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REVIEW ARTICLE

Capillary hemangioma – A review

Meenakshi Wadhwani, Rahul Singh

Department of Ophthalmology, Chacha Nehru Bal Chikitsalya, New Delhi, India

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Address for correspondence:
Dr. Meenakshi Wadhwani, Chacha Nehru Bal Chikitsalya, New Delhi - 110 031, India.
Phone: +91-9211543453.
E-mail: mkgang08@gmail.com

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Abstract

Capillary hemangioma (CH) also known as strawberry nevi can present as a small red raised isolated lesion. Imaging techniques such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) may be used to differentiate CH from other vascular tumors, to identify the extent of tumor. Management should be customized according to the age of the child, extent and size of the tumor(s), growth rate, depth (superficial, deep or mixed).

Capillary Hemangioma

Capillary hemangiomas (CHs) also known as infantile hemangiomas, strawberry nevi, or strawberry hemangiomas. CHs are one of the most common benign periocular and orbital vascular tumors of childhood. In the most of the cases, the natural progression starts with enlargement followed by spontaneous lapse without management over a period, without sequelae. Cutaneous CHs can present as a small, red, raised isolated lesion, or as dark blue subcutaneous lesions and may extend into the orbit or huge mass that can result in visual impairment, or rarely might be associated with systemic impairment or syndrome. Mainstay of therapy is β-blockers given their comparatively low-risk profile and efficiency. More recently, angiotensin-converting enzyme (ACE) inhibitors such as captopril have been used.

Demographics and Risk Factors

CHs are the most common periorbital tumor of childhood. They occur in 5–10% of children.[1-3] Major risk factors comprise female gender, Caucasian ethnicity, low birth weight, multiple pregnancies, prematurity, chorionic villus sampling, and a positive family history of vascular anomaly.[1-3] Females are expected to be affected thrice as compared to male counterpart. There is about 10 times high incidence in infants born to females who go through chorionic villus sampling during pregnancy. The incidence of orbit and periorbital CHs is one-tenth that of systemic CHs, which typically occurs in 10% of all births by 1 year of age.[4] No distinct hereditary pattern or higher incidence among siblings has been found.

Pathology

CHs are endothelial cells hamartomas. Histology varies with the stage of the natural course. Early CHs may be cellular nests of solid plump endothelial cells and minimal vascular lumen. Matured CHs consist of established, flattened, endothelial lined capillary channels in a lobular arrangement. Involuting CHs demonstrate fibrosis and hyalinization of capillary walls and luminal obstruction.

The exact mechanism of natural course of proliferation followed by involution is unclear; though, fibroblast growth factor and vascular endothelial growth factor (VEGF) have been recognized to play major role.[5]

CHs are involves the benign endothelial-like cells proliferation that possesses glucose transporter-1 (GLUT-1), Lewis Y antigen, FcγRII, and merosin histochemical markers; these markers are also present on placental blood vessels which lead to the placental embolization hypothesis. This hypothesis further intensifies on injecting human CH endothelial progenitor

cells injected into immunodeficient mice lead to recapitulation of CH life cycle and expression of GLUT1.

Recent studies have demonstrated considerably high serum levels of renin, angiotensinogen II, and VEGF in patients with CHs when compared to age-matched controls suggesting a possible association to the renin-angiotensin system (RAS).[6,7] Furthermore, a decrease level of RAS factors post-surgical removal of CH signifying that CHs may have subsequent changes in their prospective RAS, rather than innate changes in their RAS disposing to CH formation.[6]

Signs and Symptoms

Typically, CHs usually present within the initial 6 months postnatal (30% present at birth, 50% by 1 or 2 months, and 90% by 6 months). Most often natural course involves proliferative phase for initial 1 year, followed by stabilization and spontaneous involution over several years. Full resolution without intervention follows in about 49% and 72% by 5 and 7 years of age, respectively, which may extend to 10 years.[8] CH may present as a cutaneous, subcutaneous, or orbital lesion. Most common sites are eyelid or brow, with a predilection for the upper eyelid. CH may initially present as a small macular red spot well-known as herald patch. Superficial cutaneous lesions present as raised, nodular, and bright red mass (strawberry nevus) limited in the superficial dermis while a deep subcutaneous lesion comprises the dermis and hypodermis (subcuticular), may appear blue or purple in color. Mixed subtype has features of both formerly mentioned subtypes. A lesion located deeper inside the orbit may present as proptosis and absent skin changes or discoloration. Often, CH may expand and/or alter color on crying; and a cutaneous lesion may blanch on applying compression. However, CHs have no pulsation or bruit.

