HAEMANGIOMA: UPDATE

Review Article

Salem *A.**,****Alboushy*** *A.**.*

*Vascular surgery unit**, General surgery department, Faculty of Medicine, Zagazig University.*

ABSTRACT

Background: Vascular anomalies are a heterogeneous group of congenital blood vessel disorders more typically referred to as birthmarks. Subcategorized into vascular tumors and malformations, each anomaly is characterized by specific morphology, pathophysiology, clinical behavior, and management approach**.**

Diagnosis: The diagnosis of a hemangioma is best made by clinical history and physical exam. In cases of unclear diagnosis, the best radiographic modalities to use are either a Doppler ultrasound or MRI.

Management: includes conservative, surgical, medical and minimall invasive approaches.

Conclusion: There are important clinical differences between haemangiomas and vascular malformations and adequate differentiating between the two lesions is a must. There are different modalities to manage haemangiomas, each modality may be used combined with another one or single according to many factors, including the natural history of haemangioma, the size and extent of the lesion, social situations, and surgeon's comfort or experience with any given treatment modality. These modalities include: conservative management, Laser therapy, steroids, interferon alpha, chemotherapy, surgery, embolization, some experimental modalities and propranolol.

Keywords: Haemangioma; Vascular malformation;treatment; Laser therapy; steroids; interferon alpha; chemotherapy;surgery;embolization; propranolol.

Abbreviations: bFGF: basic fibroblast growth factor**, FPDL**; flash pulse dye laser,**HBMEC**: human brain microvascular endothelial cells,**GLUT1**: Glucose transporter 1,**KTP**: potassium-titanyl-phosphate,**MMP-9**: Matrix metallopeptidase 9,**Nd:YAG**: neodymium:yttrium-aluminum-garne, **NICH**: noninvoluting congenital hemangioma,**PDL**: Pulsed dye laser,**PHACES** :posterior fossa brain malformations, hemangiomas of the face, arterial cerebrovascular anomalies, cardiovascular anomalies, eye anomalies, and sternal defects or supraumbilical raphe,**RICH**: rapidly involuting congenital hemangioma**,TGF-beta 1:**tumour growth factor beta one**, VEGF**: vascular endothelial growth factor.

INTRODUCTION

Vascular anomalies are a heterogeneous group of congenital blood vessel disorders more typically referred to as birthmarks. Subcategorized into vascular tumors and malformations, each anomaly is characterized by specific morphology, pathophysiology, clinical behavior, and management approach.[1]

Haemangiomas are soft, raised swellings on the skin, often characterised by a bright, red surface. They are a benign (noncancerous) overgrowth of blood vessels in the skinmade up of cells that form the inner lining of blood vessels. They are commonly known as 'strawberry birthmarks' [2]

Haemangiomas are the most common tumors of infancy affecting approximately 1 in 10 children. [3]Haemangiomas are more common in Caucasians, being evident in up to 12% of all children and occurring more frequently in females than in males, in a ratio of 3:1. Sixty per cent of haemangiomas are located in the head and neck area, whereas 25% occur on the trunk and 15% on the extremities. [4]

The influence of hemangiomas on children is various, and can be life-threatening when involving the larynx and trachea. Hemangiomas involving the eyelids can result in visual impairment such as amblyopia and refractive errors or even blindness. Massive hemangiomas can also lead to ulceration, necrosis, and infection of important structures. Disfigurement can also lead to psychological issues such as inferiority complex, unsociable stubbornness, and low self confidence.[5]

Haemangioma or Vascular malformation

A primary distinction is made between a vascular tumor, which grows by cellular hyperplasia, and a vascular malformation, which represents a localized defect in vascular morphogenesis. Due to the differences in biologic and radiographic behavior, both vascular tumors and malformations may occur anywhere on the body. Hemangiomas are vascular tumors that are rarely apparent at birth, grow rapidly during the first 6 months of life, involute with time and do not necessarily infiltrate but can sometimes be destructive.[1][6]

