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1. Introduction

Vascular anomalies are heterogeneous group of congenital lesions of abnormal vascular development and may occur anywhere on the body. There is a primary distinction 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 behavior and radiographic features, malformations are further subdivided into low-flow and high-flow lesions [1]. The common characteristic feature of all vascular anomalies is extreme bleeding during surgical excision. Clinicians throughout the world use the classification by Mulliken and Glowacki (1982) to classify these lesions. This classification is based on the vascular lesion’s histology, biological behavior and clinical findings [2]. Some of the lesions cause esthetic problems, while some of them are malignant; thus, the therapeutic approach is variable.

<table>
<thead>
<tr>
<th>Vascular tumors</th>
<th>Vascular malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile hemangioma</td>
<td>Slow-flow</td>
</tr>
<tr>
<td>Congenital hemangioma</td>
<td>Capillary malformations</td>
</tr>
<tr>
<td>Tufted angioma</td>
<td>Venous malformations</td>
</tr>
<tr>
<td>Kaposiform hemangioendothelioma</td>
<td>Lymphatic malformations</td>
</tr>
<tr>
<td></td>
<td>Fast-flow</td>
</tr>
<tr>
<td></td>
<td>Arteriovenous malformations</td>
</tr>
</tbody>
</table>

Table 1. Classification of vascular anomalies by Mulliken and Glowacki.

One of the most seen vascular tumors involving the head and neck region are hemangiomas. These benign, generally painless lesions, are a proliferating mass of blood vessels that do not
undergo malignant transformation; 60% percent of cases are localized in the head and neck region. The rest are located in the trunk area (5%) and the extremities (15%)[3,4]. Hemangiomas are mostly seen on the surface of the skin, although internal organs such as the liver, larynx, lung or gastrointestinal tract may be also be affected. In the oral cavity, they may occur on the tongue, lips, buccal mucosa, gingiva, palatal mucosa, salivary glands, alveolar ridge and jaw bones [5,6]. In the majority of patients hemangiomas occur as a single lesion, however 20% of patients may have more than one hemangioma [7].

In the literature, multiple hemangiomas are described as one of the components of so called „PHACES” syndrome. The syndrome includes: Posterior fossa defects, Hemangiomas, Arterial abnormalities, Coarctation of the aorta and cardiac malformations, Eye anomalies, and Sternal defects [8].

In this chapter we will try to describe and document the clinical features and management of the head and neck hemangiomas.

2. Hemangiomas

The term hemangioma was originally used to describe any vascular tumor-like structure, whether it was present at or around birth or appeared later in life. The term is comprised of the Greek words “haema” which means blood, “angeio” meaning vessel and “oma” meaning tumor. Histologically hemangiomas are composed of hyperplastic endothelial cells, which are line the inner surface of the blood vessels in the human body, with the capacity for intensive proliferation. The diameter of the blood vesels is important in classification of hemangiomas to capillary and cavernous types [9]. The capillary type, also known as the strawberry hemangioma is composed of small thin-walled vessels of capillary size that are lined by a single layer of flattened or plump endothelial cells and surrounded by a discontinuous layer of pericytes and reticular fibers [9,10] (Figures 1 and 2). It was first described in the literature in 1973 by Sznajder et al.[11], under the term “Hemorrhagic hemangioma”[10].

![Figure 1. Capillary lip hemangioma](Image)
The cavernous type is characterized by large blood-filled spaces, so called cavities, that are separated by a scanty connective tissue stroma [9]. Some lesions of hemangiomas are mixed, which means that they have histologic components of both types [10] (Figures 3 and 4).

Figure 2. Capillary lip hemangioma 20X

Figure 3. Cavernous lip hemangioma

Figure 4. Capillary hemangioma of lips 20X
Clinically, hemangiomas are characterized as a soft, smooth or lobulated, sessile or pedunculated mass and may be seen in any size from a few millimeters to several centimeters [12]. The color of the lesion ranges from pink to red or purple and blanches on the application of pressure; hemorrhage may occur either spontaneously or after minor trauma [3]. Hemangiomas are subdivided into two types: “infantile” and “congenital” [1,13]. However, there is a hypothesis that these two entities are the variations of a single entity ab initio [14].