Mechanical ptosis can occur with upper eyelid CHs which subsequently can cause decreased vision because of amblyopia from induced astigmatic anisometropia, strabismus, or occlusion by the eyelid [Figure 1]. Astigmatic anisometropic amblyopia is the leading reason of visual dimension due to direct compression on the cornea by the thickened eyelid. Deprivational amblyopia follows when the CH obstructs the visual axis. Orbital hemangioma results in strabismus either exerting mass effect on the globe producing displacement or involving the extraocular muscles.

Systemically, hemangiomas are now classified into three primary subtypes: Segmental, focal, and indeterminate. Focal hemangiomas were 3 times more common than diffuse or segmental hemangiomas on the face while segmental subtype is associated with higher complications, deformities, functional compromise, and ulceration, as well as an intensified need for therapy. Other high-risk lesion hemangioma found in central facial, lumbosacral, liver, and genital region. One of the most important complications associated with segmental CHs is PHACE syndrome (discuss below).

Diagnostic Techniques

The International Society for the Study of Vascular Anomalies (ISSVA) classification is the International Standard Classification system which clearly distinguishes vascular tumors (neoplastic lesions) from vascular malformations (non-neoplastic lesions) based on the presence of vascular endothelial cells proliferation and thus extremely helpful in determining therapeutic measures. According to the ISSVA classification, infantile hemangiomas and congenital hemangioma are vascular tumors corresponds approximately to strawberry mark, hemangioma of infancy, and capillary hemangioma in the WHO classification.

CHs are almost always diagnosed clinically. Imaging techniques such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) may be used to differentiate CH from other vascular tumors, to identify the extent of tumor, and to observer the lesion progression. Ultrasonography (USG) helps to detect the extent of periorbital involvement while CT or MRI may be more helpful if deeper orbital extension is suspected. On USG, CH shows high to variable internal reflectivity with irregular acoustic structures. On CT, CH demonstrates low flow prominence homogenous soft-tissue mass with no bony destruction. It enhances with contrast facilitating to detect the margin and relation to surrounding structures such as optic nerve and extraocular muscles. The lesion appears hypointense to of intermediate signal intensity on T1-weighted MRI and moderate to hyperintense on T2-weighted MRI because of the slow blood flow through the vascular channels. T1 MRI images should be taken in fat suppression mode to better visualize the lesion. Lesion may enhance with gadolinium contrast.

Differential Diagnosis

The differential diagnosis includes nevus flammeus (port-wine stain) of Sturge-Weber syndrome, lymphangioma, rhabdomyosarcoma, chloroma, neuroblastoma, orbital cysts, cellulitis, congenital form of Kaposiform hemangioendothelioma, and tufted angioma.

Two less common types of congenital hemangiomas infantile CHs, non-involuting congenital hemangiomas (NICH), and rapidly involuting congenital hemangiomas (RICH) are often confused with CHs. They are "fully formed" at birth and may possess telangiectases and a rim of pallor. They lack GLUT1 surface markers, in contrast to infantile CH. RICH lesions rapidly involute, often within the 1st year, whereas NICHs persist for a prolonged period.

Management

Often, the natural course of CHs is initial enlargement followed by spontaneous regression. Typically 40% and 80% of tumors entirely involute by age of 4 and 8, respectively.[1]

Management should be customized according to the age of the child, extent and size of the tumor(s), growth rate, depth (superficial, deep, or mixed), site, and existing or possible

complications (such as scarring or risk to vision or vital organ function).[9] Coarsely, there is 4% increase in the requirement for intervention and 5% increased complication for every 10 cm^2 increase in lesion size.[10]

Hence, the management is indicated if the lesion causes visual impairment which includes occlusion of the visual axis, amblyopia, optic nerve compression, proptosis causing exposure keratopathy, severe cosmetic defect, infection, or necrosis.

Uncomplicated, small, localized, superficial CHs often require reassurance, counseling, and observation with serial photographic documentation and hemangioma activity score (HAS) of the tumor. Serial documentation is essential to assess level of progression and likely complications.

