Infantile Hemangioma: A Brief Review of Clinical Manifestations, Associations and Treatment

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Abstract

Infantile hemangiomas (IH) are the most common vascular tumors in children, occurring in 4-10% of infants [1]. They are benign growths of endothelial cells that are often easily diagnosable by history and physical examination and usually require no treatment because they regress spontaneously in the first few years of life. In some cases, however, the location and morphology of the lesion can cause ulceration, disfigurement, or impairment of essential functions (e.g. vision or breathing). Early referral to a Pediatric Dermatologist is imperative since treatment is most effective when started before complications develop.

INTRODUCTION

Infantile hemangiomas (IH) are the most common vascular tumors in children, occurring in 4-10% of infants [1]. They are benign growths of endothelial cells that are often easily diagnosable by history and physical examination and usually require no treatment because they regress spontaneously in the first few years of life. In some cases, however, the location and morphology of the lesion can cause ulceration, disfigurement, or impairment of essential functions (e.g. vision or breathing). Certain types of IH are associated with congenital structural abnormalities. Early identification of lesions that are at high risk for developing complications, including ulceration, disfigurement, or impairment of essential functions (e.g. vision or breathing). The pathogenesis of IH is still under investigation, but angiogenesis and vasculogenesis are two proposed mechanisms. Hemangioma stem cells, which are primitive mesenchymal cells that can be isolated from proliferating IH, are one cell type implicated in vasculogenesis. These cells show self-renewal properties and in cultures can differentiate into cell types found in IH, including endothelium, adipocytes, and pericytes. Furthermore, when transplanted into mice, they cause de novo vessel formation [2]. Infantile hemangiomas are positive for GLUT 1 (Glucose Transporter 1), an immunohistochemical marker that helps distinguish it from other vascular tumours and is also found on placental cells. Hypoxia may play a role in IH development, which may explain risk factors associated with IH, such as low birth weight and prematurity.

RISK FACTORS AND NATURAL HISTORY

Several risk factors have been identified. Females and white, non-Hispanics are more likely to develop IH [3], and low birth weight, prematurity, and placental anomalies (which are often associated with one another) are additional risk factors [4]. Drolet et al. showed that for every 500 gram decrease in birth weight, there is a 40% chance increased risk of IH [5].

IH are not fully formed at birth, but a premonitory mark, which appears as a patch of ecchymosis, pallor or telangiectasias, may be present [6]. IH typically proliferate rapidly during the first 2 to 3 months, with one study demonstrating that the most growth, especially for superficial IH, occurs between 5.5 and 7.5 weeks of life [6]. IH reach 80% of their maximum size on average by 3 months; however, the mean age of visit with a specialist is not until 5 months of age [7]. Deep IH may have a prolonged growth phase [8]. After rapid proliferation the tumor stabilizes around one year of age and begins to spontaneously involute, with maximum involution usually occurring by 3.5 years of age [9].

DIAGNOSIS AND CLINICAL MANIFESTATIONS

Most IH can be diagnosed with a complete history and physical examination. The differential diagnosis includes vascular tumors, vascular malformations, and other neoplasms (Table 1) [10]. Congenital hemangioma, a rare vascular tumor that is included in the differential of IH, is distinguishable from IH in that it is fully formed at birth. These lesions often present as exophytic masses or plaques, often with a halo of pallor, and have two major subtypes: non-involuting and rapidly involuting. IH can be single or multiple and are found anywhere on the body but are most commonly on the head and neck [11]. IH can be subdivided into superficial, deep or mixed presentations [12]. Superficial IH are
Central bright pink or red, minimally raised papules, plaques, or nodules (Figure 1). Deep IH are paler, blue-tinged nodules that are often larger. Deep IH tend to present at later ages and involute more slowly than superficial IH [7]. Mixed presentations are common and have both superficial and deep components [12] (Figure 2).

In addition to depth of tumor, IH can be described as focal or segmental (aka. regional). Focal IH form a solitary nodule, papule, or plaque and appear to arise from an isolated point. Segmental IH are often plaques and occupy a larger subunit of the body, such as part of the face or extremity. Segmental IH are more likely than focal IH to develop complications [13] (Figure 3). If found on the head or lumbosacral areas, they may be associated with underlying extracutaneous structural anomalies (PHACE syndrome and LUMBAR syndrome, respectively) [14,15].

**PHACE AND LUMBAR SYNDROMES**

PHACE syndrome is a neurocutaneous syndrome that includes large segmental IH of the face and associated structural anomalies. PHACE is an acronym that stands for posterior fossa brain malformations, hemangioma, arterial anomalies, cardiovascular/aortic anomalies, and eye abnormalities. Ventral midline defects, such as sternal defects, are also associated. Definite diagnosis of the syndrome requires a segmental facial or scalp IH (at least 5 cm wide) and one major anomaly. In one study, 20% of patients with segmental facial hemangiomas had PHACE syndrome [14]. Work-up for infants with segmental IH of the face or scalp should include MRI brain, MRA of the head and neck, echocardiography, and ophthalmology assessments to evaluate for the presence of associated anomalies.