2.1. Infantile hemangiomas

Infantile hemangiomas are the most common tumors of infancy and occur in approximately 10% of infants by the age of 1 year, with a female predominance [15]. Studies suggest that the ratio between female-male is 3-5 : 1, and a higher prevalence is seen in cases of premature neonates especially when their weight at birth is less than 1500 g. [4,10]. As we mentioned before, the most common localization of hemangiomas is the surface of the skin; thus, hemangiomas usually appear as a barely visible pale, spot, red stain macula, telangiectatic or pseudoecchymotic patch, 2-4 weeks after birth. Massive life threatening lesions usually occur in the liver or central nervous system [16].

Infantile hemangiomas consist of rapidly dividing endothelial cells [13]. Chang et al. [10] state that growth of infantile hemangiomas pass through 3 phases; Proliferation, involuting and involuted phases. The proliferative phase is characterized by rapid growth of the hemangioma during the first year of life. A cellular mass without a defined vascular architecture and nascent blood vessels with red blood cells are evident within the lumen [17]. This phase is the most pronounced during the first 3 - 6 months. However, it may be followed by a phase of slower growth. Regardless of subtype or depth, hemangiomas reach an average of 80% of their final size during the early proliferation stage, a stage that ends at a mean age of 3.2 months. Infantile hemangiomas at the beginning of the proliferation phase, can show an early or late proliferation growth pattern. This means that in cases with an early proliferation growth pattern proliferation starts earlier and essentially is complete after 5 months of age. While in cases of late proliferation growth, proliferation starts later and lasts longer [10] (Figures 5A and 5B).

![Figure 5. A) Infantile hemangioma of the cheek. (B) Frontal view](image-url)
The involuting phase follows the previous phase; thus in some cases it starts in a few months, while in most cases by 12-18 months of age [10] and continues for 3 to 5 years [17]. Proliferation slows or stops in this phase, and histologic examination shows that the blood vessel architecture becomes more obvious and vessel size enlarges [17]. It is important to mention that in some cases different parts of the hemangioma may be under proliferation and involuting at the same time [10]. Clinical signs of involution are characterized by a color change from bright red to dull red to gray and usually begins centrally and spreads out over the lesion with time. Generally, involution takes place at an estimated rate of 10% per year, so that approximately 50% have involuted by 5 years of age, 70% by 7 years, and 90% by 9 years [10]. The involuted phase is the third phase in the hemangiomas and occurs at 5 to 8 years of age, at which point blood vessels are replaced with a fibrofatty residuum and capillary-sized channels [17]. In this phase depending on the size of the hemangiomas the form changes and may include restoration to normal skin (in 50%) or fibro-fatty form of hemangioma residuum and redundant skin. The later a hemangioma starts to involute, the higher is their risk for residual changes after involution is completed. An involuted hemangioma will never start to grow again; tumor growth in the completed involution phase is always finished [10]. Glucose transporter-1 (GLUT-1) has been shown to be a specific marker for endothelium in all phases of infantile hemangioma, comparing with congenital hemangiomas, in which this marker has not been detected [18,19].

2.2. Congenital hemangiomas

Congenital hemangiomas are fully developed at birth which do not exhibit accelerated postnatal growth. They may be diagnosed on a prenatal ultrasound. In 2000, congenital hemangiomas were identified as rapidly involuting congenital hemangiomas (RICH) and non-involuting congenital hemangiomas (NICH) [10,13]. Both subtypes have many similarities, such as appearance, location, size, and sex distribution [14,18]. Also they have some overlapping histologic features with infantile hemangioma [18].

