INTRODUCTION

Infantile hemangiomas (IH) are the most common benign tumor in pediatric patients. They are a specific type of vascular tumor which are usually not present at birth and involute in the first few years of life. Most of these lesions are found in the head and neck. They can be in delicate anatomical areas including the parotid, nose and eye. They may also involve the upper aerodigestive tract including the subglottis with patients presenting with airway symptoms including stridor. Most IH are easily diagnosed and usually do not need any active treatment; however, some may need very specialized care regarding cosmetics, feeding and respiratory function. Other types of vascular neoplasms in the head and neck including other types of hemangiomas must be included in the differential diagnosis as the treatment varies. Most of the subject material here will be about IH.

VASCULAR ANOMALY CLASSIFICATION

Mulliken and Glowacki originally came up a way to classify vascular tumors in 1982. Other classifications including the WHO classification came about. The current, most accepted one today is the binary classification system made by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996. The 2 categories distinguishes between vasoproliferative neoplasms and vascular malformations. Vasoproliferative neoplasms are characterized by increased endothelial cell turnover and mitotic figures. Vascular malformations are structural abnormalities with either the capillary venous, arterial and/or lymphatic system which grow in proportion with the child (refer to PowerPoint file for chart).

IH are usually what people refer to as hemangiomas. It affects approximately 1 in 10 children. It has an increased incidence in the following populations: premature infants, multiple gestational babies, in vitro fertilization, Caucasians, females. IH is characterized by being positive to glucose transporter 1 or GLUT-1. IH have distinct phases in their natural life and are responsive to propranolol therapy.
Congenital hemangiomas are a separate entity from IH and have 2 types, rapidly involuting congenital hemangioma (RICH) and Non-involuting congenital hemangioma (NICH). These are usually difficult to distinguish from IH in a cross-section of time; usually following the natural course or response to treatment can determine diagnosis. These are GLUT-1 negative and usually require mechanical removal as medical therapy is ineffective. Lobular capillary hemangiomas, commonly known as pyogenic granulomas, occur more in adults, especially pregnant females. The etiology is unknown, although some evidence shows cause may be secondary to trauma or hormones.

Kaposiform Hemangioendothelioma is a vascular tumor that may look similar to a hemangioma but are usually more Violaceous in color and nodular in shape, extending into deep tissue. Tufted angiomas are more localized and usually are deep without skin involvement. Both of these lesions are diagnosed with biopsies. They are both connected to Kasabach-Merritt Syndrome. Both do not have standardized treatment.

INFANTILE HEMANGIOMA OVERVIEW

As stated before, IH are the most common benign tumor in pediatric patients including the head and neck area. 10-12% of Caucasian children are diagnosed with a hemangioma. These incidence in Asians and blacks are much lower. IH is much more common in females ranging from a 3:2 to a 5:1 male to female ratio. There is a strong association of atopy. There is a 36% increased risk of allergic rhinitis, 67% increased risk of asthma and an 82% increased risk of eczema. There is some genetic predisposition although there is no consensus on any particular gene or set of genes. A retrospective chart review showed that out of 2512 patients aged 12 years old and younger with an ICD-9 code of 228.01, siblings had a relative risk of 2.52 with a p > 0.0001. Three isolated families showed some linkage and locus heterogenecity to chromosome 5q.

IH are best diagnosed with a thorough history and physical examination. These lesions are generally not present at birth, although there might be a dusky area with telangectasias. Examination will show a red papule or papule with clear boundaries. Color may deepen with time. When there is more than 5 lesions found on exam, liver imaging with MRI is recommended as there is a high incidence of hepatic hemangiomas.

There are 2 phases of IH, the proliferative phase and the involutional phase. The proliferative phase begins shortly after birth and usually continues up to 12-18 months of age. They can reach 85% of their eventual total size by 5 months of age. Ulceration is worrisome during this phase as it can cause unsightly cosmetic sequelae. The involutional phase starts at around 6 to 9 months and takes months to years to complete. Superficial bright red lesions turn dull red, followed by a gray hue as well as flattening and softening. Most complete involution by 10 years of age with an imperceptible scar although larger ones may leave dense fibrofatty tissue and subcutaneous telangectasias.

