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Review

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Infantile Hemangioma

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ABSTRACT

Infantile hemangiomas typically appear in the first few weeks of life as areas of pallor, followed by telangiectatic patches. They then grow rapidly in the first 3 to 6 months of life. Superficial lesions are bright red, protuberant, and sharply demarcated and are often referred to as "strawberry hemangiomas". Deep lesions are bluish and dome-shaped, feel like a "bag of worms", and are compressible. Infantile hemangiomas have a predilection for the head and neck region. Most infantile hemangiomas exist as solitary lesions. Infantile hemangiomas continue to grow until 9 to 12 months of age, at which time the growth rate slows down to parallel the growth of the child. Half of these lesions will show complete involution by the time a child reaches age 5; 70% will have disappeared by age 7; and 95% will have regressed by ages 10 to 12. The majority of infantile hemangiomas require no treatment. Indications for active intervention include severe or recurrent hemorrhage unresponsive to treatment, threatening ulceration in areas where serious complications might ensue, interference with vital structures, pedunculated hemangiomas, and significant disfigurement. Treatment options include systemic corticosteroids, intralesional corticosteroids, topical and oral beta blockers, pulsed-dye laser, and less commonly interferon-α or surgical resection. In recent years, propranolol, a nonselective β-blocker, has been preferentially used as a first-line treatment of problematic infantile hemangioma.

KEYWORDS: Infantile hemangioma; Involution; Propranolol; Corticosteroids; Laser; Surgical resection.

INTRODUCTION

Infantile hemangiomas are the most common tumors of infancy, yet most are not present at birth but appear as areas of pallor, followed by telangiectatic patches in the first week of life.[1-3] These lesions are characterized by a distinctive life cycle, in which proliferation is generally limited to the first year of life, at which time the growth rate slows down to parallel the growth of the child, followed by a variable involution phase over the next several years of life.[2,4]

EPIDEMIOLOGY

In the white population, infantile hemangioma affects approximately 1.1 to 2.6% of newborn infants and 10 to 12% of children by the first year of life.[2] The female to male ratio is approximately 3:1.[5,6] Other risk factors for developing infantile hemangiomas include prematurity, low birth weight, white ethnicity, multiple gestations, older maternal age, maternal history of infertility, *in vitro* fertilization, pre-eclampsia, placenta previa, maternal use of progesterone, and chorionic villus sampling.[1-3,7] There may also be a genetic predisposition as siblings of an affected patient have an increased relative risk for infantile hemangiomas.[8]

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PATHOGENESIS

Infantile hemangiomas arise from endothelial stem cells that later proliferate by vasculogenesis, with further angiogenesis. Hypoxia and estrogen are important stimuli and have synergistic effect on angiogenesis.[9,10] The genes encoding Vascular Endothelial Growth Factor (VEGF), indoleamine 2,3-dioxygenase, Insulin-like Growth Factor 2 (IGF2), angiopoietin-1, angiopoietin-2, basic Fibroblast Growth Factor (bFGF), and tyrosine protein kinase receptor (Tie2) are believed to play a significant role in the pathogenesis of infantile hemangiomas.[2,3,5]

An infantile hemangioma might result from a somatic mutation that slows the maturation of endothelial progenitor cells to endothelial cells.[2,5] Infantile hemangioma stains with a panel of immunohistochemical markers such as Glucose-Transporter-1 protein (GLUT-1), Allograft Inflammatory Factor-1 (AIF-1), Lewis Y antigen, and merosin that distinguishes it from other vascular malformations.[1-6] As these markers are expressed in placental microvasculature, infantile hemangioma might originate from embolized placental tissue or a somatic mutation which causes angioblasts to differentiate toward a placental microvascular phenotype.[4,9,10] In this regard, chorionic sampling has been associated with an increased incidence of infantile hemangiomas.

CLINICAL MANIFESTATIONS

It is generally believed that infantile hemangiomas are not clinically apparent at birth.[4,5,11] They usually appear in the first few weeks of life as areas of pallor, followed by telangiectatic patches.[12,13] In contrast, a more recent study showed that infantile hemangiomas were present at birth in 65% of patients.[14] Infantile hemangiomas then grow rapidly in the first 3 to 6 months of life (proliferative phase).[15] They continue to grow until 9 to 12 months of age, at which time the growth rate slows down to parallel the growth of the child (quiescent or plateau phase).[1] Involution begins in most cases by the time the child is 3 to 4 years old (involution phase).

