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Infantile Hemangioma: Modern Perspectives on Pathogenesis and Treatment

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ABSTRACT

Infantile hemangioma (IH) is a significant and common interdisciplinary issue in the pediatric population. The etiology of this condition is not fully understood. Several hypotheses exist regarding the origin of IH: the placental hypothesis, genetic mutations, and the influence of external factors. Treatment approaches for IH are diverse and include systemic pharmacotherapy, local treatment, and surgical intervention. Each of these methods has both advantages and limitations, making it impossible to use any single approach as a universal solution for all patients. The beta-blocker propranolol is currently recognized as the first-line medication. The authors of the lecture presented a literature review of modern approaches to selecting treatment for IH, as well as predictors of propranolol efficacy and its possible mechanism of action.

Keywords: hemangioma, malformation, children, propranolol

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источники финансирования. Авторы заявляют об отсутствии источника финансирования при проведении исследования.

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Инфантильная гемангиома: современный взгляд на патогенез и лечение

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РЕЗЮМЕ

Инфантильная гемангиома (ИГ) – значимая и распространенная проблема междисциплинарного характера в детской популяции. Этиология данного заболевания до конца не известна. Существует несколько гипотез возникновения ИГ: плацентарная, в результате генетической мутации и воздействия внешних факторов. Подходы к лечению инфантильных гемангиом разнообразны и включают системную фармакотерапию,

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местное и хирургическое лечение. Каждый из них обладает как достоинствами, так и ограничениями, что делает невозможным использование одного из методов в качестве универсального для всех пациентов. Препаратом первой линии в настоящее время признан β-адреноблокатор пропранолол.

Авторы лекции представили литературный обзор современных подходов к выбору лечения инфантильных гемангиом, а также предикторы эффективности применения пропранолола и его возможный механизм действия.

Ключевые слова: гемангиома, мальформация, дети, пропранолол

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

The aim of the lecture was to provide a literature review of data on the pathogenesis and treatment methods of infantile (neonatal) hemangioma (IH), as well as to present the results of current research on potential predictors of pharmacological therapy efficacy.

IH represents a benign vascular tumor formed through proliferation of vascular endothelial cells resulting from impaired local angiogenesis. Among all vascular pathologies, IH is the most prevalent, occurring in 5–10% of children during their first year of life [1]. The condition is more frequently diagnosed in girls, Caucasian children, and twins. It has been observed that IH develops particularly often in newborns with low birth weight and in preterm infants. This makes the pathology a significant concern in pediatric practice [2].

GENERAL INFORMATION

IH has a diverse localization, but in 60% of cases, it occupies the head and neck region [3]. Clinical manifestations usually begin in the first weeks of life. A distinctive feature of IH is the dynamic nature of the tumor. During the first six months of life, active proliferation is observed, during which hemangioma reaches its maximum size. At the age of 8–9 months, a stabilization phase occurs, characterized by slowing of the formation growth, followed by a regression stage, which can last from one to several years [4]. The average age of spontaneous involution cessation is 3.5 years [5]. To determine the treatment strategy, it is important to differentiate IH from other vascular anomalies presented in the ISSVA (International Society for the Study of Vascular Anomalies) classification of 2014 [6]. Differential diagnosis is made between vascular malformations and rarer forms of vascular tumors: congenital hemangioma, tufted angioma, and kaposiform hemangioendothelioma [2]. The diagnosis is made on the basis of anamnestic data and a specific disease pattern. Ultrasound and magnetic resonance imaging can be used as additional diagnostic methods [5]. In complicated cases, the immunohistochemical marker GLUT1 (glucose transporter 1) allows for differentiating IH from other vascular anomalies, except for verrucous venous malformation. This protein is responsible for glucose transportation and is expressed in any form of IH at all stages of its development [7].

There are three clinical forms of IH: nodular, appearing as a single locus (the most common form); segmental, limited to an anatomical segment, and multifocal, manifested by multiple hemangiomas with visceral lesions, more often of the liver. Depending on the depth of the skin lesion, the following forms are distinguished: superficial, affecting only the upper layers of the dermis and accounting for about 60% of all IHs; subcutaneous, located in the deep layers of the dermis and hypodermis, accounting for 15% of IHs; and mixed, accounting for about 25% in the profile of IHs [8].

Most hemangiomas are small asymptomatic masses that tend to regress on their own. However, about 10% of IHs can lead to local complications: ulcers, hemorrhage, necrosis, cosmetic defect and less often – to functional disorders of vital organs. Complications occur in the proliferation phase and are most typical of segmental forms of IH [9, 10]. Multifocal IH with liver damage can be accompanied

