Periocular Infantile Hemangiomas

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6.1 Introduction

Infantile hemangiomas (IH) are the most common benign vascular tumors of infancy, and they can present as small isolated lesions to large masses with segmental involvement anywhere on the body. Depending on the location and size of the IH, complications can arise ranging from ulceration to vital functional impairment to poor cosmesis upon regression. Due to the prevalence and significant ocular complications associated with periocular infantile hemangiomas, a thorough understanding of the natural history, clinical presentations, treatment, and complications will be valuable for ophthalmologists who will be encountering these cases. This chapter will review the epidemiology, pathogenesis, clinical manifestations, diagnosis, and latest updates on the management of patients with periocular IH [1].

6.2 Epidemiology

Infantile hemangiomas have an estimated incidence of about 4–5% [2]. IH are more common in females and white non-Hispanic infants [3–5]. The most significant risk factor is prematurity and low birth weight [3]. In infants weighing less than 1000 g, up to 23% have at least one IH while the incidence in full-term infants is 1–4% [3]. Other risk factors include advanced maternal age, multiple births, in vitro

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fertilization, amniocentesis, chorionic villus sampling, prenatal maternal vaginal bleeding, and multiple gestations [3, 6].

Twelve percent of all infantile hemangiomas occur in the periocular region [2]. Complications from periocular or orbital IH arise in about 60% of cases, leading to significant morbidity [7]. Amblyopia is a common sequelae of periorbital/orbital IH with a prevalence of 43–60% (Lyons, Chap. 20). Early recognition and treatment initiation of periorbital IH can lead to significant improvement in morbidity and patient outcomes.

6.3 Pathogenesis

The pathogenesis of infantile hemangiomas has not been fully elucidated. These vascular tumors are characterized by a proliferative phase and an involution phase, and evidence suggests that the blood vessels found in IH are unique from normal vasculature. Vasculogenesis, or formation of new primitive blood vessels from stem cell precursors, leads to the growth of these vascular tumors through clonal proliferation of vascular endothelial cells. Studies have shown that endothelial cells within proliferating and involuting hemangiomas are unique in that they have high expression of glucose transporter-1 (GLUT-1) and placenta-associated vascular antigens, and these markers can help distinguish between IH and other vascular tumors or vascular malformations. The only other vasculature known to have similar gene expression is placental chorionic villi, suggesting a connection between IH and placental pathogenesis [8, 9]. During the proliferative growth phase, vasculogenic factors are overexpressed, including fibroblast growth factor, proliferating cell nuclear antigen, vascular endothelial growth factor (VEGF), and type IV collagenase [10]. As IH transition into the involution phase, apoptosis of endothelial cells outpaces vasculogenesis, and fibrofatty tissue deposition begins to occur (Khan 2008). Histologically, fibrosis of the capillary lamina heralds the involution process, and higher numbers of mast cells are seen. Expression of tissue metalloproteinases increases, and this inhibits blood vessel formation [10]. The underlying mechanism that triggers transition from the proliferative to regression phase is unknown.

Similarities between retinopathy of prematurity and IH have also been found. “Premature infants with IH have been found to be more likely to have retinopathy of prematurity than those without IH” [11].

6.4 Clinical Presentation

The natural history of infantile hemangiomas, including periocular IH, is characterized by a proliferative growth phase during the first year of life, followed by an involution phase thereafter. About one-third of IH’s have a precursor lesion noted at birth, often a faint telangiectatic patch with a circumferential pale halo of vasoconstriction or an erythematous to violaceous patch that can be mistaken for a bruise or abrasion. Shortly after birth, the proliferative phase begins, with the fastest growth

period between 5.5 and 7.5 weeks of age [12]. By 3 months of age, most hemangiomas have reached 80% of their final size and 80% of hemangiomas have completed growth by 5 months of age [2, 12]. In the remaining IHs, growth may continue through months 6–12, but the rate is slower. After about 9–12 months old, IHs begin the involution process, which can last a variable number of years. By 4 years of age, about 90% of IH involution has occurred [13]. It is important to recognize that even after complete involution, 55% of IHs leave permanent skin changes, such as telangiectasias, atrophy, or fibrofatty tissue deposition, which depending on the location, can be cosmetically undesirable [13].