Clinically, superficial lesions are bright red, protuberant, and sharply demarcated and are often referred to as "strawberry hemangiomas" or "capillary hemangiomas" (Figures 1 and 2).[1,3]

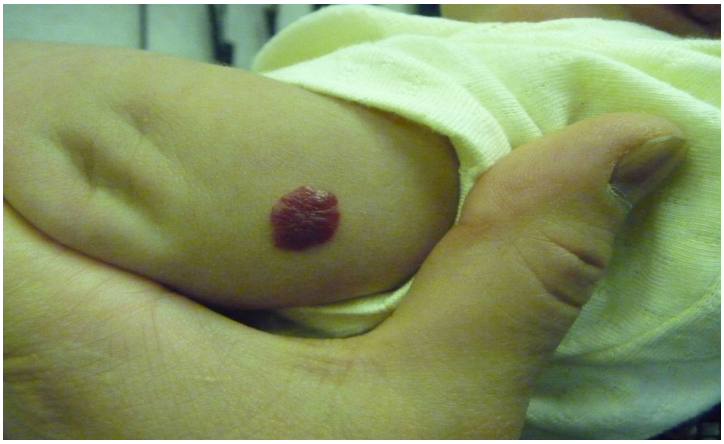

Figure 1: A 6-month old girl with a superficial infantile hemangioma on the left elbow.

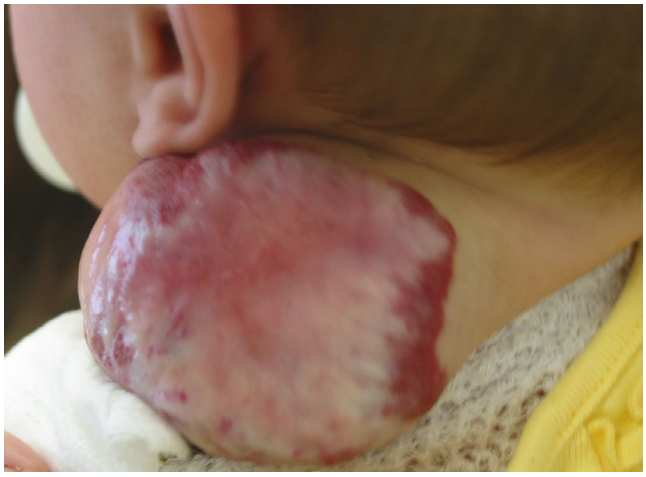

Figure 2: A 10-month old girl with a superficial infantile hemangioma on the left shoulder.

A plaque type is a distinctive variant of superficial hemangioma and is often termed "segmental".[16] A segmental hemangioma is more prone to ulceration and has a stronger association with developmental structural anomalies.[16,17] Deep lesions are bluish and dome-shaped and are noted on average 1 month later than superficial hemangiomas and reach their maximun size between 1 and 2 years of age.[18,19] Deep infantile hemangiomas feel like a "bag of worms" and are compressible.[16] Approximately 60% of infantile hemangiomas are superficial, 15% deep, and 25% mixed superficial and deep.[16] Mixed hemangiomas (both superficial and deep) may show characteristic features of both, often presenting with a red plaque overlying a bluish nodule.

Although infantile hemangiomas can appear anywhere on the skin, internal organs or mucous membrane, they have a predilection for the head and neck region.[16,20] Most infantile hemangiomas exist as solitary lesions,[4,20] although up to 20% of affected children have more than one lesion.[15,16] Infants with multiple lesions may have extracutaneous involvement.[9] Benign neonatal hemangiomatosis is characterized by multiple hemangiomas occurring exclusively in the skin.[21] In most cases, the hemangiomas resolve spontaneously during the first few years of life. In contrast, diffuse (disseminated) neonatal hemangiomatosis is characterized by multiple cutaneous and visceral hemangiomas and associated with a poor prognosis.[21]

An infantile hemangioma usually occurs sporadically and in isolation.[20] Occasionally, it is associated with PHACES syndrome (Posterior fossa malformations, Hemangiomas, Arterial anomalies, Cardiac defects or Coarctation of the aorta, Eye abnormalities, and Sternal defects) and PELVIS syndrome (Perineal hemangioma, External genitalia malformations, Lipomyelomeningocele, Vesicorenal abnormalities, Imperforate anus, and Skin tags).[1,4] Lesions over the lumbosacral area may be associated with spinal dysraphism, urogenital abnormalities, and rectal abnormalities.[1] Segment

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al hemangiomas, multiple hemangiomas, and hemangiomas at a high-risk site are associated with a higher risk of extracutaneous anomalies and require referral to a physician or clinic specializing in the management of these lesions.[3,6,16]

