Hemangiomas of Infancy

İnfantil Hemanjiyomlar

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ABSTRACT Hemangiomas of infancy are the most common benign vascular tumors in children. The incidence is 1-2% in neonates and 12% by age 1 year. For unclear reasons, girls are 3 times more likely to be affected than boys. The natural history of hemangiomas is characterized by a rapid proliferation of capillaries begins first 3 to 6 months of life and maximum size by 9 to 12 months of age (the proliferating phase), followed by slow, inevitable regression for the next 1-5 year (the involuting phase). There is complete regression of hemangiomas in over 50% of children by age 5 year and in over 70% by age 7 year, with continued improvement in the remaining children until 10-12 year (the involuted phase) The pathogenesis of hemangiomas is not well understood. They are usually seen on the head and neck areas. The most common complication of rapidly proliferating hemangiomas is ulceration, which may result in secondary infection, pain, and/or scarring. The majority of hemangiomas are minor vascular birthmarks that require no treatment. Only few cases, however, become problematic, endangering or even life-threatening. Most commonly used treatments include corticosteroids (systemic, intralesional, and topical), pulse dye laser, interferon alfa, vincristine, and surgical exsicion.

Key Words: Hemangioma, diagnosis, complications, therapy

ÖZET İnfantil hemanjiyomlar çocukluk çağında en sık görülen benign vasküler tümörlerdir. Yenidoğan döneminde görülme sıklığı %1-2 iken, 1 yaşında bu oran %12'lere kadar yükselir. Nedeni henüz bilinmemekle birlikte kız çocuklarında erkeklerden 3 kat fazla görülür. Klasik olarak, ilk 3-6 aylık bebekte başlangıç belirtilerinin ardından, karakteristik hızlı büyüme fazı (proliferatif faz) başlar ve 9-12 aylık bebekte maksimum büyüklüğe ulaşır. Daha sonraki 1-5 yıl değişken derecede küçülmenin görüldüğü gerileme fazıdır (involuting faz). İnfantil hemanjiyomların %50'si 5 yaşında, geriye kalanların %70'i 7 yaşta tam gerileme gösterir. Az sayıda çocukta tam gerileme 10-12 yaşa kadar uzayabilir (involuted faz). Patogenezi henüz tam olarak anlaşılamamıştır. İnfantil hemanjiyomlar en sık baş ve boyun bölgesinde meydana gelirler. Komplikasyonlar genellikle hemanjiyomda büyümenin en hızlı olduğu proliferatif fazda meydana gelir. En sık görülen komplikasyon ağrı, infeksiyon ve/veya skatrisleşme ile sonuçlanabilen ülserasyondur. İnfantil hemanjiyomlar genellikle spontan gerileme gösterdiğinden tedavi gerektirmezler. Sadece problem yaratan, hatta hayatı tehtid edebilecek infantil hemanjiyomlar tedavi gerektirir. En sık kullanılan tedaviler kortikosteroidler (sistemik, intralezyonel ve topikal), pulse dye lazer, interferon alfa, vinkristin ve cerrahi eksizyondur.

Anahtar Kelimeler: Hemanjiyom, tanı, komplikasyonlar, tedavi

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Hemangiomas of infancy (HOI) are the most common benign vascular tumors in children. The incidence is 1-2% in neonates and 12% by age 1 year. While they occur in any race, they are more frequent in Caucasian infants. Girls are affected 3 times more often than boys, and in

infants with a birth weight below 1,000 g.[1] They are also more common in infants born to mothers who have undergone prenatal chorionic villus sampling.[2] While almost all hemangiomas occur sporadically, familial transmission in an autosomal dominant fashion has been reported.[3]

The term "hemangioma" has been applied misleadingly to a variety of vascular anomalies with diverse biologic and pathologic features. However clinical observations and pathologic studies, have clearly distinguished HOI from other vascular tumors and from vascular malformations.