Classification of infantile hemangiomas is based on the depth of skin or soft tissue involvement (superficial, deep, mixed) and extent of the lesion (localized, segmental, indeterminate). Superficial hemangiomas present as a bright red, vascular papules or plaques, without a deep subcutaneous component (Fig. 6.1a). Deep IHs are subcutaneous growths without overlying skin changes, and therefore can have a bluish hue noted beneath the skin. Mixed hemangiomas exhibit features of both deep and superficial lesions. It is important to recognize these different hemangioma subtypes when evaluating a patient because their growth pattern is slightly different. The average onset of growth for deep IH is 1 month later than superficial hemangiomas, and they also continue growing for longer [14]. Segmental and periorbital hemangiomas also exhibit prolonged growth phases and are associated with increased morbidity. Because of this, these IH subtypes typically require longer follow-up, treatment, and monitoring [11].

Periocular infantile hemangiomas can be classified based on location in relation to the orbit. IHs can be anterior to the globe with eyelid involvement, extraconal or behind the bony orbit but not involving extraocular muscles, or intraconal or within the cone of extraocular muscles. Periocular infantile hemangiomas are most often found on the upper eyelid or within the orbit. In patients with periocular IH, about 30% have hemangiomas elsewhere on the body, showcasing the importance of a full-body skin exam when the diagnosis of IH is entertained. The natural history of periocular hemangiomas coincides with visual axis development in infants thereby leading to the risk of amblyopia.

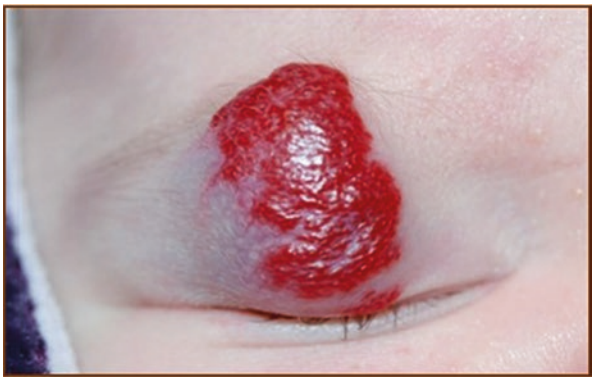

Fig. 6.1 Right upper eyelid hemangioma causing ptosis and visual obscuration

Periocular infantile hemangiomas or other large facial segmental IH can be associated with systemic disorders, including PHACE (posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities/aortic coarctation, eye anomalies) syndrome. It is important to be familiar with this entity because specific imaging and specialty consultation are necessary. PHACE syndrome should be considered in any patient with a large, segmental IH measuring >5 cm. The hemangioma may or may not directly involve the periocular region, but due to associations with structural eye abnormalities, ophthalmologic examination is prudent (controversial though).

Periocular IH and other possible systemic associations

- PHACE syndrome (posterior fossa anomalies, hemangioma, arterial lesions, cardiac abnormalities/aortic coarctation, eye anomalies).
- IH in PHACE are segmental and large (>5 cm).
- IH in PHACE may be periocular.
- Separate from the IH, PHACE is associated with structural eye abnormalities which include posterior segment abnormalities (major criteria for PHACE diagnosis) and anterior segment abnormalities (minor criteria for PHACE diagnosis).
- While controversial [11], states that all infants undergoing workup for PHACE should be evaluated by an ophthalmologist ([15]—states eye exam is low yield in patients with PHACE syndrome without a periocular infantile hemangioma).

6.5 Diagnosis

Infantile hemangiomas are typically diagnosed clinically, and rarely require further investigation with imaging or biopsy. Obtaining a detailed history from the family elucidating the onset of the lesion and growth history coupled with clinical appearance is often enough to make the diagnosis. However, clinical diagnosis can become challenging in certain scenarios, particularly when the lesion mimics vascular malformations, capillary malformations (like port-wine stains or nevus simplex), or other subcutaneous tumors. For instance, during the first few weeks of life, IH and port-wine stains can be challenging to differentiate, and the lesion would need to be monitored for signs of growth and thickening, as this is suggestive of IH. Deep IH can also be difficult to differentiate from other subcutaneous tumors or vascular malformations, and a high index of suspicion is needed and imaging and/or biopsy should be completed early if there is any doubt in the diagnosis.