DIAGNOSIS

The diagnosis is mainly clinical. Timing of appearance of the lesion, changes in size and color over time, and tactile qualities provide clues for accurate diagnosis.[15] Dermoscopy is useful for evaluating the precise vascular structure.[22] Imaging studies are usually not necessary but should be considered if the diagnosis is in doubt or an associated anomaly is suspected. Color Doppler ultrasonography, computed tomography, and magnetic resonance imaging will reveal specific characteristics of different types of vascular anomalies and delineate the extent of the lesion.[15]

DIFFERENTIAL DIAGNOSIS

Infantile hemangiomas have to be differentiated from Rapidly-Involuting Congenital Hemangiomas (RICH) and Non-Involuting Congenital Hemangiomas (NICH) which are fully formed at birth, have no sex predilection, are pink or violet in color, do not grow postnatally, and lack GLUT1 surface markers.[3,9,18] Lesions are usually noted around the elbows and knees and along the mandibular border.[18] Rapidly-involuting congenital hemangiomas typically shrink rapidly after birth and disappear by 6 to 12 months of age.[19] Non-involuting congenital hemangiomas, on the other hand, do not change after birth. Other differential diagnoses include tufted angioma, Kaposiform hemangioendothelioma, pyogenic granuloma, infantile hemangiopericytoma, glomangiomatosis, port-wine stain, salmon patch, venous malformation, and lymphatic malformation.[16,18]

COMPLICATIONS

Complications include hemorrhage, ulceration, infection in an ulcerated lesion, disfigurement, and compromise of vital functions such as airway obstruction, cardiac failure, visual impairment, and feeding difficulties.[15,16,23] In general, the risk for complications is closely related to the size of the lesion.[24] The risk is greatest in children younger than 6 months of age and in premature infants.[14,25] Incomplete involution may leave residual atrophic scars, hypopigmentation, or telangiectasia. Facial, segmental, or large-sized lesions are more likely to have incomplete involution.[19,22] The condition can be unsightly and cosmetically disfiguring, especially if it occurs on the face. The quality of life may be adversely affected due to psychosocial sequelae, although a recent study showed that affected children do not have a negative quality of life or low self-esteem.[26]

PROGNOSIS

Approximately 50% of infantile hemangiomas will show complete involution by the time a child reaches age 5; 70% will have disappeared by age 7; and 95% will have regressed by ages 10 to 12.[4,13] A central graying of the lesion and shrinkage in size are the visible stages of this process.[4] When involution is complete, the skin looks completely normal; partial involution may result in telangiectasia or an atrophic scar.

MANAGEMENT

The majority of infantile hemangiomas require no treatment.[4,23] Parents should be educated about the natural history of infantile hemangiomas. Follow-up with reassurance to the family is essential. Indications for active intervention include severe or recurrent hemorrhage unresponsive to treatment, threatening ulceration in areas where serious complications might ensue, interference with vital structures, life- or function-threatening complications such as ocular compromise and respiratory distress, pedunculated hemangiomas, and significant disfigurement.[4,6,20,23,24]

Until recently, systemic corticosteroids, mostly oral prednisolone or prednisone, were the mainstay of treatment for complicated infantile hemangiomas.[20] Treatment with systemic corticosteroids is only effective during the proliferative phase.[10,16] Presumably, corticosteroids work by down-regulating the secretion of VEGF-A by hemangioma stem cells.[27,28] The recommended dose is 1 to 3mg/kg/day, depending on whether the lesion is superficial (lower dose) or deep (higher dose).[9,28] The course usually lasts 4 to 8 weeks and an additional few weeks to taper off.[10] Response rates range from 69 to 90%.[10,29] Lesions on the tip of the nose tend not to respond well to steroid treatment.[19] Side effects are increased risk for immunosuppression, hypertension, Cushing's syndrome, adrenal suppression, cataracts, glaucoma, diabetes mellitus, gastrointestinal hemorrhage, osteopenia/osteoporosis, and growth retardation.[27] To minimize adrenal and growth suppression, it is recommended that the steroid should be given in a single dose in the morning. Expert care and monitoring is required when using systemic steroids.

Intralesional corticosteroids can be used for small, localized infantile hemangiomas.[20] Multiple intralesional injections of triamcinolone acetonide over a period of several weeks are often needed. Each dose should not exceed 3 to 5 mg/kg. Complications include bleeding, subcutaneous fat atrophy/necrosis, dyspigmentation of the skin as well as other complications associated with oral corticosteroid administration.

