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Review Article

Infantile Hemangioma: An Overview of the Pathology and State of The Art of Therapeutic Approach

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Abstract:

Infantile hemangioma is a benign vascular tumor of childhood characterized by a proliferation of endothelial cells. Infantile hemangiomas represent the main childhood soft tissue cancers and affect 3% to 10% of the population. The tumors are not visible at birth but develop during the first 4-6 weeks of life showing a typical evolution distinguished by a first rapid proliferation, then a period of stabilization followed by a slow spontaneous regression. The increasing phase can last up to 6 months of age and is supported by a regression phase which can last 3 or 7 years. While most infantile hemangiomas are not a reason for concern, about 12% of cases are of relevant complexity and require specialist consultation for investigation and treatment. Nowadays there are many therapeutic strategies for the management of the condition. The therapeutic outcomes of hemangioma have lately improved thanks to the accidental finding of the efficacy of a beta-blocker, oral propranolol. The aim of our review is to characterize and discuss the current knowledge about the disease and all the available treatments, with a focus on the topical use of propranolol.

Keywords: Infantile, hemangioma, vascular, therapy, beta-block, propranolol.

Introduction:

1.1. Infantile Hemangioma

Infantile Hemangiomas [IHs] are benign vascular tumors that occurs in 10–12 % of Caucasian infants at birth (about 30%) or in the first 4 weeks of life (70–90 %), with a sex bias of 3:1 in females vs. males [1]. Most often, they develop on the head or neck, increasing rapidly over the first 6–12 months of life, then progressively regressing in several years. Isolated congenital forms that involute rapidly (rapidly involuting congenital hemangioma, RICH) or that fail to involute (non-involuting congenital hemangioma, NICH) have

been also identified. IHs can be noticed in all ethnicities, but they result to be more frequent in the Caucasian population and less in those of African descent.

1.2. Genetics and risk factors

The majority of IHs appear sporadically, but the familial condition has been documented. The autosomal dominant transmission has been also documented, with the locus involved identified at 5q 31-33 [2]. Heterozygous missense mutations in the endothelial cell (EC) tyrosine kinase receptor for vascular endothelial growth factor VEGF-A/VEGFR2 (KDR; p. Cys482Arg) and the anthrax receptor ANTXR1 (TEM8; p. Ala326Thr) are raised in patients with IHs [3]. The two receptors form a complex with β1-integrin on the surface of ECs, which operates in the transcription factor NFATc1 to assemble VEGFR1 (FLT1). VEGFR1 in turn competes for VEGF-A, thereby regulating the level of ligand-stimulated VEGFR2 signaling. The mutations identified in IHs may destabilize this receptor complex, rising from a decrease in the level of VEGFR1 and a simultaneous increase in VEGFR2 signaling [3]. All hemangioma-derived ECs seem to be characterized by enhanced VEGFR2 signaling, which continues to its proliferative nature, showing it as an example for target therapy. On the other side, hereditary mutations have only been recognized in a fraction of samples [3].

IHs risk factors are female gender (female-to-male ratio of 3:1), prematurity, low birth weight (especially <1,500 g). Low birth weight (LBW) was the most important risk factor; with less than 2,500 g for every 500 g decrease in birth weight, the risk of IHs increased 40 % [4]. The rate of IHs may be as high as 25 % in early infants of low birth weight (fewer than 1,000 g). The medium age when hemangioma forms are 2 weeks. The female gender predominance may be due to hormonal differences.

The majority of IHs were classified as localized 66.8 %; 16.5 % were indeterminate, whereas 13.1 % were segmental, and 3.6 % were multifocal. Segmental hemangiomas were 11 times more likely to encounter complications and eight times to get treatment than localized hemangiomas[5-6].

Multiple hemangiomas were acquired in preterm infants; however, female predominance was less than in term infants [7-8]. Endothelial parent cells could play a key role in IHs development explaining both the progress in frequency and numbers of hemangiomas, especially in preterm infants because of the higher number of these progenitor cells in a preterm newborn than in a mature one.