IH are classified by their depth of penetration and location. Depth is divided into either superficial or deep. Superficial lesions are restricted to the upper dermis and are strawberry red in color. Deep lesions involve the deeper dermis and subcutaneous tissue. These may seem darker and can be palpable.
as a mass because of their anatomical location. Location is more emphasized in the head and neck areas. Focal lesions involve one segment of the face, while segmental lesions involve multiple segments being larger and widespread. The head is divided into 4 segments: Frontotemporal, maxillary, mandibular, frontonasal.

PATHOPHYSIOLOGY

There are multiple theories on the cause of IH, but the exact cellular mechanisms are not proven. IH is a result of aberrant angiogenesis, formation of new blood vessels from preexisting vasculature, and vasculogenesis, formation of new blood vessels from progenitor cells. Stem cells may have a hand in formation of IH. CD133 positive primitive mesenchymal stem cells have been isolated leading to believe that dysregulated differentiation of these cells are the origin. Theses stem cells can form GLUT-1 positive vessels within 7-14 days. GLUT-1 is positive in all IH. Normally, it is only expressed in placental blood vessels and blood-brain barrier blood vessels.

Vascular endothelial growth factor (VEGF) secreted by endothelial cells bind to the receptors on the stem cells and stimulate angiogenesis. In vitro studies have shown that hypoxia and estrogen synergistically enhance hemangioma proliferation. Other molecule receptor pathways mentioned in the literature include angiopoietins, tyrosine protein kinase receptors (Tie-2), the Notch pathway and the mammalian target of rapamycin complex (mTOR).

The beta-adrenergic pathway has been implicated secondary to the serendipitous discovery of propranolol on IH. It is thought that beta adrenergic vasoconstriction decreases the bulk of the tumor as well as decreasing the flow. Ultrasound of IH showed decreases in the lesions’ volume and vessel density after therapy initiation. There is also thought that it this receptor pathway has a direct effect on apoptosis of capillary endothelial cells. There is down regulation of VEGF-A and Hypoxia-inducible factor (HIF-1 alpha), which in turn has a direct cytotoxic effect in the form of decreased endothelial cell migration and apoptosis.

IH in its different phases has distinct microarchitecture although not clinically useful. In the proliferation phase, there is a proliferation of immature endothelial cells. There is an abundance of perivascular cells positively staining for alpha-smooth muscle actin. The basal lamina is thickened and multilaminate deep to the endothelial cells. There is a formation of syncytial masses with lumens. Light microscopy shows large numbers of vascular plexuses. There are some occasional mitotic figures. There is also a presence of mast cells. In the involuting phase, there is diminished cellularity with flattening of endothelial cells. There is relative dilation of vessels. Tissue becomes replaced with perivascular, intralobular, and interlobular fibrous tissue. There is a high number of mast cells which leads to think that they may have a role in regression of IH. After complete involution, there are “sponge-like” structures with scattered thin-walled blood vessels lined with flat endothelial cells.
INFANTILE HEMANGIOMAS IN THE HEAD AND NECK

Most IH are not life-threatening nor functionally impairing, but the ones that do need special attention. Cutaneous disfigurement may result including telangectasias, anectoderma, epidermal atrophy, hypopigmentation and residual fibrofatty tissue. If ulceration occurs, there can be unsightly scarring. There may be psychosocial implications as the patient can have a negative self-image and lack self-confidence. When they form near the eye, more immediate attention may be needed. Astigmatic amblyopia, which is physical deformation of the eye from local compression, or deprivation amblyopia, which is caused by obstruction of the visual axis, may result from periocular IH. Large IH can lead to high-output cardiac failure.

IH can occur in the upper aerodigestive tract, most commonly in the subglottic region. There is a high incidence of subglottic IH in patients with cutaneous segmental IH in a beard distribution. Up to 63% of patients with beard distribution IH have been found to have subglottic IH. Patients can present with stridor, exacerbated by agitation, crying, or upper respiratory tract infection. Patients are initially misdiagnosed as croup. There can also be feeding difficulties and sleep disturbances. So, when a pediatric patient presents with a large hemangioma in the chin, lip, neck, preauricular region along with stridor, there must be a high suspicion of subglottic IH. Hospital admission and urgent upper airway endoscopy are warranted.