PATHOLOGY AND PATHOGENESIS

On routine histology, proliferating HOI are composed of microvessels lined by plump, mitotically active endothelial cells and pericytes. As involuting progresses, the vascular lumens dilate, endothelial cells flatten, and fibrous tissue is deposited, giving the hemangioma a lobular architecture. Involuted hemangiomas contain few capillary-like feeding vessels and draining veins with flattened endothelium in a stroma of fibrofatty tissue, collagen, and reticulin fibers.

The pathogenesis of HOI is not well understood, but recent findings suggest an intrinsic defect of the precursor endothelial cells that, through somatic mutation in a gene regulating angiogenesis, develop a phenotype that induces clonal proliferation. Another theory is that they might arise from cells originating in the placenta that embolize in foetal tissue during pregnancy or delivery, although this has recently been shown not to be the case.[4]

Immunhistochemical studies of HOI demonstrate their vascular origin. Endothelial cells in all phases express CD31, von Willebrand factor, and urokinase. Whereas CD133, also called AC133 antigen is a novel human stem/progenitor cell marker, CD34 is a known marker for endothelial cell. The coexpression of both markers suggests endothelial progenitor cells are play an important role in the hemangiomagenesis, perhaps as precursors of the clonal endothelial cells.[5] GLUT1, a glucose transporter, has been described as a specific and useful immunohistochemical marker for HOI in all phases of their development, while its expression was negative in other vascular tumors and malformation.[6] Most notably, insulin like growth factor 2 (IGF 2), which is a known mitogen which supresses apoptosis, is highly expressed during the proliferative phase and substantially decreased during involution.[7,8]

Although a specific genetic mutation has not been identified for HOI, nonrandom X-inactivation has been demonstrated.[9] Rare kindreds in which they seem to be inherited are reported. In 3 families, linkage to the locus 5q31-33 has been established. Candidate genes in this area include FGFR4, PDG-FRB, and FLT4.[10] Loss of heterozygosity at 5q in 6 sporadic hemangiomas has also been demonstrated.[11]

CLINICAL CHARACTERISTICS

HOI may occur on any part of the body, however they are usually seen on the head and neck area, followed by trunk and extremities. Unlike other types of birthmarks, hemangiomas are either absent or barely evident at birth (nascent phase). Most HOI begin their growth in the first few weeks of life, although deep hemangiomas are usually not noticed until a few months of age. The natural history of HOI is characterized by a rapid proliferation of capillaries beginning in the first 3 to 6 months of life with maximum size by 9 to 12 months of age (the proliferating phase). This is followed by slow, inevitable regression for the next 1-5 years (the involuting phase). Complete regression of hemangiomas occurs in over 50% of children by age 5 years and in over 70% by age 7 years, with continued improvement in the remaining children until 10-12 years (the involuted phase).[4]

Hemangiomas range from a few millimeters to several centimeters in diameter. They are usually solitary, but as many as 20 percent of affected infants have multiple lesions. Some hemangiomas may have precursor lesions like faint hypopigmentation resembling nevus anemicus, a telangiectatic patch, a bruise-like area (often misdiagnosed as perinatal trauma) and skin ulceration. The appearance of the proliferative phase of cutaneous hemangiomas depends on which levels of the skin are affected. Superficial hemangiomas are well-de-

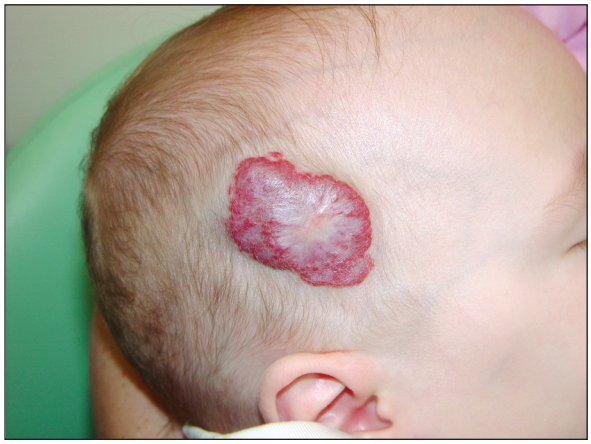

FIGURE 1: The appearance of superficial hemangioma at 10 months of age with central grayish-white hue.