Vascular malformations are irregular vascular networks defined by their particular blood vessel type resulting from anomalous development of vascular plexuses. The malformations have a normal endothelial cell growth cycle that affects

the veins, the capillaries, or the lymphatics and they do not involute.[6] In contrast to hemangiomas, they are present at birth, slow growing, infiltrative, and destructive. Almost all vascular malformations and nearly 40% of hemangiomas eventually require intervention. [1]

PATHOGENESIS

Hemangiomas are further categorized into two types: "infantile" or "congenital." The rare "congenital" hemangioma is less understood and present at birth. Congenital hemangiomas either rapidly involute (rapidly involuting congenital hemangioma (RICH)) over a very brief period in infancy or never involute (noninvoluting congenital hemangioma;(NICH)).[1]

Infantile haemangiomas vary tremendously from small, benign growth to large, function threatening tumors [7] Infantile haemangiomas are characterized by an inconspicuous appearance at birth, but undergo rapid and intermittent growth throughout the first year of life. By the age of 5 years usually 50% of the lesions have involuted. This increases to nearly 70% by the age of 7 years and about 90% by the age of 9 years. Nevertheless, in 40–50% of all affected children teleangiectatic cutaneous vessels, fibrous-fatty tissue or scar formations can be observed as a residue of the lesions. [8, 9]

The pathogenesis of infantile hemangiomas remains unclear, although two theories dominate current thought. The first theory suggests that hemangioma endothelial cells arise from disrupted placental tissue imbedded in fetal soft tissues during gestation or birth. Markers of hemangiomas have been shown to coincide with those found in placental tissue [10]. This is further supported by the fact that they are found more commonly in infants following chorionic villus sampling, placenta previa, and preeclampsia.[11] A second theory arose from the discovery of endothelial progenitor and stem cells in the circulation of patients with hemangiomas.[12] The development of hemangiomas in animals from stem cells isolated from human specimens supports this theory.[13] However, infantile hemangiomas most likely arise from hematopoietic progenitor cells (from placenta or stem cell) in the appropriate milieu of genetic alterations and cytokines. [1]

Haemangioma endothelial cells exhibit constitutive vascular endothelial growth factor signaling the endothelial cells comprising infantile haemangiomas show intense and persistent immunoreactivity for a number of tissue-specific markers that is highly characteristic of placental microvasculature like GLUT-1. Therefore there is the hypothesis that haemangiomas possibly stem from placental tissue or resemble it [[8],[9]].

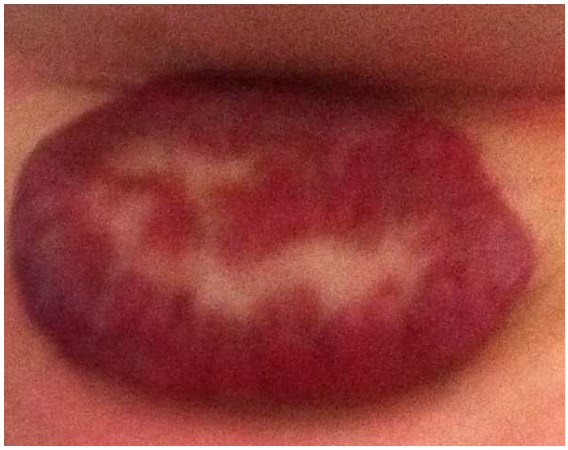
Abnormal levels of matrix metalloproteinases (MMP-9) and proangiogenic factors (VEGF, b-FGF, and TGF-beta 1) play a role in hemangioma pathogenesis. [14] Genetic errors in growth factor receptors have also been shown to affect development of hemangiomas[15]

DIAGNOSIS

The diagnosis of a hemangioma is best made by clinical history and physical exam. In cases of unclear diagnosis, the best radiographic modalities to use are either a Doppler ultrasound or MRI. [1]

Infantile hemangiomas present shortly after birth most often as well-demarcated, flat, and erythematous red patches. At this stage, hemangiomas may be confused

with other red lesions of birth, but rapid proliferation and vertical growth will trigger the diagnosis (Figure 1).[1]