2.2.1. Rapidly involuting congenital hemangiomas

Rapidly involuting congenital hemangiomas (RICH) are also present at birth as protuberant, hemispherical, violaceous tumors with an average diameter of 5-6 centimeters, that often have a central depression, scar or ulceration [18]. Histologic features are variable including large and small lobules separated by dense fibrous tissue, and in some lesions there is a sponge-like network of large capillaries [18]. RICH goes through a rapid regression phase and may be completely gone by the time the child is 12 to 18 months old, leaving a mark as some degree of atrophic or redundant skin [20]. In some cases rapidly involuting congenital hemangiomas can undergo rapid but incomplete involution, with a resulting clinical appearance and histology similar to noninvoluting congenital hemangiomas. Because of this, it has been suggested that RICH and NICH may lie within the same spectrum of vascular tumors [14,18,20]. Rapidly involuting congenital hemangiomas are usually located on the limb, head and neck regions and may be associated with decreased giotplatelets, thought to be due to localized intravascular coagulation [21].
Non-involuting congenital hemangioma (NICH) is present at birth, grows proportionately with the child, exhibits persistent fast-flow and does not regress [18]. This lesion occurs more often in male patients. Usually it is a single lesion with an average diameter of 5 cm. Shapes may vary from round-to-ovoid or plaque-like, while the color may also be a variable from pink to purple [18,22]. The overlying skin is frequently punctuated by coarse telangiectasia, often with central or peripheral pallor [22] (Figures 6A and 6B).

Histologically, NICH is characterized by lobules with high cellular density: each lobule contains one or more large, irregular intralobular vessels surrounded by multiple small vessels with indistinct lumens [18].

<table>
<thead>
<tr>
<th>Congenital hemangioma</th>
<th>Infantile hemangioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present at birth.</td>
<td>Visible between 2 weeks and 4 months of age.</td>
</tr>
<tr>
<td>Growth is complete at birth or may grow proportionately as the child grows.</td>
<td>Grows rapidly for about 6 to 12 months (average is around 8 months).</td>
</tr>
<tr>
<td>Males : females = 1:1</td>
<td>Males : females=1: 3:5</td>
</tr>
<tr>
<td>Less common but not rare.</td>
<td>Common [4-5 percent incidence in newborns].</td>
</tr>
<tr>
<td>Rapid or no involution (shrinking).</td>
<td>Slow shrinking that takes months or years.</td>
</tr>
<tr>
<td>GLUT-1 negative</td>
<td>GLUT-1 positive</td>
</tr>
<tr>
<td>Proliferating phase characterized by large and irregularly shaped vessels</td>
<td>Proliferating phase characterized by small regular capillaries</td>
</tr>
</tbody>
</table>

Table 2. Differences between congenital hemangioma and infantile hemangioma
3. Etiology

Hemangioma development is also known as hemangiogenesis [23]. Although pathogenesis and origin of hemangioma remains incompletely understood, medical literature describes different hypothesis for its development in which extrinsic and intrinsic factors play an important role of endothelial cell proliferation. Placental, estrogen signaling, genetic theory, theory of hypoxia and role of the growth factors involved in angiogenesis such as vascular endothelial growth factor (VEGF), tissue growth factor beta (TGF-beta) and insulin-like growth factor-2 (IGF-2), are just some of theories of hemangioma development.

3.1. Placental origin theory

In the placental theory, there is an opinion that the infantile hemangioma originated from placental trophoblast [23-25]. The hypothesis is based on shared expression of distinct endothelial markers such as GLUT1, Fcγ RII, α2-laminin, Lewis Y antigen, type III iodothyronine deiodinase, indoleamine 2,3-deoxygenase, and insulin-like growth factor 2 in the placenta and hemangioma [22]. Also an incidence of hemangiomas occurrence is more common in infants born to mothers with placental abnormalities, such as preeclampsia and placenta previa, as well as those exposed to chorionic villous sampling (CVS)[26,27], which once more contribute to the placental theory of hemangioma development.