fined, bright red, nodules or plaques located clinically above normal skin They are the most common subtype and constitute 50-60% of all hemangiomas. In contrast, deep hemangiomas are raised, skin-colored nodules, which often have a bluish hue or a overlying telangiectatic patch. Deep hemangiomas (previously called "cavernous hemangiomas") proliferate in the lower dermis and subcutaneous tissue without significant penetration of the papillary dermis. Mixed hemangiomas have both superficial and deep components. Involution of superficial lesions begins at the central portion of the hemangioma and spreads peripherally with color changes from bright red to dull red-purple and eventually grayish-white color (Figure 1). As the hemangioma involutes, its volume decreases and it becomes softer and more compressible as fibrofatty tissue replaces the endothelium. Deep hemangiomas also become softer and less blue. Diffuse neonatal hemangiomatosis (DNH) is where there are numerous small hemangiomas with a high risk of internal involvement (e.g. liver, gastrointestinal tract and/or brain) and heart failure. In contrast to other hemangiomas, the hemangiomas in DNH mostly involute by age of 2 years).

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of HOI is mainly clinical. They may be confused with other vascular anomalies such as capillary malformation, venous malformation, lymphatic malformation, and nasal glioma, rhabdomyosarcoma, myofibromatosis, encephalocele, neurofibroma.[4] Consumptive coagulopathy does not occur with HOI, for this reason it is not necessary to check platelet counts in infant with HOI. Imaging studies such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound can be helpful in differentiating hemangiomas from many of these conditions. Dermoscopy is a widely used method to evaluate vascular lesions and hemangiomas.[12] Biopsy with immunohistochemical phenotype, if needed, should be considered when diagnosing HOI in the lesion which is unusual.[13]

COMPLICATIONS

Complications usually occur during the first 6 months, when growth is most rapid. The most common complication of rapidly proliferating hemangiomas is ulceration, which may result in secondary infection, pain, and/or scarring (Figure 2). It occurs in approximately 15% of cases. Hemangiomas that are located around the mouth, nose, ear and diaper area have higher risk of ulceration. Ulcers heal slowly and can last for months. Local wound care is the mainstay of ulcer therapy, and is especially important for lesions in locations subject to trauma and infection, such as the perineum.[14,15]

Bleeding is a very rare complication, although frequently expressed by parents as a concern. When hemangiomas bleed, they tend to bleed ra-

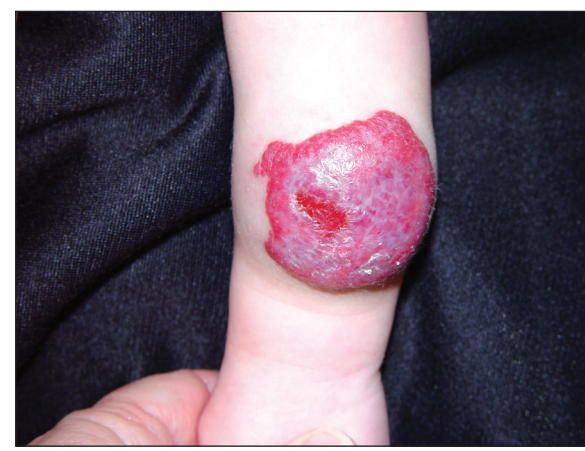

FIGURE 2: Ulcerated hemangioma.

pidly, however direct pressure to the area for several minutes usually stops the bleeding.

If a hemangioma around the eye grows rapidly, it may obstruct the infant's vision or cause pressure on the globe causing astigmatism causing irreversible loss of sight. It is important to closely monitor hemangiomas on the eyelids and they should be referred to a pediatric ophthalmologist. Airway passage obstruction usually is associated with large hemangiomas in the beard area (preauricular area, chin, anterior neck, and lower lip) and may be life-threatening.[16] Infants with HOI in this distribution need to be observed closely particularly in the first 3 to 4 months of life. If symptoms develop, the infant should be evaluated promptly with direct laryngoscopy and treated with oral steroids.