Ischemic changes in placental circulation could be connected to hemangioma growth and they have a high incidence of placental pathology in preterms <1,500 g with IHs [9].

Maternal vaginal bleeding and progesterone therapy during the first trimester of pregnancy seem to be independent risk factors for IHs [9]. Increased levels of progesterone and local tissue ischemia could boost hypoxia-inducible growth factor (HIF-1alpha) and vascular endothelial growth factor, expanding the capillaries in the hemangioma tissue beds [10].

1.3. Development

IHs have a distinctive vascular phenotype like placental microvasculature expressed by staining markers such as glucose transporter 1 (GLUT-1) which is present in all phases of IHs, merosin, and Lewis Y antigen [11].

In the growth phase, IHs can be distinguished in early proliferative, late proliferative, plateau, involuting, or abortive mimicking a port-wine stain [5]. A distinct subset of IHs, called diffuse hemangiomatosis, has several little lesions measuring from a few millimeters to 1–2 cm with a more elevated risk of visceral involvement, more frequent the liver and gastrointestinal tract [12]. Another rare variant is the reticular hemangioma, occurring in the extremity and associated with intractable ulceration, anogenital-urinary-sacral-anomalies, and sometimes cardiac overload.

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Infantile hepatic hemangiomas are categorized into three types: focal (RICH analog), multifocal, and diffuse. Congenital Hemangioma (CH) are much rarer than IHs, clearly characterized by their typical clinical, histological, and immunophenotypic features. CH is entirely formed in utero, being noticeable immediately after birth, they never proliferate, and they show a lack of immunoreactivity for GLUT-1 marker.

Two types of CH have an early progression: rapidly involuting congenital hemangiomas (RICH), non-involuting congenital hemangiomas (NICH), and partially involuting congenital hemangiomas (PICH). RICH are round and extensive vascular tumors most frequently found close to a joint on the limbs or the head. They undergo postnatal involution generally achieved in 6–12 months, lipoatrophy or a telangiectatic plaque can occur.

In large tumors, temporary thrombocytopenia may occur in the first week of life, as Kasabach-Merritt syndrome. Antenatal diagnosis of RICH during a prenatal ultrasound or MRI follow-up is possible before the 18th week of pregnancy. NICH is mainly located on the head or neck and limbs and prenatal color Doppler ultrasound or MRI follow-up during pregnancy rarely leads to their detection [13].

1.4. Clinical Picture

Lesions generally first emerge at about 2 weeks of age as a blanched, blushed, or telangiectatic patch or with a ulcerated appearance, and they can rapidly progress [14]. The classification of IHs are based on the involvement of the various layers of the skin. The greater is the vertical growth, the greater is the severity of the disease: superficial, deep, and mixed hemangiomas [15].

Superficial lesions involve the upper dermis as bright red thickened maculae or more rounded papules or nodules. Deep hemangiomas extend throughout the dermis and subcutis and are blue or dimmer to skin-colored nodules. Mixed hemangiomas have both superficial and deep elements and therefore have features of both. Chiller et al. [inserire qui voce bibliografica] created a new classification based on the spatial distribution of lesions. localized, segmental, indeterminate, and multifocal hemangiomas.

“Segmental hemangiomas” seem to retain the histological structure of embryologic bumps, originating from the neuroectoderm. They are the least frequent among all types and occur often with a more extensive and irregular structure, presenting as plaque-like lesions. They have an irregular shape, large, and can be reticular or telangiectatic or flat cherry-red [15]. With regard to the face, IHs are classified into 4 types, depending on the involved region (frontotemporal, nasal, zygomatic-malar, mandibular), and tend to present in a segmental fashion:.

Segment 1: the lateral forehead and temporal and lateral frontal scalp.

Segments 2: zygomatic region and maxilla.