3.2. Estrogen signaling theory

Estrogen signaling theory suggests that because of increased incidence in females, evidence of estrogen receptor (ER) positivity in endothelial cells of proliferating hemangiomas, and elevated levels of circulating 17-β estradiol (which is known to be protective for hypoxia-induced apoptosis) in affected children, the estrogen may be involved in the growth of infantile hemangioma [16,28]. In the perinatal period free estrogen increases, which may stimulate areas of hypoxic endothelium to induce hemangioma formation [16,29].

3.3. Hypoxia theory

In the hypoxia theory, the hypoxic environment leads to an upregulation of factors that promote the recruitment and proliferation of endothelial progenitor cells. These factors include; hypoxia inducible factor-1alpha (HIF-1alpha), stromal cell derived factor-1alpha (SDF-1alpha) and vascular endothelial growth factor (VEGF) [18,27]. However, in this theory there is link between hypoxia and estrogen contribution in hemangioma formation. In explanation, increased estrogen hormone levels in the postpartum period create a milieu that promotes new blood vessel development and growth of the lesion [27,29].

3.4. Theory of angiogenesis involved growth factors

Growth factors specifically involved in angiogenesis such as vascular endothelial growth factor (VEGF), insulin-like growth factor-2 (IGF-2) and tissue growth factor beta (TGF-beta) are often increased during the proliferation phases of hemangioma growth; while
during the involution phase of hemangioma, they decrease [30]. Vascular endothelial growth factor (VEGF) was originally identified as an endothelial cell specific growth factor stimulating angiogenesis and vascular permeability [18,29]. Studies suggest that in the patients with proliferating hemangiomas, the serum vascular endothelial growth factor concentrations are significantly higher than in patients with involuting hemangiomas, vascular malformations and healthy patients [18,31,32]. Insulin-like growth factor-2 (IGF-2) is known to be highly expressed in infantile and congenital hemangiomas [19]. Links between this factor and angiogenesis would be that IGF-2 induce hypoxia-inducible factor 1-α (HIF-1α), and HIF-1α is known to up-regulate glucose transporter-1 (GLUT-1) [18]. However, GLUT-1 is specific only for infantile hemangiomas [19]. An expression of tissue growth factor beta (TGF-beta) in proliferative hemangioma is significantly higher comparing with the other stages of hemangiomas [33,34].

3.5. Genetic theory

In the genetic theory, a hereditary component is presumed to be the cause of hemangiomas [34,35]. Hemangioma may be passed from parent to child as an autosomal dominant trait with incomplete penetrance [35]. Although the gene responsible for hemangioma/malformation development is not identified, there is an opinion that the gene locus could be on chromosome 5q [34]. Genetics and race may play an important role in hemangiomas occurrence, due to the fact that the majority of hemangiomas occur in infants of Caucasian descent, rarely in Asian and almost never occur in infants of African-American descent [4,36].

4. Clinical findings

The majority of hemangiomas are located on the skin as a soft, smooth or lobulated, sessile or pedunculated masse. Their size may vary from several millimeters to several centimeters [1,3]. The color of the lesions range from pink to red purple and tumors blanch on the application of pressure [3]. Hemangiomas can be superficial, deep, or compound [1]. The superficial hemangioma (affecting only the superficial skin) is red and nodular with no subcutaneous component. A deep hemangioma (affecting only the deep skin) presents as a protrusion with an overlying bluish tint or telangectasia. Compound (mixed) hemangioma has both deep and superficial components [1,10]. By statistics, 60% of hemangiomas are superficial, 15% are deep, and 25% are compound [10].