EXTRACUTANEOUS COMPLICATIONS

The most common extracutaneous site of involvement is the liver. Hepatic hemangiomas can be single or multiple and can occur in the absence of cutaneous lesions. Many infants with hepatic hemangiomas may be asymptomatic, however some may lead to hepatomegaly, high-output congestive heart failure, anemia, and rarely thrombocytopenia. Because of their risk for bleeding and other morbidities, these lesions rarely undergo biopsy, making the diagnosis difficult. Abdominal ultrasound should be considered as a first test for infants with more than 5 cutaneous HOI, clinical hepatomegaly, or symptoms suggesting hepatic involvement. MRI is needed in those patients with multiple, unusually large, or symptomatic HOI. After the liver, the most commonly involved organs are the central nervous system, lungs, and gastrointestinal tract. Recently, thyroid abnormalities in association with large hepatic hemangiomas have been published.[17]

ASSOCIATED STRUCTURAL ANOMALIES

PHACES syndrome (OMIM 606519) stands for posterior fossa brain malformations (e.g. Dandy-Walker malformation), hemangiomas (especially large, segmental, plaque-like, facial hemangiomas), arterial anomalies, coarctation of the aorta or other cardiac defects, eye abnormalities, sternal cleft or supra-umbilical raphe. The pathogenesis is unknown, but is thought to represent a developmental field defect occurring during early gestation.[18] Female infants are predominantly affected. Its sequelae may be significant and infants with an extensive segmental facial hemangioma on the face should be followed closely. Since neonates have open fontanelles, a head ultrasound is important to detect major structural defects. Attention to neurologic status and head circumference is mandatory. If any neurologic symptoms arise, MRI is the gold standart for the posterior fossa imaging.

Hemangiomas located over the lumbosacral spine may be associated with spinal dysraphism or other underlying congenital anomalies. Reported underlying anomalies include tethered cord, imperforate anus, bony anomalies of the sacrum, abnormal genitalia, renal abnormalities, and lipomeningomyelocele. Infants with lumbosacral and perianal hemangiomas should have MRI performed to exclude tethered cord which is the most devastating complication.[19]

MANAGEMENT AND TREATMENT

The management of HOI depends on the location, size, and complications. Many cases do not need to be treated at all, but just observed for resolution. Frequent visits every few weeks during the proliferative phase are the mainstay of management. The natural history of HOI should be discussed with the patient's family to alleviate their concerns. Current guidelines recommend treatment for (a) life- and function-threatening hemangiomas (vision impairment, airway obstruction, congestive heart failure, or hepatic involvement), (b) large, disfiguring facial hemangiomas, (c) hemangiomas in locations that may lead to permanent scarring or deformity (eg, nose, ear, etc), and (d) ulcerated hemangiomas.[20] Most commonly used treatments include corticosteroids (systemic, intralesional, and topical), pulse dye laser, and surgical exsicion.

SYSTEMIC CORTICOSTEROIDS

Systemic corticosteroids are the mainstay of treatment for complicated hemangiomas. Although their mechanism of action is poorly understood, they are used for large or agressive hemangiomas.