(Figure 1) *Superficial infantile hemangioma.*

Generally speaking, hemangiomas do not spread outside their original anatomical boundaries. Hemangiomas follow a predictable course with three distinct developmental phases: proliferation, quiescence, and involution. In most hemangiomas, eighty percent of proliferation occurs by three months of life but may last longer. [3]During proliferation, rapid growth can lead to exhaustion of blood supply with resulting ischemia, necrosis, ulceration, and bleeding. [1]

Hemangiomas can be superficial, deep, or compound. The superficial hemangioma is red and nodular with no subcutaneous component. A deep hemangioma presents as a protrusion with an overlying bluish tint or telangectasia. Compound hemangiomas have both deep and superficial components. Another subclassification for hemangiomas is focal versus segmental disease. Focal hemangiomas are localized, unilocular lesions which adhere to the phases of growth and involution. Multifocal hemangiomatosis also

exists, and infants with greater than 5 lesions should undergo workup to rule out visceral involvement. Segmental hemangiomas are more diffuse plaquelike and can lead to untoward functional and aesthetic outcomes (Figure 2).[1]

(Figure 2) *Segmental hemangioma.*

Patients with segmental hemangiomas should also undergo investigation to rule out PHACES syndrome (posterior fossa brain malformations, hemangiomas of the face, arterial cerebrovascular anomalies, cardiovascular anomalies, eye anomalies, and sternal defects or supraumbilical raphe). [16]

MANAGEMENT

According to the 1997 "Guidelines of care for hemangiomas of infancy" in the Journal of the American Academy of Dermatology[17], the major goals of haemangioma management are: (1) preventing or reversing life-threatening or function-threatening complications; (2) preventing permanent disfigurement after involution; (3) decreasing psychosocial stress for the patient and family; (4) avoiding aggressive and possibly scarring treatments for those lesions likely to have an excellent prognosis without therapy; and (5) preventing or treating ulceration to lower scarring, infection, and pain. There are special considerations for lesions in specific areas (airway, intestinal tract, orbit, liver, etc.) which require unique considerations and expertise.[18]

There are different modalities to manage haemangiomas, each modality may be used combined with another one or single according to many factors, including the natural history of haemangioma, the size and extent of the lesion, social situations, and surgeon's comfort or experience with any given treatment modality.[1]

A useful approach to the management of haemangiomas can be based on the stage of the lesion (proliferative or involutive phase), type of lesion (superficial, deep, compound) and the management of residual deformity.[19] In general, life-threatening and sight-threatening haemangiomas should be dealt with, regardless of the stage of the lesion. Active intervention should be considered in all disfiguring haemangiomas, but each case should be managed on its merits after careful discussion and counselling, to prevent potential psychosocial trauma and cosmetic deformity. [20-22]

These modalities include: conservative management, Laser therapy, steroids, interferon alpha, chemotherapy, surgery, embolization, propranolol and some experimental modalities. [18]

Conservative management (benign neglect):

Historically, hemangiomas have been managed with close observation over their lifecycle. [23] However, research suggests that nearly 40% of children require further intervention because of bleeding, ulceration, visual axis obstruction, airway obstruction, high-output cardiac failure, or risk for permanent disfigurement. [24] With novel therapeutic options as well as a better understanding of disease, benign neglect is declining as the sole means of treating hemangiomas as it is misleading and the availability of other types of safe management of haemangiomas. Nonetheless, inconspicuous lesions are still best treated with observation alone.[1, 18, 21]

Surgery:

Excision is the appropriate for localized lesions the fibrofatty remnants (residuum) of involutedhemangiomas. Elective subtotal excision of massive protuberant proliferating hemangiomas can be employed in order to maintain aesthetic facial boundaries. Small remnants of disease are then left for involution.[1]

Surgery may be indicated also for small pedunculated lesions. It is thought that these are associated with a better cosmetic outcome after surgery as spontaneous resolution often leaves a visible fibro-fatty scar. Some authors propose early surgical excision in large scalp lesions to reduce the residual effects [25](alopecia, alteration of the hairline, trauma). There are no randomised studies or reviews addressing this. [18]

Surgery is also indicated for lesions that cause symptoms and fail to respond to other modalities of treatment. Lesions that cause bleeding in the gastrointestinal tract may require surgical excision. Splenectomy has been performed for problematic lesions in the spleen. Multiple hepatic haemangiomas may require the need for operative intervention, but this should be done in centres with considerable liver experience.[18]

MEDICAL MANAGEMENT

Different lines of medical therapy are used in managing haemangiomas depending on time of diagnosis, site and extent of the lesion.