More than 80% of hemangiomas are solitary lesions [7]. Hemangiomas may be further subdivided into focal, multifocal and segmental hemangiomas. Focal hemangiomas are localized, unilocular lesions which adhere to the phases of growth and involution. Multifocal hemangiomas usually involve a visceral organs, while segmental hemangiomas are more diffuse plaque-like and can lead to untoward functional and esthetic outcomes [1]. Deep segmental hemangiomas proliferate longer, while superficial and focal hemangiomas start to involute earlier [10].
In 60% percent of cases hemangiomas are localized in the head and neck region with the distribution of the trigeminal nerve \([1,3,4]\). They can be localized even in the infraorbital nerve canal \([37]\). A beard-like distribution is associated with a subglottic hemangioma \([1]\). In cases of deeply located hemangiomas such as those in eye, symptoms might be amblyopia (lazy eyes) and distortion of the cornea. Hemangiomas in the respiratory system can block breathing, while those located in the liver may be asymptomatic, unless due to huge size stresses the heart. In the oral region, hemangiomas are not that common. If they are present, they may occur on tongue (Figure 7), lips, buccal mucosa, gingiva, palatal mucosa, salivary glands, alveolar ridge and jaw bones \([3,5,6]\).

**Figure 7.** Hemangioma of the tongue.

In cases of gingival hemangiomas, the lesions often appear to arise from the interdental gingival papilla and spread laterally to involve adjacent teeth \([3]\). Masticatory trauma plays an important role in development of symptoms such as bleeding of the gingiva or tongue. In hemangiomas of the jaw, clinical signs usually develop after extraction of tooth associated with the lesion. Oral bleeding may be spontaneous in cases that violate the epithelial basement membrane by penetration of the hemangioma \([38]\).

### 4.1. Diagnosis

The diagnosis of a hemangioma is based on clinical history, physical, radiographic, laboratory and pathohistological examinations. In previous parts of the chapter we have described clinical and histological findings of hemangiomas.
Radiographic examinations are usually performed in cases of deeply positioned hemangiomas. The examinations include conventional radiography with panoramic radiographs, angiography, computed tomography (CT), magnetic resonance imaging (MRI) and Doppler ultrasonography. Conventional radiography is used mostly for diagnosis of bone hemangiomas. Findings are multicystic “soap bubble” appearances. On CT the changes are in bone trabeculae. In diagnosis of soft tissue hemangiomas CT, MRI and Doppler ultrasonography are performed. MR imaging can be used to classify vascular malformations as either low-flow or high-flow lesions, especially when combined with dynamic contrast-enhanced MR angiography. Also, evaluation of extrasosseous extension can be diagnosed by MRI [39]. Doppler ultrasonography is the least invasive and most cost-effective imaging to document blood flow in hemangiomas.

Pathohistological examinations for diagnosis and distinguishing hemangiomas from other lesions sometimes do not offer a proper diagnosis. For example in the differential diagnosis from oral pyogenic granuloma, both lesions share the histologic designation "capillary hemangioma" [38].

Laboratory examinations are important in differential diagnosis of hemangiomas to the other arteriovenous malformations and pathologies. Glucose transporter-1 (GLUT-1), vascular endothelial growth factor (VEGF), insulin-like growth factor-2 (IGF-2) and tissue growth factor beta (TGF-beta) are just some of the examined factors. For example, as we mentioned before, positive staining for GLUT-1 is considered highly specific and diagnostic for hemangioma, and it is useful for making differential diagnosis between hemangioma and other vascular lesions clinically related to it [12].

4.2. Differential diagnosis

Differential diagnosis of the head and neck hemangiomas include several lesions such as pyogenic granuloma, chronic inflammatory gingival hyperplasia, epulis granulomatosa, telangiectasia, angiosarcoma, squamous cell carcinoma, and other vascular appearing lesions such as Sturge Weber syndrome.

Rapidly involuting congenital hemangioma (RICH) as single large tumor associated with lesional ulceration and congestive heart failure, can easily be confused with congenital infantile fibrosarcoma and arteriovenous malformation [19]. Because of this, arteriography in order to exclude infantile fibrosarcoma and arteriovenous malformation play an important role in proper diagnosis. In these cases biopsy is not advantageous because of the high risk of bleeding. It may be reasonable only in cases of previously reported congenital infantile fibrosarcoma [19].