Segments 3: Mandible

Segments 4: frontal region, superciliary arches.

The dimensions are variable usually up to 5 cm and can affect both halves of the face [16].

“Localized hemangiomas” appear to extend from a single focal point or were enclosed to an area without any apparent linear or developmental arrangement. They are usually oval or round [16].

“Indeterminate hemangiomas” were not classified as either localized or segmental, and “multifocal hemangiomas” were defined as more than ten cutaneous hemangiomas [17].

Although approximately 60 % of hemangiomas occur on the head and neck, they can also occur in any area of the body on the trunk (25 %), extremities, and genitals (15 %). In the literature it is reported that in 60% of cases HI affects the neck and head, the trunk is the second most frequently affected region of the body 25%, and the genital area 15% [18].

Hemangiomas usually present a standard of behaviour, characterized by three distinct stages: a proliferating high-flow stage (8–12 months), followed by a prolonged involuting one (1–12 years), and finally a typical end-stage with residual telangiectasias [35-36]. Most of the hemangioma growth occurs in the first 5–9

months, at which point 80 % of the final size have been reached, whereas the deep and mixed IHs with the segmental or indeterminate distribution [????] sometimes appear later and continue to grow for a longer time, even up to 2 years of age [19].

Another subgroup of IHs display minimal growth, presenting a reticular or telangiectatic formation with a main peripheric proliferative part, consisting of a few millimeters papules. They are selectively located in the trunk, limbs, and lumbosacral region [19]. The beginning is usually signed by the shift in color from intense red to a paler red, with a whitish discoloration always in the center of the hemangioma, disseminating centrifugally. Deep-seated lesions shift to less blue and less warm.

1.5. Complications

The majority of IHs are benign (80 %), but the rapid evolution could have significant complications such as ulceration, bleeding, disfigurement, compromised organ function, vision and airway obstruction, or high output cardiac failure, needing an aggressive therapeutic approach [20].

1.5.1. Ulceration

The most afflicted areas are the anogenital region, head, and neck, with a preference for the lips/ perioral and intertriginous zones. The ulcer could last for several weeks or months and is accompanied by pain, bleeding, infection, and permanent scarring [21]. Ulceration is more common in mixed or superficial and larger segmental hemangiomas than in the focal subtype [5].

1.5.2. Visual involvement

Periorbital hemangiomas often involve the upper lid, usually sparing the lower lid and the retrobulbar space. The site of the ocular hemangiomas can be perceptual, extraconal, and intraconal [21].

1.5.3. Multifocal Hemangiomas

Diffuse neonatal hemangiomatosis (DNH) portrays infants with numerous hemangiomas touching the skin and viscera with varying degrees of involvement from only skin benign neonatal hemangiomatosis (BNH) to combined cutaneous and visceral involvement diffuse neonatal hemangiomatosis (DNH) [22].

Lesions differ in size from a few millimeters to centimeters in diameter and maybe observed at birth but grow during the first week of life. More than five cutaneous lesions have been defined as a diagnostic clue for visceral hemangiomas [22]. All these patients should be screened for inner organ involvement mostly observed in the liver but also in the lungs, bowel, and brain. Large diffuse hemangiomas of the liver can also cause hypothyroidism because IHs expresse type 3 iodothyronine deiodinase, an enzyme that inactivates blood thyroid hormone [23].

Hemangiomas and are often associated with skeletal anomalies or visceral hemangiomas known as Associated Structural Anomalies Segmental hemangiomas . Patients with segmental hemangiomas should also undergo an assessment to evaluate PHACE syndrome (posterior fossa brain malformations, hemangiomas of the face, arterial cerebrovascular anomalies, cardiovascular anomalies, eye anomalies, and sternal defects or supraumbilical raphe) [24]. Different acronyms have been created: PELVIS syndrome (perineal hemangioma, external genitalia malformations, lipomyelomeningocele, renal abnormalities, imperforate anus, and skin tag), SACRAL syndrome (spinal dysraphism; anogenital, cutaneous, renal, and urologic anomalies; and hemangioma with “angioma” of lumbosacral localization), and LUMBAR syndrome (lower body hemangioma and other skin defects, urogenital abnormalities, ulceration, myelopathy, bony deformities, anorectal malformations, and arterial and renal abnormalities) [25]. The patients at risk normally have segmental IHs which cross the midline. In some circumstances, the hemangiomas are bulky, but more often they are flat with a telangiectatic formation.