In recent years, propranolol, a nonselective β-blocker, has been used as a first-line treatment of problematic infantile hemangioma.[23] Propranolol-resistant infantile hemangiomas are rare.[30] With a response rate of 98% even in the most complicated cases and a favorable safety profile, propranolol has replaced former treatment options such as corticosteroids and laser therapy.[31] Lou et al performed a meta-analysis on 35 studies that estimated the efficacy of propranolol therapy involving 423 patients with infantile hemangiomas and 248 control subjects.[32] The authors found that efficacy of propranolol was

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more than other therapies in treating infantile hemangiomas (odds ratio:9.67; 95% confidence interval:6.62 to 14.12; P<0.001). In stratified analysis by sites of tumor, propranolol was more effective when compared to corticosteroids (odds ratio: 9.67; 95% confidence interval: 6.61 to 14.15; P<0.001), vincristine (odds ratio: 9; 95% confidence interval: 2.15 to 37.66; P=0.003), and laser (odds ratio: 9; 95% confidence interval:1.42 to 57.12; P=0.02) in treating cutaneous infantile hemangiomas (odds ratio: 24.95; 95% confidence interval:9.48 to 65.64; P<0.001), periocular infantile hemangiomas (odds ratio:9.39; 95% confidence interval: 3.88 to 22.71; P<0.001), airway infantile hemangiomas (odds ratio: 20.91; 95% confidence interval: 7.81 to 55.96; P<0.001), and hepatic infantile hemangiomas (odds ratio: 9.89; 95% confidence interval: 20.81 to 81.54; P=0.033). The mechanisms whereby propranolol works include vasoconstriction of the high-flow blood vessels feeding the hemangioma, suppression/blockade of VEGF and bFGF with induction of apoptosis of capillary endothelial cells, blockade of GLUT1 receptors, and accelerated adipogenesis of hemangioma stem cells.[9,33,34] Other authors suggest that propranolol does not induce apoptosis of infantile hemangioma stem cells, which is in contrast with the result of capillary endothelial cells.[35] In contrast to corticosteroids, propranolol is effective in treating hemangiomas in children of all ages, and not limited to the proliferative stage of the lesions.[36] The recommended dose is 1 to 3 mg/kg/day divided in three doses.[37] Clinical improvement is evident in the majority of patients within the first week of treatment.[32] Side effects are uncommon and include hypoglycemia, hypotension, sinus bradycardia, cold extremities, bronchial hyperreactivity, constipation, nocturnal restlessness, somnolence, seizure, and electrolyte disturbances.[9] Contraindications to the use of propranolol include hypoglycemia, reactive airway disease, significant cardiac disease (heart failure, cardiogenic shock, hypotension, second or third degree heart block), compromised renal function, central nervous system disorders, and hypersensitivity to propranolol.[10] Facial and mixed hemangiomas with both superficial and deep components tend to respond less well.[10] Rebound growth after discontinuation of treatment has been reported.[37] Expert care and monitoring is required when using oral propranolol.

Timolol maleate, a nonselective topical β-blocker, may have a role in the treatment of superficial lesions. Topical timolol has fewer side effects than systemic administration of β-blocker.[38] However, systemic absorption following topical application of timolol can occur, especially in young infants. Pruritus may occur at the application site.[38] Topical timolol may be considered in patients at risk for potential side effects from oral administration of propranolol.[39]

Interferon-α may be considered if there is no response to corticosteroid or propanolol. The mode of action can be attributed to its anti-angiogenesis and bFGF inhibition properties. The recommended dose is 3 million IU/m2/day. The medication is usually given subcutaneously for a few months.[19] Neurotoxicity such as spastic diplegia and developmental delay occurs in 10 to 30% of patients.[24] Other side effects include fever, irritability, depression , anemia, neutropenia, thrombocytopenia, hypothyroidism, and hepatotoxicity. Interferon-α is best avoided in infants as they have a higher risk for complications.[24]

Treatment with pulsed-dye laser with a wavelength of 595-nm, typically performed by a dermatologist, may be useful in the treatment of superficial infantile hemangiomas.[40] Pulsed-dye laser works by targeting intravascular hemoglobin resulting in vascular injury. Early treatment is associated with better cosmetic results. Pulsed-dye laser may also be used to reduce the telangiectasia that may occur after the involution phase. Adverse effects include hypopigmentation, skin atrophy, ulceration, and scarring.[40] A recent study showed that facial-segmental infantile hemangiomas treated with propranolol and pulsed-dye laser displayed more rapid and complete clearance and required a lower cumulative propranolol dose to achieve near-complete clearance.[41]

Surgical excision is indicated for function- or life-threatening or disfiguring lesions when pharmacologic agents are contraindicated, not tolerated, or fail. It may also be considered for lesions on the tip of the nose or eyelid, pedunculated lesions, ulcerated lesions, and lesions with a thick dermal component.[10]

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