Imaging should also be considered if there is a concern for systemic involvement. For instance, when PHACE syndrome is suspected, MRI/MRA with contrast of the head and neck should be completed to evaluate for anatomy. If there are five or more IH, a liver ultrasound to evaluate for intrahepatic hemangiomas should be obtained. Also, MRI orbit is considered for deep orbital hemangioma to evaluate the extent of lesion.

6.6 Differential Diagnosis

Below is the differential diagnosis of infantile hemangiomas, particularly of the periocular region. This is not an exhaustive list but describes the most commonly encountered alternative diagnoses.

- Capillary malformations.
  - Nevus simplex.
  - Port-wine stain.
- Other vascular tumors.
  - Venous and/or lymphatic malformations.
  - RICH (rapidly involuting congenital hemangioma).
  - NICH (non-involuting congenital hemangioma).
  - Tufted angioma.
  - Kaposiform hemangioendothelioma.
- Deep IH vs intra/periocular tumors.
  - Rhabdomyosarcoma.
  - Neuroblastoma.
  - Plexiform neurofibroma.
- Deep IH vs orbital cysts.
  - Dermoid cyst.
  - Epidermoid cyst.
  - Teratomas.
  - Choristomas.

6.7 Complications

Periocular IH are more often associated with complications compared to the overall complication rate in hemangiomas, with complications occurring 63% vs 24% of the time, respectively [2, 7].

- Amblyopia due to periocular IH can result from three different mechanisms:
  - Astigmatism or myopia can occur from compression of the eye by the mass of the hemangioma, and this can lead to asymmetric refractive error between the two eyes (anisometropia). Subsequent refractive amblyopia can develop if not corrected quickly. This is the most common cause of amblyopia in patients with periocular IH.
  - Partial or complete obstruction of the visual axis can lead to deprivation-associated amblyopia.
  - Globe displacement from the mass effect of the IH tumor or involvement of extraocular muscles can lead to strabismus (misalignment of the eyes), which can then subsequently lead to amblyopia.
  - Luckily, amblyopia occurs less commonly in the post-propranolol versus pre-propranolol era [2].

- Proptosis from the IH mass can lead to exposure keratopathy.
- Extension of IH into the retrobulbar space can lead to compressive optic neuropathy or compression of orbital structures, although this is rare.
- Nasolacrimal duct obstruction can also occur depending on the location of the mass.
- Ulceration tends to be less common in periocular IH than other sites, but can still occur.
- Permanent disfigurement or skin changes can result from IH proliferation including fibrofatty tissue residua, anetoderma, telangiectasias, skin discoloration, distortion of facial landmarks (eyelid skin, lid margin, eyelashes, eyebrows), or indentation. In one study by [2], 42% of children had residual skin changes are involution of periocular IH.
- Complications associated with periocular IH are more likely when the hemangioma is classified as deep or mixed-type, larger in size measuring >1 cm, involving the upper eyelid (particularly if causing ptosis), nasally located, segmental, intraconal, or extraconal [2].

6.8 Management

- While most infantile hemangiomas do not require treatment due to their favorable location and small size, a significant number of more complicated hemangiomas do require treatment [16]. Because periocular hemangiomas are more often associated with morbidity, a high proportion of them require treatment. In one study by [2], 89 patients with periocular IH were included and 89% of those required treatment of some kind [2]. Morbidity resulting from these more complicated hemangiomas is reduced when treatment is initiated prior to the significant growth phase, which occurs from 5.5 to 7.5 weeks of age [12].
- Comanagement and close communication between pediatric dermatologists and ophthalmologists can be helpful, especially in complex cases.
- The current mainstay of treatment is oral propranolol (Fig. 6.2a, b) and, in certain circumstances, topical timolol. Oral propranolol is effective in treating and promoting regression of IH in 97% of cases and is generally well-tolerated [7].
- The dose of oral propranolol is typically 2–3 mg/kg/day divided twice daily or three times daily. Higher doses of propranolol (3 mg/kg/day) are often needed for deep IH, including those in the periocular region. Treatment ideally should start before the rapid proliferative phase and should be continued through at least the first year of life. A propranolol wean can then begin with close monitoring for rebound growth. Occasionally, hemangiomas require treatment with oral propranolol for several years [17].
- Topical timolol has been shown to induce regression of small and superficial IH (Fig. 6.3a, b) but should be used cautiously for periocular hemangiomas. Response rates to topical timolol are slower than systemic beta-blockers and