Similar to PHACE syndrome, LUMBAR syndrome includes large segmental IH of the lower body and associated structural anomalies. LUMBAR stands for lower body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies. Children with LUMBAR syndrome may require extensive diagnostic imaging to detect

<table>
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<th>Table 1: Differential Diagnosis of IH [10].</th>
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<tr>
<td><strong>Vascular Tumors and Malformations</strong></td>
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<tr>
<td>Congenital Hemangioma</td>
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<td>- rapidly involuting</td>
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<td>- partially involuting</td>
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<td>- non-involuting</td>
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<tr>
<td>Tufted angioma</td>
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<td>Pyogenic granuloma</td>
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<td>Kaposiformhemangioidendothelioma</td>
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<td>Spindle cell hemangioma</td>
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<td>Congenital eccrine angiomatous hamartoma</td>
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<td>Capillary malformation</td>
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<td>Lymphatic malformation</td>
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<td>Combined vascular malformation (Klippel-Trenaunay syndrome)</td>
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<td>Verrucous &quot;hemangioma&quot; and angiokeratoma</td>
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<td>Arteriovenous malformation</td>
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<td>Hereditary hemorrhagic telangiectasia</td>
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<td>Multifocal lymphangioendotheliomatosis</td>
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**Figure 1** Superficial infantile hemangioma.

**Figure 2** Deep infantile hemangioma.

**Figure 3** Segmental infantile hemangioma.
and monitor anomalies, but all children less than 3 months of age with lower body segmental IH should have ultrasound of the spine, abdomen, and pelvis to look for common malformations, such as spinal dysraphism [15].

MULTIFOCAL IH

IH can have a multifocal presentation, in which there are many small, local IH. The tumors can be similar in appearance or vary in size and shape. Multifocal presentations can be associated with visceral involvement, and a common site for extracutaneous IH is the liver. Intrahepatic IH follow a similar course as cutaneous IH, with proliferation and involution growth phases. They are benign tumors; however, if there are extensive intrahepatic IH, heart failure, hypothyroidism, and abdominal compartment syndrome are possible complications. One prospective study showed that 16% of children with 5 or more IH had hepatic hemangiomas [16]. Therefore, screening abdominal ultrasonography is indicated in infants younger than 6 months of age with 5 or more cutaneous IH to evaluate for hepatic involvement.

COMPLICATIONS

Although most IH regress spontaneously without requiring treatment, 24% of IH seen at tertiary centers may develop complications [13]. Ulceration is the most frequent complication and is more likely to occur on segmental IH and areas with high friction or moisture, commonly the neck, lips, and anogenital regions. Ulcerations can lead to pain, super infection, and scarring and are more often treated than non-ulcerating IH [17].

Other complications include functional impairment and/or disfigurement due to location of the IH. Periorbital IH can cause visual complications, such as astigmatism or amblyopia, due to pressure on the globe or visual field obstruction. IH with laryngeal involvement can cause airway obstruction and require systemic and/or surgical treatment. IH on the central face, nasal tip, pinna, or eyelids can involute leaving destruction of anatomical structures, residual fibrofatty tissue, scars, anetoderma, or telangiectasia [9].

TREATMENT

Prior to 2008, treatment options for IH were limited to oral corticosteroids, with interferon alpha and vincristine used for refractory cases, and intralesional steroids and surgical excision performed in certain situations [9,18-20]. Because of the adverse effects of corticosteroids, [21] treatment was reserved for tumors that threatened vital functions (e.g. vision or breathing). In 2008, Léauté-Labrèze et al., discovered the effectiveness of oral propranolol in treatment of severe IH [22]. A subsequent randomized, controlled trial of 40 patients confirmed the efficacy of oral propranolol in reducing IH color, volume, and elevation at doses of 2 mg/kg/day for 6 months [23]. Another larger randomized, controlled trial of 460 patients demonstrated 60% complete or nearly-complete resolution of IH in patients treated with oral propranolol at a dose of 3 mg/kg/day for 24 weeks, versus just 4% in patients treated with placebo [24]. The mechanism of action of propranolol is not completely understood; however, propranolol is a non-selective beta-adrenergic antagonist that has been shown to bind beta-receptors of hemangioma stem cells. Binding causes decreased cAMP levels and increased MAPK signaling, which reduces proliferation of stem cells and promotes apoptosis [25]. Side effects of oral propranolol are rare but include bradycardia, hypoglycemia, hypotension, acrocyanosis, and diarrhea [24,26]. The relative efficacy and safety of using propranolol has made it a viable option for treating IH that are not just functionally threatening but also pose his risk for disfigurement or ulceration.

Propranolol appears to be effective throughout all stages of tumor development, unlike corticosteroids, which are most effective during the proliferative stage [23]. However in order to reduce complications of IH, propranolol should be started early for IH that are high risk. Doses are usually between 1 and 3 mg/kg/day divided over two doses, and initiation may occur as an inpatient for infants with less than 8 weeks corrected gestational age, pre-existing concern for hypoglycemia, cardiovascular or respiratory comorbidities, or inadequate social support. Inpatient initiation is recommended for high risk patients with PHACE syndrome and cerebrovascular anomalies, due to the theoretical risk of stroke [27]. Pretreatment electrocardiograms can be done for patients with bradycardia. Other therapies for IH include topical timolol, pulsed-dye laser, [28] intralesional or topical steroids, and excision. These are less commonly used than oral propranolol. Topical timolol may be effective for small superficial IH [29]. Fully formed pedunculated IH that will ultimately leave prominent residual fibro fatty tissue or persistently ulcerated IH may be treated by excision [10,30].

SUMMARY

IH are common tumors in children that often require no treatment. Infants with large segmental facial or lower extremity IH or those with multifocal presentations should have further imaging to rule out structural anomalies or hepatic involvement. Indications for treatment include tumors that are threatening vital functions (vision or breathing), located in places at high risk for disfigurement, or ulcerating. Early referral to a Pediatric Dermatologist is imperative since treatment is most effective when started before complications develop. Oral propranolol is now considered first line for treating IH, with several recent trials indicating its safety and efficacy. More research needs to be done comparing safety and efficacy of different topical and systemic beta blockers.

REFERENCES