Steroids:

This can be oral, intra-lesional or intravenous; the last route being reserved for severe cases. [18]Until recently oral corticosteroids are considered as first-line therapy for such troublesome and severe haemangiomas. Systemic steroids have proven effectiveness, but the risks of long-term and high dose use include growth disturbances and immune system dysfunction as well as ulcerations up to severe tissue loss. Moreover, there are cases of fast growing infantile haemangiomas which show no response to steroid therapy. [26]

Propranolol:

Propranolol was the first clinically useful beta adrenergic receptor antagonist. Invented by Sir James W. Black, it revolutionized the medical management of angina pectoris and is considered to be one of the most important contributions to clinical medicine and pharmacology of the 20th century. Beta-blockers may also be referred to as beta-adrenergic blocking agents, beta-adrenergic antagonists, or beta antagonists. [27]

A paradigm shift has occurred regarding the treatment of hemangiomas over the past few years. In 2008, propranolol, a nonselective β-adrenergic antagonist, was serendipitously discovered to cause regression of proliferating hemangiomas in newborns receiving treatment for cardiovascular disease. [28]Numerous studies demonstrating the success of propranolol for shrinking hemangiomas have followed suit. [28-30] In fact, over ninety percent of patients have dramatic reduction in the size of their hemangiomas as early as 1-2 weeks following the first dose of propranolol. [1]

Potential explanations for the therapeutic effect of propranolol on haemangiomas include vasoconstriction, which is immediately visible as a change in colour, associated with a palpable tissue softening. Other included suggestions are a down-regulation of angiogenetic factors such as VEGF and bFGF and an up-regulation of apoptosis of capillary endothelial cells. [4, 28] There are also data published which indicate a selective role of propranolol in inhibiting the expression of MMP-9 (angiogenic and extracellular matrix degrading enzyme) and HBMEC (human brain microvascular endothelial cells). These facts may potentially add to propranolol's anti-angiogenetic properties. HBMEC play an essential role as structural and functional components in tumor angiogenesis. [31] A further interesting issue is the fact that haemangiomas are more frequent in premature infants. Up to now there is no explanation for this observation. Pregnant women with premature contractions receive tocolytics. Tocolytics are vasodilator beta-sympathomimetic drugs, the antidote of beta-blockers. As a result of the knowledge that beta-blockers are effective for treatment of haemangiomas, it seems possible that tocolytics may contribute to their incidence in premature infants. [27]

Dosing for propranolol in treating hemangiomas is recommended to be 2-3mg/kg separated into two or three-times-a-day regimens. [32]These doses are dramatically below the concentration employed for cardiovascular conditions in children. Thus, reported side effects of propranolol for hemangiomas have been minimal. Nonetheless, serious concerns for hypoglycemia and lethargy that can occur with this medicine should not be brushed aside. [33, 34] To address these concerns, parents are instructed to give propranolol with meals, report any unusual sleepiness, and not administer it during infections. Early and frequent visits to assess vital signs are recommended in young infants while on therapy. Exacerbation of gastroesophageal reflux may result due to beta-receptor blockade at the lower esophageal sphincter. [29]

Monitoring the administration of propranolol varies among institutions and practitioners. A unified approach has not yet been determined. However, elective admission with cardiovascular monitoring may be necessary. Outpatient administration with close monitoring has also been successfully performed. [35]Nonetheless, an electrocardiogram must be reviewed by a pediatric cardiologist prior to administration. Cardiopulmonary conditions at risk for propranolol therapy such as heart block or reactive airway disease should draw careful consideration before administering.[1]

