INTRODUCTION

Infantile hemangioma or hemangioma of infancy is recognized as a benign vascular tumor according to the International Society for the Study of Vascular Anomalies (ISSVA). This is a part of a new classification presented by ISSVA and has been accepted by various specialties. This classification is based on natural history, cellular turnover, and histological features of vascular anomalies. Infantile hemangioma, juvenile hemangioma, hemangioblastoma, benign hemangioendothelioma, and hypertrophic hemangioma are other referral terms used to describe the vascular nature of the disease.[1] This lesion may present as a small isolated lesion or as a large mass with visual impairment. Moreover, it may be associated with extensive systemic involvement.[2] Infantile periocular hemangioma (IPH) mainly involves young children. IPH usually shows a nonlinear growth pattern, and most of its growth occurs between 5.5 to 7.5 weeks of age, while 80% of the final size is reached by the age of approximately 3 months. Although most of the lesions follow a predictable course with spontaneous involution, others may result in serious ocular or systemic complications such as amblyopia and cardiac failure.[3,4] Considering the notable prevalence, specific natural course, and significant ocular complications of this disease, thorough knowledge about the nature of the disease, its clinical manifestations, and treatment indications and modalities is very beneficial for ophthalmologists who will likely be consulted in these cases. In this manuscript, we present a brief review of recent opinions regarding the pathogenesis, diagnosis, and treatment of the patients with IPH.
Epidemiology
Infantile hemangioma is found in approximately 4-5% of infants.\cite{5,6} The annual incidence of IPH has been reported as 5.4 per 100,000 patients (less than 19 years old) and a birth prevalence of 1 in 1586 live births.\cite{7} It is three times more frequent in females and is more prevalent in preterm infants. Risk factors attributed to this condition include multiple births, advanced maternal age, low birth weight, and in vitro fertilization.\cite{8} Other risk factors such as preeclampsia, placental anomalies,\cite{9} chorionic villus sampling, amniocentesis,\cite{10} prenatal maternal vaginal bleeding, progesterone therapy during early pregnancy, low level of maternal education, mother engaged in manual labor, multiple gestations, maternal medication use in periconceptional period, and positive family history of hemangioma have been reported.\cite{11} Although this tumor is more often seen in Caucasians, this race has not been reported as a considerable risk factor.\cite{12}

Pathogenesis
IPH is a benign vascular tumor without a well-understood pathogenesis. It arises from primitive stem cells referred to as hemangioma stem cells (HemSCs). Several studies, through the infusion of these cells into immune-deficient mice or growth in culture, have detected their vascular properties, and have suggested that these cells are capable of differentiation to both endothelial cells and pericytes. Hence, some authors categorized this tumor as a disease of stem cells.\cite{15-17} Tumor growth occurs in different phases. The proliferative phase is determined by the rapid proliferation of HemSCs that continues up to several months after birth. In this phase, the endothelium is metabolically active and immature, and vessels cannot be distinguished well histologically. By the end of the proliferation phase, differentiation begins with the development of mature and enlarged vessels. Subsequently, the involution phase begins with apoptosis of the endothelial cells and deposition of fibro-fatty tissue.\cite{15} The HemSCs in the proliferative phase express some of the pericyte markers such as \( \alpha \)-smooth muscle actin (\( \alpha \)-SMA), neural glial antigen-2 (NG2), platelet-derived growth factor receptor-\( \beta \) (PDGFR\( \beta \)), calponin, and smooth muscle myosin heavy chain. Other investigations have shown the critical role of Notch genes in angiogenesis. Specifically, NOTCH3, a normally expressed gene in vascular smooth muscle cells, was found to be expressed in HemSCs.\cite{15,16,18-21} Other studies found that genes such as HES and HEY genes, which interfere with Notch protein markers, may play a role in infantile hemangiomas as well.\cite{22} These studies have proposed that HES/HEY genes act as a downstream effector of Notch receptors in infantile hemangiomas. Moreover, HES/HEY gene transcription is decreased with the addition of a gamma-secretase inhibitor, another substance attributed to the infantile hemangioma.\cite{13-17,23} It is noteworthy to indicate that some capillary hemangioma patients carry germ line mutations in VEGFR1, VEGFR2, or TEM8. Some of these patients carry heterozygous missense mutations in VEGFR2 or TEM8. Low-level expression of VEGFR1 and subsequent increase in VEGFR2 may contribute to hemangioma formation.\cite{24}