They are most effective when initiated during the first 6 months of life (in the proliferative phase). The recommended starting dose of prednisone or prednisolone is 2 to 3 mg/kg per day in either a single morning dose or divided twice a day. The addition of raniditine helps colicky symptoms. The dose if ranitidine suspension 75 mg/5cc, given 1 cc (15 mg) twice daily. For severe cases such as hemangiomas causing airway obstruction higher doses can be used to abruptly stop the growth. The drug should then be slowly tapered to physiologic doses (2 mg/m^2 per day of prednisone or equivalent) for 1 to 2 months, and slowly decreased over another 1 to 2 months before therapy is terminated.[21-23] Although there are potential side effects of high doses of systemic corticosteroids, most treated infants do very well. Short-term effects are more likely to develop with steroid courses of 6 months or longer, and resolve with drug tapering. The most common of such complications is the development of a cushingoid facies, which usually begins within the first 1 to 2 months of treatment. Personality changes such as depressed mood, agitation, insomnia, or restlessness occur in approximately one third of infants, usually in the first 2 weeks of therapy. Delayed skeletal growth, which is often readily apparent since a child grows more rapidly in the first year of life than at any other time, results from a temporary inhibition of collagen synthesis. However, most children catch up to their normal growth curve by 2 years of age. Gastric upset occurs in approximately 20% of infants and resolves with histamine$_1$-blockers such as ranitidine or cimetidine. Hypertension, though less common in children, has also been reported. Blood pressure monitoring should be performed in those infants undergoing systemic corticosteroid therapy.[21] Children should also avoid exposure to individuals with varicella infection. The varicella vaccine is not usually given until 1 year of age, when most treated infants will have been tapered off the drug. The response rate to systemic corticosteroids has been reported to be 84%.[21]

INTRALESIONAL AND TOPICAL CORTICOSTEROIDS

Intralesional corticosteroids therapy is effective for actively growing small hemangiomas. Doses should not exceed a maximum of 3-5mg/kg triamcinolone per treatment session. The procedure may be repeated at montly intervals with succeed rate of 85%. Potential adverse reactions include cutaneous atrophy, anaphylaxis, infection and bleeding.[24] Superpotent topical corticosteroids have been reported for very early, small superficial hemangiomas at risk for ulceration or small periocular lesions. Early involution can be seen when this is used (personal observation).

VINCRISTINE

It is a second-line treatment for corticosteroid-resistant hemangiomas, because of recognition of potential neurotoxicity of interferon. Administration via a central venous line is almost always necessary in young infants.[25]

INTERFERON ALFA

Interferon alfa, a known inhibitor of angiogenesis, has been used successfully in the treatment of endangering hemangiomas. It is given subcutaneously at a dose of 1 to 3 million U/m² of body surface area daily. Hemangiomas which have not responded to systemic corticosteroids are candidates for interferon therapy. The common side effects are fever, malaise, and neurotoxicity.[26]

LASER THERAPY

Laser therapy is divided into 3 indications: treatment of proliferative phase, treatment of ulcerated hemangiomas, and treatment of residual telangiectases after involution. Pulse dye laser (PDL) is an effective for ulceration, residual erythema and telangiectasias. Because PDL penetrates only 1.2 mm into the lesion, it has not been effective in treating thicker hemangiomas. The risk of scarring of PDL for HOI is much more higher than that for treating port-wine stains, particularly in the proliferative phase.[27] Many physicians who treat a lot of HOI recommend waiting until 6 months of age to treat non-ulcerated hemangiomas.

SURGERY

Because most hemangiomas undergo regression, usually there is no need for surgical intervention. Indications for surgery can de divided into early infancy or after 3 to 4 years of age. In early infancy,

surgery may be considered for localized, deep hemangiomas that are likely to resolve with permanent changes. Persistent bleeding or ulceration are other indications. For children between the ages of 3 and 5 years who have unresolved hemangiomas and they are becoming aware of the deformity, surgery may be considered.[28]

Sclerosing agents and embolization may be helpful in serious, life-threatening hemangiomas and hemangiomas complicated by congestive heart failure. They are not used for routine management. Cryotherapy or isotope radiotherapy is seldom used for the treatment of hemangiomas, due to the high incidence of scarring, pigmentation, or depigmentation.[4]

CONCLUSION

HOI are the most common tumors of infancy, yet the origin of these lesions remains controversial and the predictable life cycle is poorly understood. Children and their parents need frequent follow-up visits for emotional support and reassurance. The aim of treatment is to counter the proliferative growth, reduce the volume of hemangioma, and initialize the process of regression. A successful treatment of hemangiomas should be individualized and based on the size of the tumor, the localization, and the therapies available. Unusual or complicated hemangiomas should be followed at a center familiar with the difficulties these lesions can present.

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