Consensus on patient monitoring and best dose regimens remains to be determined, but prospective research is underway. Propranolol is currently employed for "problematic" hemangiomas, those that would have received either surgical or some other systemic therapy to prevent untoward side effects. Subglottic, periorbital, and massive hemangiomas seem to respond well. [36]Despite the success of propranolol in reducing hemangioma size, adjuvant therapy may be necessary in up to 50% of patients. [28] Propranolol's mechanism on treating hemangiomas remains unclear but may involve the regulation of vascular growth factors and hemodynamic cytokines.[1]

Interferon Alpha:

Interferon alpha, first used for haemangiomas in 1989, is usually the next line treatment in complicated haemangioma. Some advocate its use as first line treatment instead of steroids; however, there are no randomised trials confirming its exact place in the management. Many retrospective and prospective studies have attempted to define its success. The dose used in one study was 1 million units/m2/24 h for the first week and advancing up to a sustained dose of 3 million units/m2/24 h. [37]

Ezekowitz et al. [38]reported the first non-randomised clinical trial for the treatment of life- or sight-threatening corticosteroid resistance haemangiomas with interferon. In 18 of their 20 patients the haemangiomas regressed by 50% or more. Overall remission is reported to be complete in 40 and 60%, partial/substantial in 20 to 40%, and a lack of response in 10 to 20%. Lesions in the parotid and cheek area appear to respond best. [39]No rebound growth has been reported after cessation of therapy.[18]

Chemotherapy:

Chemotherapy is rarely used but is reserved for cases of severe life-threatening haemangiomas and haemangiomatosis that do not respond to other modalities of treatment. Vincristine (0.5 to 1.5 mg/m2 intravenously weekly) can be used alongside steroids. The most common adverse effect is neurotoxicity, with others being alopecia, rash, constipation, local reactions like phlebitis and necrosis and uncommonly, myelosuppression. [18]

Cyclophosphamide (10 mg/kg/24 h) over 3 or 4 days has also been anecdotally used (e.g. diffuse/liver haemangiomatosis). [40][41] However, the serious side effects of cyclophosphamide like avascular necrosis, cardiomyopathy, pulmonary fibrosis, gonadal damage, and subsequent malignancies [42] have to be kept in mind and therefore the application of cyclophosphamide in the therapy of infantile haemangiomas needs to be carefully considered.[1]

Combination chemotherapy with vincristine, actinomycin (1 mg/m2); cyclophosphamide (500 mg/m2) can be used in life-threatening cases that fail to respond.[43] Although many reviews and case studies are available on the use of chemotherapy in the management, no controlled trial exists.[18]

Experimental Modalities:

Experimental anti-angiogenic treatments, such as natural inhibitors of angiogenesis and monoclonal antibodies to angiogenic protagonists, are being tested in animal models but are not appropriate for clinical use yet.[18]

Imiquimod is a novel immunomodifier, which can be used for small and intermediate-sized hemangiomas[44] located in inconspicuous sites, with alternate day topical application, for a cycle of 3 to 5 months. The advantages are the ease of use, controllability, safety, and lack of local irritation or systemic effects. The disadvantage is that it may cause hyperpigmentation; thus care has to be taken for application on the face for aesthetic reasons.[5]

Minimally invasive management:

Embolization:

Embolisation of feeding vessels in those lesions with suitable vascular anatomy is possible. Neovascularisation is possible with recurrence of the lesion and symptoms; sometimes repeated embolisations are required before resolution. This should be taken into account, as should the invasive nature of both the radiological investigations and intervention. It may be however invaluable in management of problematic lesions (e.g. hepatic haemangioma causing cardiac failure or coagulopathy [18, 43]

Laser Therapy:

Residual erythema and telangiectasias frequently remain in involutedhemangiomas and are best treated by selective photothermolysis using the flash pulse dye laser (FPDL). Similarly, ulcerative lesions during proliferation can be treated with FPDL to induce healing and new epidermal growth.[1]