Two systems have been proposed to evaluate disease severity in the management of CH. Hemangioma severity scale (HSS) (2012) categorizes patients into subgroups on the basis of complication profile to guide necessity for intervention. Children scored higher than 10, usually require topical or systemic beta-blocker therapy.[11] Higher HSS found to be associated with higher risk of ulceration, structural anomalies, and permanent disfigurement, thus subspecialty referral should be taken if score totals more than 6.[11] HSS should be used as a screening tool by non-specialized practitioners in the early evaluation of lesion. The HAS (2011) is based mainly on color profiles of CH.[12] A prospective study compared HSS against HAS and established that the HAS system was superior in assessing intervention result.[12] It is recommended to do HAS at every visit to track management response overtime.

CH varies in size, depth, and morphology. Due to this fact, none of the classification system mentioned above able to define complicated lesions. Usually, tumors should be considered complicated if they are segmental, multiple in number, ulcerated, threat to cosmesis, periorbital or if the lesion is in a visceral organ. Furthermore, one should think of underlying extension if lesion is greater than 5 cm in diameter.[13] Large lesions and visceral hemangiomas require intensive medical management and monitoring; as they are related with high output heart failure. Complicated lesions can be accompanied with severe developmental anomalies, such as PHACE syndrome (posterior fossa anomalies, hemangiomas, arterial anomalies, cardiac anomalies, and eye anomalies).[13] Any patient with complicated lesion should be referred immediately to a specialist including a pediatric dermatologist and an ophthalmologist. Thorough history and cardiovascular and respiratory systems, assessment is essential for every patient who is undergoing for medical treatment.

PHACE syndrome is a rare disorder with predominance in Caucasian female patients.[13,14] The acronym PHACE denotes to posterior fossa brain abnormalities, hemangiomas, arterial malformations, coarctation of the aorta and other cardiac defects, as well as eye abnormalities. Infants with PHACE syndrome having large facial hemangiomas should be assessed with echocardiography or cardiac MRI to rule out aortic coarctation prior to systemic β-blocker use.[14] Furthermore, PHACE syndrome may predispose patients to stroke in the setting of hypotension, MRI head and neck with angiography is suggested before treatment to rule out any vascular anomalies associated.[14]

Medical Management

Non-selective β-blocker, propranolol applied topically or used systemically is the first line of treatment modality with high efficacy, low incidence of side effects, and decreased risk of recurrence after therapy. Several recent studies and randomized clinical trials have established its efficacy.[15] The mechanism of action is unknown and could be multivariate and includes vasoconstriction, decreased expression of proangiogenic signaling of VEGF, and basic fibroblast growth factor which are present through the growth stage of the CH,[16] as well as the initiating the apoptosis in later stages of treatment.[17] The US Food and Drug Administration has approved systemic propranolol for proliferating infantile hemangiomas since 2014. CHs commonly resolute after 3–6 months of treatment during the proliferative phase.[15]

The recommended dosage of oral propranolol is 2–3 mg/kg/day, divided twice daily, and adjusted for weight changes through growth of the infant. Initial recommended dosage of oral propranolol is 0.5–1 mg/kg/day in 2–3 divided doses which can be regularly augmented by 0.5 mg/kg/day over 2 weeks to objective dose of 2 mg/kg/day, with divided doses as above. Dosing with food is highly suggested to prevent hypoglycemia.[18] The most common side effects associated with systemic propranolol medication comprise acrocyanosis, diarrhea, and sleep disorder. Less common side effects comprise bronchospasm, hypoglycemia, mood disorders, bradycardia, and hypotension.[15,19] Treatment should be stopped for some days if mild respiratory distress happens, such as wheezing, till the respiratory condition reverts back to normal and then treatment can be restarted at a lower dose with a slower uptitration. Accordingly, target dose should be reduced based on symptom severity. Severe side effects are expected to arise in nearly 2.6% of children, with bronchospasm, followed by hypoglycemia and bradycardia in decreasing frequency.[19] Contraindications to systemic β-blocker therapy include cardiogenic shock, chronic sinus bradycardia, chronic hypotension, second or third degree heart block, heart failure, history of reactive airway disease, preterm infants of corrected age under 5 weeks, aortic coarctation, and vascular anomalies associated with PHACE syndrome (predisposing to stroke in setting of hypotension).[20] Infants and toddlers with deprived oral diet, simultaneous infection, or those formerly or presently getting oral corticosteroids are more prone to hypoglycemia.[21] It is advised that to get cardiac assessment done before starting management and to monitor blood pressure, heart rate, and blood sugar during the first 24 hours of treatment initiation. Closer monitoring with hospitalization should be done in newborns less than 5 weeks of age, preterm infants of corrected age over 5 weeks, infants with deprived social care, children with a history of cardiovascular disease, respiratory disease, or hypoglycemia.[21] Close follow-up at 4–12 week intervals should