Noninvoluting congenital hemangioma (NICH) may vary from plaque-like with a pink or purple color, to prominent overlying coarse telangiectasias, and be difficult to diagnosed or distinguish from the other, even malignant pathologic lesions [20].

The differentiation between hemangioma and vascular malformations is made on the basis of clinical appearance, histopathology, and biological behaviour [12].
5. Complications

Complications associated with hemangiomas may include: bleeding, ulceration, infection, airway obstruction or visual complications. The incidence of complications such as ulceration is between 5-13% [3]. Ulceration usually occurs in the proliferative phase because the growth of the lesion surpasses epidermal elasticity and blood supply. Large lesions and lesions in the area of the skin flexion such as intertriginous, perineal, and perioral are more prone to develop ulcerations [8,26]. Bleeding and infection development are in many cases just sequels of ulceration [8]. In the oral region bleeding and infection may develop after masticatory minor trauma. Airway obstruction is caused by hemangiomas located in the respiratory system. Infantile hemangioma lesions in a “beard-like” distribution along the jaw are at increased risk of airway involvement. These infants, therefore, need to be monitored frequently for signs of respiratory distress, including a barking cough and/or progressive stridor, especially during the first several months of life [8]. Amblyopia “lazy eyes” and distortion of the cornea are complications associated with periocular-located hemangiomas [8,26]. Strabismus, myopia, tear duct obstruction, proptosis, and ptosis are other complications associated with the ocular hemangiomas [8].

6. Management

Management of hemangiomas include several factors including age of the patient, type, size, dissemination and depth of penetration [3,12]. There is an opinion that only 10–20% of hemangiomas due to the size, location, stages of growth or regeneration, functional compromise and behaviour, require treatment [12]. For example a large lesions prone to ulceration, bleeding, infection, vital and functional compromises must be treated. Treatment options include: surgery, laser surgery, local and systemic use of corticosteroids, Interferon alfa, Imiquimod, Propranolol, Pingyangmycin. Each treatment modality has its own risks and benefits [12].

6.1. Surgery

Surgical approach to hemangiomas is still the most performed procedure, isolated or in combination with another treatment modalities. Although in more than 80% of hemangiomas the observation is suggested, due to spontaneous involution of the lesions, in some cases such as lip hemangiomas the "wait and see" approach [40] is not welcome. Lip hemangiomas are highly visible, prone to ulcerations and have a tendency to leave residual deformity even after resolution [40,41]. Ulcerations are mostly seen during the proliferative period and can lead to increased scarring, loss of lip contour, and disfigurement [41]. The mentioned authors [40,41] stated benefits of early surgical excision of lip hemangiomas. Even lip hemangiomas that cross the vermilion-cutaneous junction can be excised and lip contour achieved without the need to extend scars beyond the junction [41]. It is worth mention that in a study by Chang et al. [41], a higher incidence of lower lip hemangiomas, comparing with hemangiomas located in the upper lip was reported. In cases of localized cutaneous infantile hemangiomas, surgical excision is also
suggested to be performed to minimize the scar after the involuted hemangioma [42,43]. As we know, in proliferative phase, the hemangioma acts like a tissue expander, destroying elastic fibers or causing ulceration resulting in telangiectases, cutaneous laxity, scarring, and fibrofatty residuum [42]. Two types of surgical excisions named lenticular and circular, may be performed in therapy of hemangiomas [42-44]. Lenticular excision of hemangiomas results in increased scar length as compared with the original lesion [43], while circular excision and purse-string closure reduces both the longitudinal and transverse dimensions and converts a large circular lesion into a small ellipsoid scar [42-44]. Also another advantage of the circular excision is minimal distortion of surrounding structures [42]. Vlahović et al. concluded that the circular excision and purse-string suture technique are applicable for hemangioma at any stage [44]. In 1985, Popescu [45], presented a new approach to cavernous haemangioma in different sites, which included an intratumoral ligation. The technique completely interrupted the intratumoral blood flow, resulting in obstruction of vascular lumina, endothelial atrophy, blood clot organization in the small diverticula between them and also subsequent fibrous hyperplasia. In this way the hemangioma mass was split into segments, thus the blood flow was eliminated (Figures 8A and 8B).