The most common benign parotid gland tumor in pediatric patients is IH. Parotid IH can grow profusely causing disfigurement, vascular shunting and facial nerve palsies.

ASSOCIATED SYNDROMES

PHACE Syndrome was first described by Frieden et al. in 1996. It is a neurocutaneous disorder that includes the following: posterior fossa anomalies, hemangiomas, arterial cerebrovasculature abnormalities, coarctation of the aorta/cardiac abnormalities, eye abnormalities and central/sternal abnormalities. Involvement of a pediatric cardiologist, ophthalmologist and neurosurgeon may be required with tests including echocardiogram, brain imaging, and ophthalmologic evaluation. There should be a low threshold for airway endoscopy. Antiplatelet therapy may be warranted to prevent stroke.

In PHACE Syndrome, hemangiomas tend to be larger than 5 square centimeters. Durr et al showed that 52% (12 out of 23) of PHACE syndrome patient with large cervicofacial segmental hemangiomas had coexisting subglottic hemangiomas.

LABORATORY TESTS AND IMAGING

IH is a diagnosis made with history and physical examination and usually do not require laboratory tests and imaging. Most laboratory testing is for research purposes without much implication in management. Some markers for IH include Lewis Antigen (LeY), Merosin, urinary basic fibroblast growth factor (bFGF) levels.
Imaging is not usually needed for IH, although it can be helpful in determining depth of involvement or airway involvement. Ultrasound can show a non-specific echogenic mass. Dubois et al. determined that 5 vessels per square centimeter and Doppler frequency shifts greater than 2 kHz as criteria in proliferative phase. This was done prospectively in 116 patients showing 84% sensitivity and 98% specificity. On magnetic resonance imaging (MRI) with gadolinium, IH are well-circumscribed, lobulated masses with a salt and pepper pattern. They have dilated feeding and draining vessels. In the proliferative phase, the mass appears solid and intermittently intense on T1-spin echo images. It is hyperintense with flow voids on T2-weighted images. In the involuting phase, IH are Nonenhancing or variably enhancing with variable fat content. Computed tomography (CT) shows a homogenous mass with intense persistent enhancement. Ct can help distinguish between venous malformations which has characteristic phleboliths.

**MANAGEMENT**

**Principles**

The management of IH has changed in the past decade due to the serendipitous discovery of propranolol. Previously, medical therapy with steroids or other drugs was used more commonly as well as ablative procedures with lasers and surgical excision. The natural course of IH is predictable so when the diagnosis is made while still in the beginning proliferative phases, close watching with possible plan of action should be developed. Early treatment can prevent large growth and future cosmetic disfigurement. Different factors are important to take into consideration for more aggressive treatment. The location of the lesion is important as cartilage involvement can cause structural damage to the nose or ear. Vision impairment and UADT involvement require closer watching and earlier treatment to prevent visual, respiratory, feeding difficulties.

**Medical Therapy**

Corticosteroids was the historical treatment of choice for over 30 years for IH in functionally impairing locations including the airway and parotid gland. It has been shown to be effective during the proliferative phase by slowing or ceasing growth. The dose for different corticosteroids differ but can for example range for prednisolone from 2 to 5 mg/kg/day for 4-10 weeks. The dose is tapered off. The response rate has been shown up to 90%. There is a high rate of complications including: behavioral changes, hypertension, immunosuppression, gastrointestinal irritation, adrenal insufficiency, cushingoid facies, and inhibition of hypothalamic-pituitary-adrenal axis. Intralional injection of corticosteroids has shown to be effective but the risk of blindness secondary to embolization of steroid molecules prevents more widespread use.

Interferon alpha-2a has been shown to have some anti-angiogenic activity and had been used in proliferative or involutional stages. The way it is administered by subcutaneous single injections daily over several months. Blood counts, liver function tests (LFT), and coagulation tests must be monitored during treatment. There is a good response rate of 80-90 %. Common side-effects include: flu-like symptoms, somnolence, anorexia, diarrhea, constipation, neutropenia, elevated LFTs. The feared
complication of this therapy is epilepsy, lower limb disability and most recognized, spastic diplegia. Because of the complications, the use of this has largely been abandoned for treatment of IH.

Imiquimod, an immunomodulatory drug used for cutaneous malignancies, showed good response used as a topical cream but there a high rate of skin complications. Other anti-cancer drugs such as cyclophosphamide, vincristine and Bleomycin has been used.