Pulsed dye laser (PDL) was the first laser developed with selective photothermolysis in mind. It reduces thermal damage by matching the laser wavelength (575 to 595 nm) to the wavelengths absorbed by target chromophores (haemoglobin). This enables the PDL to specifically target particular tissues. PDL can be used to treat both symptomatic and asymptomatic haemangiomas. Due to its physical limitations on penetration, laser treatment is more efficacious in superficial lesions.[18]

There is some debate on the use of lasers to treat childhood haemangiomas. Some advocate early treatment in asymptomatic lesions before proliferation. However a randomised trial of uncomplicated haemangiomas demonstrated no evidence that early PDL confers higher resolution rates over conservative management. [45] That study also suggested that the cosmetic result was superior in those that resolved spontaneously. Purpura, hyperpigmentation, skin atrophy and hypertrophic scarring are some of the cosmetic complications due to laser. A randomised trial [46] found that a modification of the PDL, long-pulsed dye laser (595 to 600 nm, pulse duration 1.5 to 40 ms), may cause less scarring with similar efficacy in superficial proliferating haemangiomas compared to PDL. Other lasers can be used. However, due to its lower side effect profile, PDL

seems to be the favoured choice. Other types (e.g. long-pulsed frequency-doubled Nd:YAG {neodymium:yttrium-aluminum-garne} and KTP {potassium-titanyl-phosphate}) are sometimes used for second line treatment. [47]

Deeper lesions respond less well to PDL. Burstein et al. used intralesional bare fibre KTP laser treatment directly into deep or mixed haemangiomas in 400 patients. [48]All patients had at least 75% reduction in size. Complications were minimal; 2% experienced ulceration. Intralesional KTP may offer some cosmetic advantages over PDL, but could benefit from a trial to assess differences in outcome.[18]

Complicated haemangiomas (e.g. ulcerated) may be treated with laser. [49]In this setting, the symptoms of bleeding, pain and infection seem to be reduced. There are no controlled trials on the benefits of laser over other modalities for ulcerated haemangiomas. Treatment of ulcerations may be with laser alone or alongside other modalities.[18]

CONCLUSION

Haemangiomas are the most common tumors of infancy affecting approximately 1 in 10 children. There are important clinical differences between haemangiomas and vascular malformations and adequate differentiating between the two lesions is a must. The use of common terminology and better understanding of the natural history will lead to better outcomes for our patients. There are different modalities to manage haemangiomas, each modality may be used combined with another one or single according to many factors, including the natural history of haemangioma, the size and extent of the lesion, social situations, and surgeon's comfort or experience with any given treatment modality. A useful approach to the management of haemangiomas can be based on the stage of the lesion (proliferative or involutive phase), type of lesion (superficial, deep, compound) and the management of residual deformity. These modalities include: conservative management, Laser therapy, steroids, interferon alpha, chemotherapy, surgery, embolization, some experimental modalities and propranolol.