be done to evaluate management response and for weight-based dose titration with the growth of infant. Period of management may differ according to response and presenting extent of the tumor. Usually, treatment duration is 6–12 months but the past 1 year of age when the infant is supposed to be exceeded the proliferative phase. Mixed and deep subtypes likely to have an extended growth phase compared to superficial CHs, thus the treatment duration for the former subtypes may run longer.[22] Patients with PHACES syndrome could be accompanying severe, long-segment narrowing of major cerebral or cervical arteries, lack of adequate collateral circulation, and coexisting aortic arch and cardiac abnormalities making them prone to acute ischemic stroke if kept on propranolol.[21] In such conditions, MRI/magnetic resonance angiography of the head and neck with a cardiology referral is necessary earlier to starting propranolol.

Rebound growth of CH has been known to occur with some frequency afterward oral propranolol stoppage.[23] Rebound growth is noticed more with segmental hemangioma subtype and initial depth of the lesion.[23] In cases with rebound growth, patient should be closely monitored on topical β-blocker therapy or reinitiation of systemic therapy.

CHs are defined as propranolol resistant when lesion continues to grow in the proliferative phase or fail to involute after adequately dosed therapy of more than 4 weeks. Approximately 1% of CHs have been reported being propranolol resistant.[24] And thus, alternative or adjunctive therapy should be started if treatment response shows failure by 3 weeks.

Being able to cross the blood–brain barrier, the potential long-term effect of propranolol intake on the gross motor system has been questioned. Recent studies done in treated patients compared to age-matched controls revealed no undesirable effect on psychomotor developmental, neither any increased risk of growth impairment at 4 years of age; however, further studies are desirable to outline any possible long-term sequelae.[25]

Atenolol and nadolol are alternative systemic β-blockers which should be given if side effects to propranolol are excessively troublesome or fatal. Atenolol, a cardioselective (β1) β-blocker, has shown comparable efficacy with reduced respiratory side effects.[26] In patients with sleep disturbances, nadolol, a non-selective β-blocker with superior β1 action, could be used.[27]

Topical non-selective β-blockers are the mainstay therapy for cutaneous, uncomplicated CHs.[28] They have been shown to be higher to topical steroids with a low profile of systemic side effects. In one study, 92% and 77% of children with uncomplicated tumors showed substantial improvement in color and size of the tumor, respectively, after 6–9 months of topical timolol treatment.[29] Equivalent efficacy has been shown with both topical timolol and propranolol.[30]

Topical timolol is available as ophthalmic 0.5% gel solution, one drop to be applied twice daily straight to the skin lesion for 6–12 months or until the lesion become steady or start involuting.[31] Topical propranolol as 1% cream or 4% gel formulation can be dosed twice to thrice or twice daily, respectively.

Along with the management of uncomplicated tumors, they can be used to avert rebound growth while dosing off oral β-blocker therapy or as adjuvant therapy with systemic propranolol in complicated lesions.[32] Topical non-selective β-blockers could be useful in deep lesions as recently shown in a small case series of five patients with deep periocular CHs treated with topical timolol only revealed a decrease in lesion size. The most common adverse effects associated with topical β-blockers include local irritation, ulceration, bronchospasm and rarely bradycardia.[29]

Topical brimonidine 0.2% and timolol 0.5% combination treatment (Combigan® Allergan, Irvine, CA) has shown efficacious for ulcerated lesions, however, is strongly contraindicated in children less than 2 years of age because of lethal brimonidine toxicity of central nervous system depression.[33]

In the past, systemic, intralesional injection, and topical steroids were the mainstay of treatment. However, rebound growth after stoppage, and side effects of systemic steroids such as gastrointestinal ulceration, dyspepsia, insomnia, stunted growth, immunosuppression, adrenal suppression, behavioral disturbances, Cushingoid features, hyperglycemia, delayed wound healing, arterial hypertension, and hypertrophic cardiomyopathy made the therapy suboptimal.[3] Intralesional steroid injection used to be mainstay of treatment and has shown effectiveness in diminution of the lesion size rapidly within 2 weeks of injection in several patients. However, important complications, including central retinal artery occlusion from embolization of the steroid material, skin atrophy, skin necrosis, skin depigmentation, risk of hemorrhage, calcification, and fat atrophy made it outdated.[34] Topical clobetasol steroid cream is suggested only as adjunctive therapy for superficial lesions or lesion resistant to β-blockers. Intralesional triamcinolone acetonide injections at a dose ranging from 10 to 40 mg/mL are now kept for treatment-resistant small, localized, deep hemangiomas.[35] Systemic corticosteroids are recommended to patients with a contraindication to β-blockers or in patients who have showed resistant or failed systemic propranolol therapy at a dose of 2–3 mg/kg/day every morning. The treatment course typically lasts 6–12 months followed by a gentle tapering when the treatment response is attained. Abrupt discontinuation of oral glucocorticoids should be avoided, as it can cause adrenal crisis or rebound proliferation of CHs.[3]