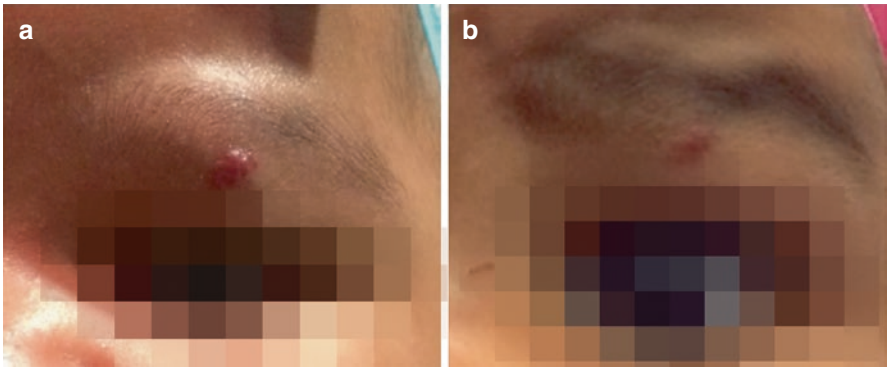

Fig. 6.2 Left upper eyelid hemangioma causing astigmatism (**a**) treated with propranolol showing a good response (**b**)

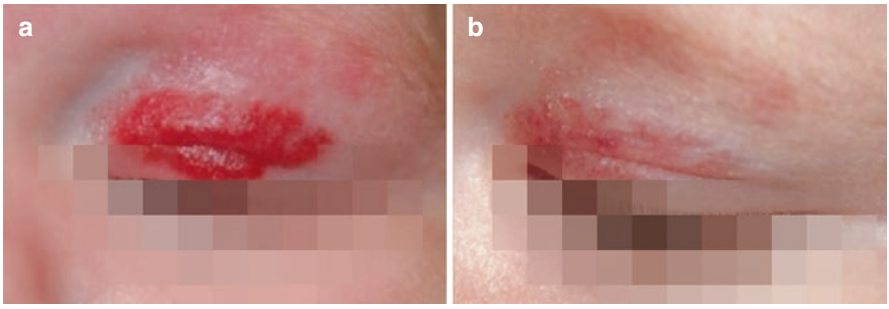

Fig. 6.3 Superficial upper eyelid hemangioma (**a**) showing a good response to topical timolol (**b**)

given the risk of vision loss, rapid onset of action with systemic medications may be necessary.

- Other treatment options available for consideration when beta-blockers are ineffective or contraindicated include corticosteroids, pulsed dye laser, or surgical debulking procedures. These therapies were utilized more often in the past before the efficacy of beta-blockers in IH regression was discovered.
- Even after management with propranolol, there may be a residual mass requiring surgical correction.
- Rarely, patients may not be able to tolerate the side effects of propranolol resulting in discontinuation of the medication. In a study by [7], propranolol adverse events occur up to 33% of the time, although the side effects were only severe enough to warrant discontinuation in 5% of patients [7]. In another study published by the American Academy of Ophthalmology in 2019 [18] only two patients out of 227 required treatment cessation because of complications from beta-blockers. Minor side effects of propranolol are more common and include sleep disturbances, acrocyanosis, diarrhea, emesis, or restlessness. Other more severe, but less common, side effects include hypoglycemia, transient bradycar-

dia, hypotension, or bronchospasm. Appropriate counseling and monitoring of infants on propranolol are crucial to reduce the likelihood of adverse events. Unfortunately, there are no consensus guidelines detailing monitoring of infants on oral propranolol for IH.

6.9 Conclusion

Periocular infantile hemangiomas are a unique subset of IH associated with increased morbidity related to vision loss. They more often necessitate treatment with beta-blockers to prevent permanent visual and cosmetic sequelae. Familiarity with periocular IH clinical presentation, diagnosis, and management is key for ophthalmologists.

Key Points

1. Hemangioma is a common benign vascular tumor seen in children and is often seen in the periocular region.
2. Amblyopia is seen in approximately half of the patients with hemangioma.
3. Propranalol is an effective treatment for hemangioma and is the first line of treatment.

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