REFERENCES

1. Richter, G.T. and A.B. Friedman, Hemangiomas and vascular malformations: current theory and management. Int J Pediatr, 2012. 2012: p. 645678.
2. Syed, S.B., Vascular birthmarks: update on presentation and management.Current Paediatrics, 1999. 9(1): p. 20-26.
3. Chang, L.C., et al., Growth characteristics of infantile hemangiomas: implications for management. Pediatrics, 2008. 122(2): p. 360-7.
4. Leaute-Labreze, C. and A. Taieb, [Efficacy of beta-blockers in infantile capillary haemangiomas: the physiopathological significance and therapeutic consequences]. Ann Dermatol Venereol, 2008. 135(12): p. 860-2.
5. Zheng, J.W., et al., Treatment guideline for hemangiomas and vascular malformations of the head and neck. Head Neck, 2010. 32(8): p. 1088-98.
6. Jackson, I.T., et al., Hemangiomas, vascular malformations, and lymphovenous malformations: classification and methods of treatment. Plast Reconstr Surg, 1993. 91(7): p. 1216-30.
7. Buckmiller, L., U. Dyamenahalli, and G.T. Richter, Propranolol for airway hemangiomas: case report of novel treatment. Laryngoscope, 2009. 119(10): p. 2051-4.
8. Eivazi, B., et al., Update on hemangiomas and vascular malformations of the head and neck. Eur Arch Otorhinolaryngol, 2009. 266(2): p. 187-97.
9. Werner, J.A., et al., Optimal treatment of vascular birthmarks. Am J Clin Dermatol, 2003. 4(11): p. 745-56.
10. North, P.E., M. Waner, and M.C. Brodsky, Are infantile hemangiomas of placental origin? Ophthalmology, 2002. 109(4): p. 633-4.
11. Haggstrom, A.N., et al., Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. J Pediatr, 2007. 150(3): p. 291-4.
12. Yu, Y., et al., Endothelial progenitor cells in infantile hemangioma. Blood, 2004. 103(4): p. 1373-5.
13. Khan, Z.A., et al., Multipotential stem cells recapitulate human infantile hemangioma in immunodeficient mice. J Clin Invest, 2008. 118(7): p. 2592-9.
14. Chang, J., et al., Proliferative hemangiomas: analysis of cytokine gene expression and angiogenesis. Plast Reconstr Surg, 1999. 103(1): p. 1-9; discussion 10.
15. Calicchio, M.L., T. Collins, and H.P. Kozakewich, Identification of signaling systems in proliferating and involuting phase infantile hemangiomas by genome-wide transcriptional profiling. Am J Pathol, 2009. 174(5): p. 1638-49.
16. Metry, D., et al., Consensus Statement on Diagnostic Criteria for PHACE Syndrome. Pediatrics, 2009. 124(5): p. 1447-56.
17. Frieden, I.J., et al., Guidelines of care for hemangiomas of infancy. American Academy of Dermatology Guidelines/Outcomes Committee. J Am Acad Dermatol, 1997. 37(4): p. 631-7.
18. McHoney, M., Early human development: Neonatal tumours: Vascular tumours. Early Human Development, 2010. 86(10): p. 613-618.
19. Williams, E.F., 3rd, et al., Hemangiomas in infants and children. An algorithm for intervention. Arch Facial Plast Surg, 2000. 2(2): p. 103-11.
20. Troilius, A., B. Wrangsjo, and B. Ljunggren, Potential psychological benefits from early treatment of port-wine stains in children. Br J Dermatol, 1998. 139(1): p. 59-65.
21. Ethunandan, M. and T.K. Mellor, Haemangiomas and vascular malformations of the maxillofacial regionâ€"A review. British Journal of Oral and Maxillofacial Surgery, 2006. 44(4): p. 263-272.