1.6. Differential Diagnosis

Differential diagnosis includes several types of cutaneous tumours. Many lesions, both benign and malignant, could mimic IHs, such as nasal

glioma, xanthogranuloma, dermoid cyst, pilomatrixoma, congenital angiofibroma, plexiform neurofibroma, hemangioendothelioma, infantile fibrosarcoma, Ewing's sarcoma, rhabdomyosarcoma, metastasis of neuroblastoma, and cutaneous lesions of leukemia cutis.

In all the above-mentioned cases anamnesis, physical examination, together with radiological findings and possible biopsy are essential to reach the diagnosis.

The majority of IHs affect the epidermis, so they could be easily recognised by their typical display; the others, being characterized by deep location, abnormal growth pattern, or visceral involvement need a more detailed assessment to obtain a differential diagnosis.

The age of onset, colour, and location, along with physical examination findings, are generally enough to have a correct management. The presentation of the lesion at birth supports the diagnosis of vascular malformation or congenital hemangioma.

1.7. Imaging

The conventional diagnostic test for congenital hemangiomas is ultrasonography with Doppler analysis: the lesions appear uniformly hypoechoic, mostly continous to the subcutaneous fat and diffusely vascular, traversed by multiple tubular vascular channels. Ultrasound Doppler can evaluate the flow of hemangiomas, represented by a shunt pattern with modified arterial resistance and increased venous velocity. In deep cutaneous or visceral hemangiomas, contrast-enhanced MRI shows the dimensions of the lesion and helps differentiate between hemangiomas and other disorders with similar findings on the US examination. Hemangiomas have a distinct solid conformation with moderate intensity on a T1-weighted spin-echo image, which is more intensely linked with venous or lymphatic malformations.

During the proliferative stage, hemangiomas have a moderately low intensity in a T2-weighted spin-echo image, while in the involution phase, they have very low intensity. Contrast-enhanced T1-weighted MRI shows mild intensity with flow voids in the proliferative phase because of the high flow at this stage. Hemangiomas show low intensity during involution due to the low flow at that stage.

Angiography is required if embolization must be done (large and irregular feeding arteries in disorganized patterns, arterial aneurysms, direct arteriovenous shunts, and intravascular thrombi are common features in RICH and are rarely seen in [IHs]) [26-27]. The type of lesion can generally be managed by medical history and clinical examination.

Treatment

In the case of small lesions as the common IHs in non-problematic areas without proliferation, especially in cutaneous hemangiomas, "see and wait" is the standard approach

However, if complications are expected, therapy is required. The following [IHs] an active treatment is required:

• Hemangiomas of the face, especially periorbital, and in the areas of the ear, lips, and nose;

• Hemangiomas at the mammary gland and in the anogenital area, particularly the vulva, the urethral orifice, and the anal derma;

• Fast-growing, diffuse infiltrating hemangiomas at any anatomic site;

• Hemangiomatosis, either aggressive, diffuse, or visceral involvement;

• Hemangiomas in difficulty zones such as the face, anogenital region should be treated in their early stages to avoid complications, such as hemangiomas near the eyes (threat to vision), lips (little regression tendency), and nose area (malformations of the nose – Cyrano nose) [3]. Treatment is also meant when hemangiomas are located on the fingers, toes, breast, and cleavage area in women.

Extended, highly proliferating hemangiomas, as well as diffuse infiltrating hemangiomas, should be treated.