It has been suggested that oral propranolol inhibits angiogenesis by down-regulating the expression of vascular endothelial growth factor (VEGF) in hemangioma-derived stem cells.\cite{25} Hypoxia and tissue markers for hypoxia are other areas of discussion in the pathogenesis of capillary hemangioma. Glucose transporter-1(GLUT-1) and Insulin-like growth factor-2 (IGF-2) are tissue markers of hypoxia.\cite{26} Prenatal hypoxia or placental cell emboli are two examples of hypoxic events associated with increasing level of hypoxia inducible factor 1 (HIF-1) and subsequent increasing of VEGF. A potent mTOR (mammalian target of rapamycin)/VEGF inhibitor, rapamycin, is able to reduce proliferation of hemangioma by reducing HIF-1-dependent expression of VEGF.\cite{27-33} Currently, the role of core 1 beta3Gal-T specific molecular chaperone (COSMC), the specific regulator molecular chaperone for T-synthase in the endoplasmic reticulum, is also being assessed. COSMC dysfunction may lead to overexpression of VEGFR2 and contribute to several vascular disorders including infantile hemangioma.\cite{24}

Clinical Presentations
Infantile hemangiomas are described according to color and shape (strawberry nevus, bluish discoloration),\cite{33} and level of involvement (subcutaneous, deep orbital, combined, segmental, focal and multifocal).\cite{34} Unilateral disease and upper eyelid involvement are more frequent in IPH.\cite{35} Superficial lesions appear a few months after birth as a red papule or nodule that may have a flat or rough surface. Blanching with pressure in these lesions can be helpful to distinguish them from port-wine stain in patients with Sturge-Weber syndrome. Deep lesions can cause some blue to purple discoloration of the skin, or they may only cause anatomical disfigurement without discoloration. [Figure 1] Hemangioma precursor symptoms are color-change, change in the thickness of the skin, and local anatomical distortion. These symptoms present at birth in 65% of patients.\cite{33,36} However, some lesions are not visible at birth but rather present at around 4 weeks of age. Infantile hemangioma exhibits different growth patterns. Deep lesions tend to grow later and longer than superficial hemangiomas.\cite{36} The distribution of facial segmental hemangiomas is associated with developmental neuroectodermal segments on the face and has a potential risk of underlying PHACES syndrome which is characterized by posterior fossa abnormalities.
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present at birth, hemangiomas, arterial lesions, cardiac anomalies, eye abnormalities, and sternal clefting.\(^{39}\) In infants with large segmental facial hemangiomas, the incidence of PHACES syndrome increases by a range of 20\% to 30\%.\(^{40,41}\) Many IPHs are diagnosed on clinical examination, but imaging may play a role in deep types with anatomical disfigurement and also in lesions with orbital involvement. Imaging is also useful to assess the depth of lesions and their relation to adjacent structures. As a brief explanation, infantile hemangiomas are described as well-circumscribed masses with hyperechogenicity on ultrasonography. They present as high-flow and low-resistance vascular masses without shunting.\(^{42-45}\) Color Doppler ultrasonography is a useful tool for both diagnosis and monitoring the response to treatment; however, these modalities are applied less frequently for periocular lesions.\(^{42,44}\) On CT scan, capillary hemangiomas are homogenous and attenuated with rapid and uniform contrast enhancement compared to muscles. Calcification and bone remodeling is very rare. On MRI, they appear as well-circumscribed masses with isointense to hyperintense properties compared to extraocular muscles. On T1-weighted images, arterial flow void is seen and on T2-weighted images, increased signal and marked enhancement on post contrast images can be evident. On MR angiography, feeding vessels with the high flow may be observed.\(^{44,46,47}\)