by severe thrombocytopenia and lead to thyroid hypofunction due to overexpression of type 3 iodothyronine deiodinase, inactivating thyroxine, and secretion of TTH-like factor thyrotropin [3]. Facial IHs are of particular concern because of possible complications in the eyes, as well as respiratory and swallowing disorders. Massive hemangiomas in this region may be accompanied by pathologies of the posterior fossa, cardiovascular, ophthalmic, and endocrine abnormalities as part of the PHACES syndrome (Posterior fossa, Hemangioma, Arterial lesions, Cardiac abnormalities, Eye abnormalities, Sternum). Among them, cerebrovascular abnormality is found in 72% of cases [11]. Voluminous IH in the sacrococcygeal and perineal region may be a symptom of LUMBAR syndrome (Lower body, Urogenital anomaly, Myelopathy, Bone deformities, Anorectal malformations, Renal anomalies), characterized by a combination of IH, urogenital anomalies, myelopathy, bone deformities, and renal anomalies. Thirty percent of patients with this syndrome have only one associated anomaly, and the risk of ulcers is about 70% [12]. These syndromes are mostly found in girls, with the prevalence of about 2% of all hemangiomas [13]. Very rare, but the most dangerous complications of IH can be disorders of vital functions. For example, hemangiomas of the upper respiratory tract can cause respiratory distress syndrome, mediastinal and liver tumors can form heart failure, and hemangiomas on the mucous membranes of the gastrointestinal tract can cause massive intestinal bleeding [8]. Voluminous hemangiomas after involution leave residual changes in the form of telangiectasias, fibrofatty changes, and skin atrophy, decreasing the quality of life of patients [14]. Despite the interdisciplinary nature of the problem, IHs often lack proper medical supervision and timely treatment, which worsens the prognosis of the disease and leads to the complications described above.

ETIOLOGY AND PATHOGENESIS

The etiology of this disease is not completely known and remains a subject of scientific research. There are several hypotheses of IH origin, including placental, following genetic mutations, and external factors.

The hypothesis of placental origin is supported by the expression of placental markers, such as laminin, merosin, GLUT-1, Lewis Y antigen, and Fc gamma receptor II (CD32) in the blood vessels of IH [15, 16]. According to this assumption, risk factors for IH include chorionic villus sampling and amniocentesis in pregnant women, in the course of which there may be transfer of mesenchymal cells of chorionic villi from the placenta into the fetal circulatory system and further into susceptible tissues, which represents the initiating stage of pathologic angiogenesis [17, 18]. According to a recent study by F. Moisan et al., endothelial cells of IH lack aquaporin-1 (AQP1), a water channel modulated during tumor cell migration and invasion, whereas endothelial cells derived from placental tissue are AQP1-positive [17].

It is believed that hemangiomas occur as a result of somatic mutation and clonal expansion of progenitor cells. The presence of the stem cell-specific SALL4 gene in IH cells supports this assumption [19]. Genetic predisposition to the development of hemangiomas is currently unconfirmed, but it is also one of the possible causes of IH development [7]. There are data on monozygotic twins with almost identical periorbital hemangiomas [20]. A number of scientific works in recent years have considered mutations and polymorphisms in genes regulating angiogenesis as possible causes of IH development [21, 22].

In the last decade, the hypothesis of the influence of external factors, such as hypoxia, increased estrogen level, and inflammation, has been widely spread [23]. Among them, the leading role is attributed to fetal hypoxia resulting from: multiple pregnancies and pregnancies complicated by preeclampsia, gestational diabetes mellitus, placental abnormalities or detachment, as well as late pregnancy, prematurity, and low birth weight [22, 24, 25]. It is not fully understood what mechanisms regulate the development of IH in hypoxia, but many researchers agree that the key process is the disturbance of vasculogenesis and the predominance of angiogenic factors over antiangiogenic ones [25, 27]. Vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2) are currently considered to be the main angiogenic factors [24, 28]. Hypoxia as a root cause of IH development is supported by the data on the increased level of renin in premature and low birth weight infants, which promotes differentiation of tumor stem cells and leads to the growth of immature vascular tissue [25]. The results of the studies by R.M. Hyland and V. Praveen showed that retinopathy of prematurity and IH have a common mechanism of development – microvascular ischemia leading to neovascularization [27, 28].

The increased level of estrogen in the postpartum period and expression of its receptors

on the endothelium of IH microvessels affect further proliferation of endotheliocytes, probably due to the effect on FGF-2 production [7]. The prevalence of hemangiomas in girls also suggests a possible role of estrogen in the etiology of the disease, by stimulating angiogenesis through the expression of the angiogenic factor VEGF [29, 30]. For the same reason, it is thought that higher estrogen levels in pregnant women may affect the vascularization process in the fetus and lead to abnormal vascular proliferation [31]. It has been shown that estrogen concentration in peripheral blood increases in the proliferative phase of IH and decreases in the involution phase, and in the profile of hemangiomas, there are significantly more receptors to estrogen than in unchanged vessels [30]. Thus, in breast cancer, estrogen increases proliferation and migration of endothelial cells [31]. Another study demonstrated the effect of estrogen on the migration of mast cell progenitors in IH tissue, where activated mast cells secreted angiogenic factors VEGF and FGF-2 [32]. In addition, these cells secrete chymotrypsin, trypsin, and matrix metalloproteinases necessary for the destruction of extracellular matrix, providing space for IH vascular growth [31].

Despite the active study of etiology and pathogenesis, none of the existing hypotheses yet explains all the features of epidemiology, course, and clinical manifestations of IH.