**Propranolol Therapy**

In 2008, Leaute-Labreze et al. were treating patients with large segmental cervicofacial hemangiomas were treated with propranolol when symptoms of high output cardiac failure occurred. They fortuitously noted rapid and dramatic regression of the cutaneous lesions as well. Since then, propranolol has been more heavily studied in the management of IH and has become the mainstay of treatment.

Propranolol is a synthetic, beta adrenergic receptor blocking agent. It is non-selective, meaning it blocks both beta-1 and beta-2 adrenergic receptors. Beta blockade leads to chronotropic, inotropic, vasodilator responses decrease when beta-receptors blocked, Inhibits renin release by kidneys, decreases sympathetic tone, which all lead to decreases in heart rate and blood pressure. Propranolol undergoes first pass metabolism by liver with only approximately 25% of the oral propranolol reaching systemic circulation. It is commonly used to treat: cardiac arrhythmias, angina, hypertension, hypertrophic cardiomyopathy, outflow obstruction in congestive heart failure. It has no Food & Drug Administration (FDA) approval for any indications in pediatric patients so consent must be obtained before use. Common side-effects are: bradycardia, hypotension, bronchospasm, hypoglycemia, hyperkalemia, gastrointestinal discomfort, diarrhea, gastroesophageal reflux disease, sleeping problems including hypersomnolence and night terrors.

Hogeling et al. in 2011 conducted a double blind randomized controlled trial of propranolol versus placebo on IH which showed better response with propranolol in volume, color and elevation. Mali et al. in 2013 conducted a prospective study comparing propranolol versus prednisolone versus both in potentially disfiguring or functionally threatening IH. The average response time was twice as fast in the arms with propranolol and the color change results were significantly better than the arm with corticosteroid alone. The arm with prednisolone also had more complications. Propranolol with a multidisciplinary approach with a pediatric cardiologist has also been shown to be safely initiated as an outpatient with relatively less complicated patients without or cardiovascular abnormalities.

In 2011, there was a consensus conference held on propranolol management on IH. They established that all treatment is individualized. Contraindications include reactive airway disease, significant cardiac disease, and hypersensitivity to propranolol. Patients less than 8 weeks of age need initiate treatment as an inpatient. The target dose was 2 mg/kg/day divided in 3 doses with a range from 1 and 3 mg/kg/day. Heart rate and blood pressure must be closely monitored especially at initiation and escalation of propranolol.
Surgical Treatment

Most IH do not need any surgical intervention but the options must be considered in complicated cases. Most of the following procedures done are more historical than actual current treatment modalities. Cryotherapy was used more in the mid-1900s, which was accompanied by much adjacent tissue damage. Different lasers have used including the argon laser, carbon dioxide laser, pulsed dye laser (PDL), neodymium:yttrium aluminum garnet (Nd:YAG) laser, potassium titanyl phosphate (KTP) laser. Argon and carbon dioxide lasers are largely not used secondary to unsightly scarring. PDL, which has a wavelength of 585-595 nanometers (nm), selectively destroys blood vessels and keeps overlying skin intact. Good cosmetic results have been obtained with this laser. Nd:YAG has a larger wavelength of 1064 nm with good depth penetration which makes it better suited for deeper lesions.

The most common surgical technique is standard elliptical excision along natural relaxed skin tension lines for focal cutaneous lesions. For subglottic IH, different approaches have been described. Tracheostomy is always an option when managing the airway. Endoscopic laser surgery with the aforementioned lasers have been described. Transcervical laryngofissure approach is also an option to get to the airway.

CONCLUSION

Infantile hemangiomas are the most common benign tumor in the pediatric head and neck, including parotid masses. The physician must distinguish between other vascular tumors and malformations. Most IH do not require active treatment with a predictable proliferation and involution phase. When IHs impinge on vital organs or affect aesthetics, treatment will be necessary. Large segmental head and neck hemangiomas have a high concurrence of an airway, particularly subglottic, hemangioma. Propranolol, although mechanisms unknown, has become the mainstay treatment for IH over corticosteroids and other pharmacologic therapies. The treatment of complicated IH requires a multi-disciplinary approach for the best individualized management of the patient.
REFERENCES