**Complications**

IPH may result in several systemic, cutaneous, or ocular complications. There are some associated eye abnormalities in PHACES syndrome such as colobomas, microphthalmia, morning glory disc, optic nerve hypoplasia, and peripapillary staphyloma.\(^{40,41}\) Furthermore, this condition may be life-threatening, and may lead to secondary cerebrovascular or neurologic problems. Therefore, in patients with large segmental hemangiomas, PHACES must be ruled out, and an urgent cardiology consultation and head MRI is needed. Ocular complications due to periocular lesions include ptosis, strabismus, telangiectasia, ulceration, scarring, and facial disfigurement, but the most common ocular complication of periocular capillary hemangiomas in infants is visual loss secondary to amblyopia. The incidence of amblyopia is interestingly high due to the early age of the tumor onset.\(^{48}\) It varies from 76\% in older studies to 21\% in recent studies.\(^{48-51}\) The rate of amblyopia was reported to increase with large lesions and also with the delay in starting the treatment after 1 year of age.\(^{40,52}\) Although the patients are highly susceptible to amblyopia in this age period, the risk of amblyopia development should still be considered until 7 years of age. Amblyopia is frequently related to visual deprivation in the affected eye due to the mechanical effect of the mass. Moreover, eyelid mass may alter the topographic parameters of the cornea which result in astigmatism and anisometropia as another predisposing factor for the development of amblyopia.\(^{40,50,53}\) Diffuse and large hemangiomas and those of PHACES syndrome are more prone to amblyopia.\(^{40}\) Astigmatism is detected in 20 to 46 percent of eyes with periocular capillary hemangiomas. It may be permanent in some cases even after tumor disappearance.\(^{50,53}\) Strabismus results from both muscle infiltration and pressure effects of the tumor in some periocular infantile hemangiomas.\(^{40-50,53}\)

**Management**

As was mentioned earlier, most of the periocular capillary hemangiomas have a benign course with spontaneous resolution; thus, the indications for treatment should be clarified. If hemangiomas have a low risk of complications and are small in size without obvious disfigurement, regular follow-up and observation are recommended.\(^{54}\) The main concern for treatment is the prevention of amblyopia and life-threatening systemic complications such as airway obstruction and high cardiac output problems. Both medical and surgical modalities are suggested for the

![Figure 1. Various presentations of periocular infantile hemangioma. Upper left: superficial, upper lid; upper right: deep upper lid and ocular surface; middle left: superficial lower lid; middle right: deep lower lid; lower left: extensive facial involvement; lower right: orbital involvement (confirmed by incisional biopsy).](image-url)
management of periocular hemangiomas. It is important to discuss the risks and benefits of each treatment with the patient’s family.

Systemic corticosteroids were considered as the mainstay therapy for IPH before the introduction of beta-blockers in recent years. Corticosteroids inhibit VEGF-A product by HemSCs, which can slow down the vasculogenesis in hemangiomas. Moreover, it can suppress other proangiogenic factors such as urokinase plasminogen activator receptor, IL-6, monocyte chemoattractant protein 1, and matrix metalloproteinase-1 (MMP-1). Oral prednisolone with a dose of 2–3 mg/kg/day in a single morning dose for the intermittent short course (2 weeks) is recommended as an effective and safe treatment for IPH. Adverse effects of corticosteroids include adrenal suppression, Cushing’s syndrome, growth retardation, hypertension, immune suppression, temperament disturbance, and gastritis. Due to potential adverse effects of systemic corticosteroids, many have turned to local injections of a corticosteroid. There are several protocols, however, injecting a maximum of 1–5 ml depending on the size and number of lesions of triamcinolone 40 mg/ml with or without betamethasone 4 mg/ml has been widely suggested. A serious but rare complication of injection is a retinal artery or vein occlusion. This problem may be prevented by aspiration prior to injection. In addition, to decrease the risk of this complication, one should inject slowly, avoiding a big bolus going in at once and also avoiding increased local vascular pressure. Eyelid hypopigmentation, subcutaneous fat atrophy, skin necrosis, and periocular calcification are other infrequent complications. Topical corticosteroids have fewer side effects, but are less effective. The use of intermediate to high potency topical glucocorticosteroids for managing superficial tumors is of clinical interest as an additional alternative.