6.2. Laser surgery

From the last few decades, laser surgery has emerged as one of the most performed therapeutic approaches for vascular lesions and hemangiomas. During the 1980’s, lasers such as
argon and carbon dioxide were mostly used for the excision of capillary / cavernous heman-
giomas because of the low incidence of bleeding [48]. From 1990’s the neodymium: yttrium-
aluminum-garnet (Nd:YAG) laser started to be in used as a new and effective mode of
treatment for vascular lesions [49,50]. Intralesional photocoagulation is the base of the
Nd:YAG laser efficacy. Many studies [49-53] evaluated hemangioma outcomes after laser
treatment. After a follow up of at least 6 months, reduction in lesion size was noted, espe-
cially in cases of large lesions. The authors concluded that the Nd:YAG laser is a safe and
effective tool for the treatment of large lesions [49,50]. However, complications such as su-
perficial ulceration or scarring, may be expected [51]. In some cases due to the fact that he-
mangioma formations do not involute completely, surgical resection or treatment of local
steroid injections due to lesion fibrosis may be performed [53].

6.3. Cryotherapy

Superficial cryotherapy with carbon dioxide snow may be effective in the case of facial he-
mangioma, but this method is completely ineffective in the management of tuberous or cav-
ernous haemangiomas [46].

6.4. Corticosteroids

In conservative therapy of hemangiomas, the corticosteroids are the first choice. They can be
used systemic or locally. Growth disturbance and risk of malformation in children is associ-
ated with the use of corticosteroids [46].

6.4.1. Systemic corticosteroids

Prednisone as the representative of systemic corticosteroids has found its place in heman-
gioma treatment. Although the mechanism of action is unknown, there are suggestions that
corticosteroids inhibit the expression of VEGF-A by hemangioma-derived stem cells and si-
kening of VEGF-A expression in these cells inhibited vasculogenesis in vivo [54]. Also they
may be responsible for vasoconstriction of arterioles and precapillaries [55]. Daily doses are
usually 2.4 mg/kg [56,57] and it is mostly in use for treatment of cutaneous infantile heman-
giomas. Parotid hemangiomas for example may be resistant to this therapy [56]. Reasons for
this may be differences in drug metabolism, caliber of blood vessels, and/or blood flow in
the parotid gland [56]. Bennett et al. [57] in their study revealed that the dose of the drug plays
an important role in the lesional response, thus higher doses show significantly higher re-
sponses and results are more visible, if initiated during the initial proliferative phase. Sys-
temic corticosteroids are mostly in use for treatment of large and aggressive lesions.

The long duration of therapy made it difficult to determine the effect the corticosteroid ther-
apy had on the hemangiomas vs spontaneous involution [57]. Systemic corticosteroids carry
well-documented risks, such as disseminated varicella and herpes infections, and some au-
thors have questioned their efficacy [47].
6.4.2. Local corticosteroids

Local corticosteroids in the form of intralesional corticosteroid injections are in use for treatment of small, bossed, facial hemangiomas. The response to the therapy is equal to response to systemic therapy. The dose of local corticosteroids is 20mg/ml in the form of triamcino-lone acetonide [58,59]. In 6-8 week intervals, 3-5 injections are needed and during application, surrounding areas must be compressed [59]. Contraindications for local corticosteroids are necrosis and secondary infection of the lesion. Local corticosteroids may be responsible for embolization of small arteries, such as retinal artery, thus their use in cases of eye hemangiomas must be limited [59].

