurity, Caucasian race, and multiple gestation pregnancies as risk factors.[1–3] Hemangiomas of the head and neck are common,[4,5] as is periocular involvement, but the exact incidence is unknown. One retrospective review found that 24.3% of all focal facial hemangiomas involved periocular sites.[6] Additional data from the Hemangioma Investigator Group of 1096 consecutively enrolled patients with ≥1 hemangioma at any site,[3] found that 12% had a periocular IH (E. Baselga, MD, personal written communication, October 2013). In contrast, a population-based cohort study estimated that periocular infantile hemangiomas occur in only 1 in 1586 live births, though the authors acknowledge that this may be an underestimate due to the retrospective design and possible incomplete data collection.[7] Whatever the true incidence, the periorbital area is a relatively frequent site for IH and a particularly important one, because it can lead to permanent visual loss or distortion of anatomic landmarks in the area. Of the 1096 patients followed by the Hemangioma Investigator Group, 41% suffered some form of visual compromise (E. Baselga, MD, personal written communication, October 2013).

The timing of appearance of IH and the timing of its proliferative phase coincides with a critical time in the development of the visual axis, which includes integration of

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signals received by the retina, and processing the images in the central visual system.[8] Abnormal visual development can result in abnormal vision at the level of the central nervous system, which cannot be later corrected as easily by simple intervention, such as the addition of glasses.[9] The critical period for the development of the visual axis in humans is thought to be between birth and 9 years of age.[8,9] Observation of monocular deprivation in humans suggests that younger age and longer duration of deprivation have more significant effect on vision[8]; however, studies done in kittens in 1970 revealed that even very brief 3-4 day periods of unilateral eye closure during the first few months of life result in irreversible changes in the visual axis.[10] Similarly, early studies in humans showed that even after involution of a periocular hemangioma, associated refractive errors did not always resolve, suggesting permanent effects on the visual axis.[11] Given the potential for permanent visual impairment, physicians managing IH need to recognize worrisome clinical features, and be aware of when, and to whom, the patient should be referred.

This contribution reviews highlights of pathogenesis, clinical features, potential complications, differential diagnosis, and management options for periocular hemangiomas.

Pathogenesis

The pathogenesis of infantile hemangiomas is still incompletely understood. Several excellent recent review contributions have discussed recent advances in our understanding of hemangioma pathogenesis.[12–14] Numerous diverse hypotheses exist, including theories of placental origin,[15,16] somatic gene mutation,[17,18] hypoxia-driven events,[19] and aberrant stem cells.[20,21]

In 2000, it was shown that endothelial cells within infantile hemangiomas are glucose transporter 1 (GLUT1) positive, a unique feature that allowed differentiation of IH from other vascular tumors and malformations.[22] GLUT1, an erythrocyte-type glucose transporter protein, is typically expressed on endothelial cells at blood-tissue barriers.[22] This group further reported unique similarities in immunoreactivity between endothelial cells of infantile hemangiomas and human placenta (FcγRII, merosin, Lewis Y antigen, and GLUT1).[16] This work led investigators to speculate regarding whether IH represent invasion of the skin with angioblasts destined to produce a placental phenotype or direct embolization of placental cells to the skin and other affected organs.[16] Further work has demonstrated genetic similarity between the placenta and hemangioma.[15] This hypothesis is most intriguing and attractive as it may explain the unique natural history of the infantile hemangioma, with rapid proliferation, followed by slow self-involution, similar to the 9-month life cycle of the human placenta.[15,16]

Another proposed theory suggests a role for hypoxia in the pathogenesis of hemangiomas.[19] GLUT1, in fact, plays an important role in cellular response and survival in hypoxic environments.[23,24] Additionally, infantile hemangiomas are remarkably similar to retinopathy of prematurity, another disorder of abnormal vascular proliferation thought to be related to hypoxia.[25] Both present exclusively in the perinatal period, are more common in premature and low birth-weight infants, have similar histopathologic features, undergo early proliferation followed by later involution, and are GLUT1 positive.[19,26] Interestingly, premature infants with infantile hemangiomas have been found to be more likely to have retinopathy of prematurity than those without hemangiomas.[27]

Clinical features and potential complications

Growth characteristics

IH have a characteristic and well-documented natural history: up to 65% of infants with superficial IH have a precursor sign at birth[28] (telangiectatic patches with a pale halo, erythematous patches, pale patches, bruise-like macules) followed by rapid proliferation, then slow involution.[2,29] Hemangiomas grow most rapidly in the first 3.2 months of life, reaching an average of 80% of their final size during this time.[30] During these first 3 months of life, IH growth is most rapid between 5.5 and 7.5 weeks.[28] After this rapid growth, hemangiomas slowly involute. It was previously thought that 30% of hemangiomas regress by 3 years, and 76% by 7 years[31]; however, newer data suggest that involution is completed much earlier, by age 3 or 4.[32,33] Compared to superficial hemangiomas, deep hemangiomas typically begin their growth phase about 1 month later and continue growing 1 month longer.[30] Features that predict prolonged growth include deep component, segmental pattern, and orbital involvement.[34,35] Although virtually all IH eventually involute spontaneously, they can be associated with significant complications during the proliferative phase. Additionally, even after involution, periocular hemangiomas can leave potentially permanent visual impairment, as well as permanent skin changes, including telangiectasia, scarring, anetoderma, or fibrofatty residua (Figure 1).

Classification

Periorbital hemangiomas may be classified based on their depth of skin involvement as superficial (Figure 2), deep (Figures 3 and 4), or mixed (ie, superficial and deep, Figures 5 and 6). Another common way of describing hemangiomas (which is also very useful for risk-stratification) is localized, segmental, and indeterminate.[5,36] Localized hemangiomas are those that are spatially confined and appear to arise from a central focus; segmental hemangiomas (Figure 7) are those that encompass a territory of skin such as a developmental segment or portion thereof; and indeterminate hemangiomas (Figure 8) are those that cannot easily be classified into these two descriptions.[36]