Early treatment can be essential for the further course, rapidly involuting congenital hemangioendothelioma (RICH) needs only

frequent ultrasound controls. For non-involuting congenital hemangioendothelioma (NICH), implemented there is color-coded duplex sonography (CCDS) and thrombocyte monitoring, one may wait for a possible natural regression as in RICH.

2.1. Oral Beta-Blockers Propranolol

Multimodal management of complicated IHs include medical treatment to control the growth of the tumor. No conventional treatment guidelines for the treatment of IHs are available; however, given the recent proven rapid efficacy and safety of beta-blockers in the therapy of IHs, many teams advise oral propranolol as first-line therapy [28-29].

Propranolol is a nonselective beta-blocker; it is responsible for the vasoconstriction of small vessels resulting in a very rapid change in color and softening of the IHs. Propranolol also decreases the rate of renin and thus has a modulating effect on angiotensin II. Also, beta-adrenergic receptors belong to the family of G-protein-coupled receptors, which, when activated by adrenergic catecholamines, can develop a series of intracellular signal transduction pathways including that of angiogenic factors such as VEGF or bFGF and some metalloproteinases such as MMP2 and MMP9 [30].

Propranolol efficacy on IHs has been fortuitously observed. Since 2008, pooling case series [31] and randomized research have established that propranolol is a short-term safety treatment, recommending oral propranolol as first-line therapy in complex IHs life-threatening, functional consequences due to IHs, risk of permanent disfigurement. After excluding contraindications, oral propranolol must be administered at the dose of 2–3 mg/kg/day for 6 months, about 10–15 % of infants, needed to be distinguished from 3–6 months more, especially if they present a large segmental IHs and/or an IHs with a deep component. Local beta-blockers, such as timolol, could be practiced for superficial IHs.

A pilot study in infants < 4 months treated with propranolol (74 mg/kg/day) showed, after only 1 month of treatment, a reduction by half in the thickness of the IHs, evaluated by ultrasound whereas in the placebo arm there was a slight IHs increase [31].

IHs resistance to propranolol is rare and only separate cases have been reported [32]. In more than 90 % of infants treated, a change in IHs colour from intense red to purple is noted 24 h after the start, combined with softening of the lesion. Symptoms such as dyspnea in airway IHs or hemodynamic abnormalities in large IHs usually resolve within 48 h [33]. The main propranolol contraindications are sinus bradycardia and partial auriculoventricular block to be excluded before the start.

Asthma is also a contraindication, difficult to detect in young infants; infants can trigger wheezing during the beta-blocker treatment, particularly in case of concomitant viral infection. In these circumstances, it is suggested to stop temporarily the propranolol or definitively in case of relapse. Parents should be well instructed on the risk of hypoglycemia [33].

Other adverse effects are asymptomatic blood pressure drop or bradycardia, insomnia, agitation, and nightmares. Some cases of hyperkalemia, a result of tumor lysis, have also been reported; as a result, blood potassium should be controlled in large and/or ulcerated IHs treated with beta-blockers [33].

Propranolol intake should be continued for 6 months.

After propranolol treatment end, mild recoloration may be noted; among these infants, 50 % needed to be retreated 3 or 6 months more because of regrowth of the IHs. Segmental IHs as well as IHs with a deep component shows a higher risk for relapse [34].

To reduce adverse effects risks and high frequency of propranolol-loaded liposomes-in-microsphere (PLIM) is administered as a novel topical release system to learn sustained release of propranolol locally leading to significant inhibition of IHs [34].

2.2. Other Beta-Blockers

Beneficial effects with other beta-blockers have also been described as small case series or case reports. Acebutolol and atenolol are both cardioselective beta-blockers; causing less bronchospasm and suggested as an alternative therapy in infants predisposed to wheezing, but the cardioselectivity is not approved at high dosages. They are also less lipophilic than propranolol with less efficient for nightmares.