22. Miller, A.C., et al., Stress and family satisfaction in parents of children with facial port-wine stains. Pediatr Dermatol, 1999. 16(3): p. 190-7.
23. Ronchese, F., The spontaneous involution of cutaneous vascular tumors.The American Journal of Surgery, 1953. 86(4): p. 376-386.
24. Haggstrom, A.N., et al., Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. Pediatrics, 2006. 118(3): p. 882-7.
25. Spector, J.A., F. Blei, and B.M. Zide, Early surgical intervention for proliferating hemangiomas of the scalp: indications and outcomes. Plast Reconstr Surg, 2008. 122(2): p. 457-62.
26. Nguyen, J. and A. Fay, Pharmacologic therapy for periocular infantile hemangiomas: a review of the literature. Semin Ophthalmol, 2009. 24(3): p. 178-84.
27. Zimmermann, A.P., et al., Propranolol therapy for infantile haemangiomas: review of the literature. Int J Pediatr Otorhinolaryngol, 2010. 74(4): p. 338-42.
28. Leaute-Labreze, C., et al., Propranolol for severe hemangiomas of infancy. N Engl J Med, 2008. 358(24): p. 2649-51.
29. Buckmiller, L.M., et al., Propranolol for infantile hemangiomas: early experience at a tertiary vascular anomalies center. Laryngoscope, 2010. 120(4): p. 676-81.
30. Leboulanger, N., et al., Propranolol in the therapeutic strategy of infantile laryngotracheal hemangioma: A preliminary retrospective study of French experience. Int J Pediatr Otorhinolaryngol, 2010. 74(11): p. 1254-7.
31. Annabi, B., et al., Propranolol adrenergic blockade inhibits human brain endothelial cells tubulogenesis and matrix metalloproteinase-9 secretion. Pharmacol Res, 2009. 60(5): p. 438-45.
32. Bagazgoitia, L., et al., Propranolol for infantile hemangiomas. Pediatr Dermatol, 2011. 28(2): p. 108-14.
33. de Graaf, M., et al., Adverse effects of propranolol when used in the treatment of hemangiomas: a case series of 28 infants. J Am Acad Dermatol, 2011. 65(2): p. 320-7.
34. Holland, K.E., et al., Hypoglycemia in children taking propranolol for the treatment of infantile hemangioma. Arch Dermatol, 2010. 146(7): p. 775-8.
35. Cushing, S.L., et al., Initial experience with a multidisciplinary strategy for initiation of propranolol therapy for infantile hemangiomas. Otolaryngol Head Neck Surg, 2011. 144(1): p. 78-84.
36. Haider, K.M., et al., Outpatient treatment of periocular infantile hemangiomas with oral propranolol. J AAPOS, 2011. 14(3): p. 251-6.
37. Ricketts, R.R., et al., Interferon-alpha-2a for the treatment of complex hemangiomas of infancy and childhood. Ann Surg, 1994. 219(6): p. 605-12; discussion 612-4.
38. Ezekowitz, R.A., J.B. Mulliken, and J. Folkman, Interferon alfa-2a therapy for life-threatening hemangiomas of infancy. N Engl J Med, 1992. 326(22): p. 1456-63.
39. Greinwald, J.H., Jr., et al., An update on the treatment of hemangiomas in children with interferon alfa-2a. Arch Otolaryngol Head Neck Surg, 1999. 125(1): p. 21-7.
40. Hurvitz, S.A., et al., Successful treatment with cyclophosphamide of life-threatening diffuse hemangiomatosis involving the liver. J Pediatr Hematol Oncol, 2000. 22(6): p. 527-32.
41. Vlahovic, A., et al., Diffuse neonatal hemangiomatosis treatment with cyclophosphamide: a case report. J Pediatr Hematol Oncol, 2009. 31(11): p. 858-60.
42. Gottschling, S., et al., Two infants with life-threatening diffuse neonatal hemangiomatosis treated with cyclophosphamide. Pediatr Blood Cancer, 2006. 46(2): p. 239-42.
43. Hall, G.W., Kasabach-Merritt syndrome: pathogenesis and management. Br J Haematol, 2001. 112(4): p. 851-62.
44. McCuaig, C.C., et al., A phase II, open-label study of the efficacy and safety of imiquimod in the treatment of superficial and mixed infantile hemangioma. Pediatr Dermatol, 2009. 26(2): p. 203-12.
45. Batta, K., et al., Randomised controlled study of early pulsed dye laser treatment of uncomplicated childhood haemangiomas: results of a 1-year analysis. Lancet, 2002. 360(9332): p. 521-7.
46. Kono, T., et al., Comparison study of a traditional pulsed dye laser versus a long-pulsed dye laser in the treatment of early childhood hemangiomas. Lasers Surg Med, 2006. 38(2): p. 112-5.
47. Stier, M.F., S.A. Glick, and R.J. Hirsch, Laser treatment of pediatric vascular lesions: Port wine stains and hemangiomas. J Am Acad Dermatol, 2008. 58(2): p. 261-85.
48. Burstein, F.D., et al., Intralesional laser therapy treatment for hemangiomas: technical evolution. J Craniofac Surg, 2006. 17(4): p. 756-60.
49. Smit, J.M., et al., Pulsed dye laser treatment, a review of indications and outcome based on published trials. Br J Plast Surg, 2005. 58(7): p. 981-7.