Immunomodulators such as recombinant interferon alpha-2a and 2b have been tried as subcutaneous injections. However, the prolonged treatment of numerous months, leading to significant adverse effects such as neutropenia, hepatotoxicity, and permanent spastic diplegia, discouraged the usage of this drug in management.[36]

Other drugs such as imiquimod, vincristine, and bleomycin A5 were now longer used often.

ACE inhibitors: In the recent reports, the RAS has been shown to play a key role the pathophysiology of CH.[6,37] Furthermore, it has been found that angiotensin I and angiotensin II play a crucial role in regulating cellular proliferation of CHs. A recent small, randomized, controlled trial, comparing captopril and propranolol establish later to be a superior therapy.[38] More studies need to be done to investigate the relation between RAS

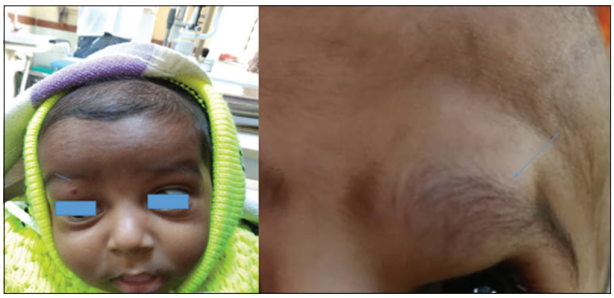

Figure 1: Various presentations of ocular hemangioma

factors and CH and the role of possible pharmacologic agents before clinical implementation.

Surgical Management

Laser photocoagulation has been found to be more effective to stimulate regression in superficial cutaneous lesions and in the management of superficial portion of more complicated lesion and less effective in deeper orbital lesions. It is presently suggested as adjunctive treatment for very superficial lesions. Lasers at a wavelength of 577 nm, target oxyhemoglobin in circulating red blood cells, which lead to selective photothermolysis and vascular injury inciting vessel closure yet prevent ulceration of the tissues. Advantages associated with laser therapy include customized approach, absence of systemic side effects, and ease to regulate management settings, and it can be repeated as required. Pulse dye laser (PDL) therapy is the laser therapy of choice as it is the only laser presently available that photocoagulate vessels without adversely affecting the overlying skin. Management is typically suggested before 6 months of age which can be repeated at every 2–4 weeks based on response and complications.[39]

Nd:YAG lasers could be useful in very deep (up to 2 cm) and large caliber vessels or telangiectatic subtypes; otherwise, Nd:YAG lasers usually are not favored over PDL.

Complete surgical removal is challenging as CHs tend to be unencapsulated. Thus, surgery is reserved for tumors that are refractory to medical and conservative therapy or if the lesion such as periocular or visceral lesions poses an immediate danger to life or function, as it is associated with a significant higher risk of intraoperative bleeding because of hypervascular nature of tumor.

Recently, microembolism created in the lesions by low-level interventional radiology which can haste the regression of the lesion has been reported good outcomes as an alternative or adjunct to surgery.

Along with the treatment of CH, it is significant to address the patient's visual rehabilitation with optimum refraction and occlusive treatment concomitantly.

Method of Literature Search

PubMed abstracts were searched without any date restrictions for capillary hemangioma with each of the following keywords: β-blocker, beta-blocker, capillary hemangioma, propranolol, and strawberry nevus. Further, literature review was conducted by means of Ovid Medline search with the following mesh headings: exp *Hemangioma, Capillary/dt, su, th (Drug therapy, surgery, and therapy), exp child/, exp infant/, limited to English language, and from 2013 to current. The articles were retrieved and read with any references therein, and further articles not in the PubMed search were also retrieved.

Conflicts of Interest

The authors declare no financial interests and do have any conflicts of interest.

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