Nadolol has shown efficacy but with the same short-term side effects as propranolol [35].

Other therapies

3.1. Local treatments

Literature has been described a beneficial effect with topical timolol in local treatment of superficial IHs which involves the mucous membranes and skin; ophthalmic gels have been used first on eyelids and then extended to the skin. A randomized controlled trial demonstrated that topical timolol maleate 0.5 % gel with a maximum dosage of 0.5 mg/day is a safe and effective option for small superficial and not complicated IHs without mucosal involvement and it is more effective under occlusion [35].

Topical timolol has comparable efficacy for IHs compared to oral propranolol, but with less occurrence of adverse events. For those with mild or moderate IHs, topical timolol may be favorable over oral propranolol. However, mixed therapy with topical timolol and oral propranolol has been suggested as a more effective IHs treatment strategy, as proved in a meta-analysis, and it can be somministred as a first-line treatment [35].

3.2. Corticosteroids

The treatment of corticosteroids for IHs is restricted to propranolol ineffectiveness. Dosages of prednisone/prednisolone range from 1 to 5 mg/kg body weight daily and several durations of treatment [36]. The possible side effects of corticosteroid therapy include hypertension, gastritis, delayed growth as well as mood changes, but they are reversible [37].

During corticosteroid treatment, the child should have a physical examination every 2–4 weeks with monitoring of blood pressure, height, weight, and glucosuria. Prescription of oral ranitidine or a beta-blocker may be necessary.

3.3. Vincristine

Vincristine is a natural vinca alkaloid separated from the leaves of the periwinkle plant Catharanthus roseus, conflicting with mitotic spindle microtubules by connecting to tubulin and inhibiting mitosis, used in the therapy of malignancies in children [38].

There are very poor reports on the use of vincristine for the treatment of proliferating, corticosteroid- and/or interferon-resistant IHs [38]. It is more used for function- and life-threatening congenital vascular tumors. In sequence with corticosteroids, vincristine can be effective in the Kasabach- Vincristine can be administered at a dose of 1 mg/m 2 (or 0.05 mg/kg body weight in children <10 kg). It is generally used intravenously with weekly injections first and then tapering down by expanding the interval between injections, depending on the clinical response [39]

Neurotoxicity is the dose-limiting side effect of vincristine. A peripheral mixed sensorial and motor neuropathy is common, but it can also give autonomic neuropathy resulting in abdominal pain, constipation, and ileus [38].

3.4. Cyclophosphamide

Alkylating agents use for the treatment of congenital vascular tumors, including IHs, have been reported. Frequent negative effects include nausea, vomiting, and reversible alopecia [40].

3.5. Rapamycin

The mTOR signaling pathway seems to be activated in the endothelial cells of vascular tumors. Therefore, the mTOR inhibitor Rapamycin had been suggested as second-line therapy for complicated vascular anomalies, including congenital vascular tumors, such as hemangioendothelioma presenting with KMP, if corticosteroids and vincristine are not effective [40].

3.6. Laser therapy

IHs has a high capacity of spontaneous regression, but sometimes it does not occur or there is extreme growth, so laser treatment may aim to give this regression by an inflammatory process because of intravascular absorption of light and vessel obstructions and generally not standard coagulation. Flashlamp-Pumped Pulsed Dye Laser ("FPDL Laser") FPDL nowadays is generally accepted as the treatment of choice for macular port-wine stains. The use of FPDL with a wavelength of 585 or 595 nm and a pulse duration of 300 μs to 2 ms is only indicated in the very early stages of IHs not thicker than 2 mm, given there is no subcutaneous part [27]. Side effects are uncommon; blisters and scabs are observed, demanding cooling and stabilization of the epidermis by a fluid cooling cuvette. An early FPDL therapy of all IHs and their precursor lesions brought no fundamental advantages compared to an untreated control group [27].

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is coherent with these guidelines.

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