6.5. Interferons ALFA-2a, ALFA 2-b

Interferon alfa inhibits the development of new blood vessels from preexisting vessels. Usually therapy with interferon is used when hemangiomas do not respond to the corticosteroid therapy. Daily doses of interferon are 3 million U/m² in the form of subcutaneous injections [56,58]. Interferon is not a very safe drug. It was shown that it is neurotoxic, thus neurologic follow up is necessary [58]. Also as in the case of systemic corticosteroids, parotic hemangiomas do not respond to their effects [56]. Complications associated with interferon therapy include neutropenia, abnormalities in liver enzymes and spastic diplegia [58].

6.6. Sclerotherapy

Sclerotherapy is a procedure in combination with surgery, by which application of some chemicals such as hypertonic saline, sodium tetradecyl sulfate, 5% ethanolamine oleate, 5% sodium morrhuate, sodium psylliate, pyngyangmycin, quinine urethrone, 5% and 1% polidocanol solutions produce thrombosis of the vessels and an indurated mass [60-62]. The procedure is most effective when the vascular spaces are small or when blood flow is slow [62]. Hemangioma size after sclerotherapy is decreased and its nature changes to a more fibrous consistency, thus surgical resection of the lesion is easily performed with minimal bleeding [61,62]. Complications of sclerotherapy may include ulceration, inflammatory reaction, necrosis and scar, mostly when the sclerosing agent is applied directly to connective tissue or when a vascular leak caused by excessive injection pressure is identified [61].

6.7. Propranolol

In 2008, Leaute-Labreze et al.[63] presented efficacy of sympatholytic non-selective beta blocker known as propranolol, in therapy of infantile hemangiomas. The mechanism of action is unknown, but there are reports that suggest that within 24-48 hours, hemangiomas respond to therapy by size reduction and changes in color [64]. Although authors report that the drug is most effective in cases of proliferative hemangiomas, results of some cases have shown that hemangiomas in the post-proliferative stage respond well [64,65]. A daily dose of propranolol is 2mg/kg and it is given in three equally doses [65]. Taking in consider that propranolol is a relatively new drug for treatment of infantile hemangiomas, there is little known of its side effects. For example, while Zvulunov et al.
[66] report no significant side effects, some other authors suggest that propranolol may mask the clinical signs of early cardiac failure and diminish cardiac performance. Also it may blunt the clinical features of hypoglycemia[67].

6.8. Imiquimod

Imiquimod is a drug with ability to induce the production of interferon, tumor necrosis factor-alpha and the antiangiogenesis factor tissue inhibitor of matrix metalloproteinase [68]. In topical form as Imiquimod 5% cream may be effective in therapy of superficial infantile hemangiomas [69-71]. Some authors suggest that the Imiquimod should be avoided in those hemangiomas located around the cavities and skin folds [69]. The most common side effects of topical Imiquimod are slight skin erythema and crusting [69,70]. Post-treatment skin reactions are texture changes, which in cases without crusting involuted to almost normal skin [70].

6.9. Bleomycin

Bleomycin is an antibiotic from the culture medium of streptomyces verticullust, with properties of an anticancer agent [72]. In treatment of infantile hemangiomas, bleomycin in the form of bleomycin A5 may be used isolated [73] or in combination with prednisone [72,73]. As intrallesional injection its efficacy is based on a high sclerosing effect on vascular endothelium [74], thus it is most effective in cases of proliferating infantile hemangiomas, inhibiting the proliferation [72]. The results of studies have show a high incidence of complete hemangioma involutions, better recovery of skin color and less scar forming in small hemangiomas, after bleomycin therapy [72-74]. Side effects of therapy include edema, ulceration, gastrointestinal symptoms such as nausea and lack of appetite [72,74], cellulitis and transient hair loss [73].

7. Conclusion

Each treatment modality of head and neck located hemangiomas has its own risks and benefits. In cases of infantile hamangiomas, oral propranolol is very useful and well tolerated, having minimal side-effects in the resolution of the hemangiomas. In adult patients surgical treatment including intratumoral ligation, isolated or in combination with laser or sclerotherapy is the most performed therapeutic option.

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