The effect of systemic beta-blockers such as propranolol in the treatment of hemangiomas was first noted in 2008 when two children showed a rapid regression of hemangiomas after receiving propranolol for cardiopulmonary indications. Oral propranolol has been associated with dramatic improvement of IPH lesions in young children [Figures 2 and 3]. This effect could be explained by the action of catecholamines, which upregulate VEGF-A and HIF1-α protein through cAMP and PKA signaling. Propranolol blocks catecholamine stimulation and leads to downregulation of other proangiogenic factors such as MMPs and IL-6 that contribute to hemangioma formation. Early effects of propranolol on hemangiomas are evidenced by shrinkage in the size and reduction of the surface redness due to a decrease in nitric oxide and subsequent vasoconstriction. Intermediate effects are a reduction in and blockage of proangiogenic factors and finally, after long time usage, it induces apoptosis in proliferating phase. The use of systemic propranolol may be indicated in lesions with difficult access for local therapy such as orbital hemangiomas. The dosage of propranolol is in the range of 1–3 mg/kg/day. Possible side effects of propranolol are bradycardia, hypotension, and bronchial hyperactivity especially in patients with reactive airways, hypoglycemia, hyperkalemia, sleep disorder, and gastrointestinal disturbance. For the best results and the least side effects, patients have been treated initially with a low dosage of oral propranolol 0.5 mg/kg/day, divided three times daily while hospitalized under pediatric specialist supervision. After toleration of two doses, the amount is doubled toward maximum dosage. Patients can be discharged after 2–3 days, and their medication is continued orally at home for several months. Topical beta blockers, such as timolol, are associated with fewer side effects and may be effective; these are recommended for localized and superficial hemangiomas. Recently this topical therapy has been recommended for deep lesions, and almost complete involution without a recurrence has been observed. Timolol maleate 0.5% solution or gel can be applied twice daily on the surface of the lesion. It takes from 4 to 8 weeks to show response and treatment should be continued until the end of the involutional phase. Few investigations in recent years support the effectiveness of intralesional propranolol in the treatment of hemangiomas. However, more studies are required to investigate its efficacy. The protocol recommends the use of 0.2 ml (1 mg/ml of propranolol) per centimeter diameter with the maximum volume of 1 ml per injection. Regression begins from the first 24 hours and continues for about 3 weeks. In patients with rebound growth of the lesion, reinjection may be effective.

Interferon alpha-2a and -2b is also recommended in lesions unresponsive to other modalities or in cases of
contraindications for corticosteroid and beta-blockers. A dosage of 1 to 3 million units/m² of body surface area can be used and continued for 2 to 12 months under the supervision of a pediatric specialist. Some notable adverse effects include transient neutropenia, liver function impairment, fever, flu-like syndrome, and neurotoxicity. Other immunosuppressive agents such as vincristine, vinblastine, and cyclophosphamide are reserved for life-threatening hemangiomas. These agents have serious potential side effects and should be prescribed under the supervision of an oncologist or pediatric specialist.

In lesions that show a poor medical response, surgery can be performed as both a diagnostic and therapeutic modality. It is also recommended at the end of the involutional phase for cosmetic purposes. Surgery is also a good option for deeper lid hemangiomas that do not have the superficial strawberry component. There is a high chance of bleeding and hemostasis should be considered especially in large masses.

Vascular-specific pulse dye laser has limited penetration of about 1.2 mm, so its application is limited to superficial types. It reduces skin redness and telangiectasia. It should be applied intermittently every 2 to 4 weeks. Adverse effects include skin atrophy, hypopigmentation, and scar formation. However, other forms of laser therapy such as long pulse dye laser with deeper penetration may be more effective.

Other treatments such as cryotherapy and intralesional bleomycin are not widely used due to the chance of scar formation or limited data.

In conclusion, periocular hemangioma is a common and potentially vision-threatening lesion in young children. Hemangioma stem cells and VEGF play a substantial role in the formation and involution of the disease. It may present as a superficial or a deep lesion, and also show a local or a more extensive involvement. Amblyopia is a major concern and usually, relates to the visual deprivation. Corneal topographic alterations, astigmatism, and strabismus, contribute to the amblyopia as well. The treatment strategy may include observation, or a series of medical treatments, injections and surgical measurements. Recently, the discovery of the effectiveness of propranolol in the treatment of infantile hemangiomas has made it the primary therapeutic option; however, there are still many unknown issues in the mechanism, pathogenesis, and treatment of the disease. Further research is warranted for better understanding of the molecular biochemistry of the disease and discovery of new treatments.

Declarations of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of Interest

There are no conflicts of interest.

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