TREATMENT

Treatment approaches to IH are diverse and include systemic pharmacotherapy, topical, and surgical treatment [33]. Each of them has both advantages and limitations, which makes it impossible to use one method for all patients. Currently, a need for a personalized approach based on individual patient characteristics, the clinical presentation of the disease, and potential risks associated with therapy is increasingly emphasized [34].

Topical treatment of IH with a nonselective β-blocker timolol is widely used for small superficial skin lesions. It is generally well tolerated and can produce excellent visual results [35, 36]. However, therapy with this drug has side effects, such as desquamation, erythema, local xerosis, ulceration, and risk of secondary infection [37].

Surgical treatments include cryodestruction, sclerotherapy, excision, and laser irradiation. Cryodestruction has been known for a long time, but with the advent of new techniques, its use has been limited. Exposure to liquid nitrogen at –195.6 °C is effective for superficial nodular hemangiomas. In case of more diffuse tumors with abundant blood supply, the method is not used due to a possible risk of cosmetic defects and hemangioma regrowth [38]. Sclerotherapy is used for small superficial masses with small feeding vessels. Its essence is to inject a sclerosant into the feeding vessel of hemangioma, which damages the endothelium and promotes thrombus formation. Disadvantages of this treatment method are risks of microcirculation disorder in tissues around hemangioma, up to necrosis of the tumor. Surgical excision is indicated in life-threatening conditions associated with the localization of IH or its complications and to eliminate residual changes in the tumor after involution, such as excess tissue. Laser irradiation is effective in eliminating residual skin pigmentation [39, 40]. Despite the effectiveness of topical and surgical treatments, they have a risk of complications, including hypopigmentation, burns, localized skin atrophy, and infection [41].

Systemic pharmacotherapy is used mainly for potentially dangerous forms of hemangiomas associated with their localization, size or structural features of the lesion area [42]. First-line drugs currently encompass β-blockers, which proved highly efficient in a multicenter randomized controlled trial in 2015. They include non-selective β-blockers acting on β1-, β2-, and β3-adrenoreceptors and selective drugs mainly blocking β1-adrenoreceptors [43]. Propranolol, a non-selective β-blocker, has become the gold-standard therapy for IHs due to its high efficacy and satisfactory tolerability [44]. However, cases of tumor resistance to therapy as well as tumor regrowth after treatment completion have been reported [25, 45]. Due to non-selectivity of the drug, side effects can develop, such as hypotension, bradycardia, bronchospasm, hypoglycemia, and electrolyte balance disorders.

The mechanism of β-blocker action in IH is not fully understood. Currently, researchers agree that the main role of propranolol is to trigger autophagy of hemangioma cells. However, the specific molecular mechanism and cellular stage of this process remain unexplored [46]. There is evidence supporting the effect of β-blockers on β-adrenergic receptors of IH mast cells, thereby promoting endotheliocyte apoptosis [47]. It was also suggested that β-blockers can increase the production of angiogenic factor VEGF-A. These studies are consistent with the conclusion that the level of VEGF-A in blood decreases in patients with IH upon propranolol

administration [48, 49]. To date, much attention has been paid to the role of glucose metabolism in angiogenesis of endothelial cells. Oxidative phosphorylation, pyruvate metabolism, and the tricarboxylic acid cycle potentially play a key role in the pathogenesis of IH. Propranolol in turn inhibits pyruvate kinase activity, suppressing glycolysis and thus inhibiting the growth of hemangiomas [50]. The mechanism of action of β-blockers in IH requires further study, as it may help develop new treatment options and identify early factors of successful therapy. In addition to β-blockers, other systemic drugs, such as glucocorticoids and metronomic chemotherapy with vinblastine / cyclophosphamide, are also used in the treatment of IH. These methods are usually used when first-line therapy is inefficient or in addition to β-blockers in the treatment of severe and complicated forms of hemangiomas [3].

PREDICTORS OF EFFECTIVE TREATMENT WITH PROPRANOLOL

A number of studies have identified early signs of effective treatment with β-blockers, namely propranolol. A reduction in heart rate by more than 20% from baseline at the initiation of propranolol therapy may be an early marker of a good response to treatment [51].

Initiation of treatment in the first six months of life is considered to be a determinant of successful treatment. This is due to the fact that overexpression of β1-adrenergic receptors is observed in the proliferative phase of hemangioma, which, according to the authors, contributes to the greatest efficacy of the drug during this period [52].

Platelet-derived growth factor PDGF-BB may be a potential marker of a response to propranolol treatment, as its level significantly decreases during therapy. However, these results were obtained on a sample of five patients and require additional studies [53]. Platelet-derived growth factor (PDGF) is a family of cytokines consisting of four isoforms: PDGF-A, PDGF-B, PDGF-C, and PDGF-D, which are produced mainly by platelets, endothelial cells, smooth muscle cells, and macrophages. The PDGF-BB isoform plays an important role in angiogenesis and tissue regeneration. Receptors to this protein are located in the vascular wall on fibroblasts and smooth muscle cells, through which a cascade of signals is initiated, leading to the activation of cell proliferation and the production of factors related to angiogenesis and extracellular matrix remodeling [54].

The level of cytokines IGF-1, IL-6, IL-8, PIGF, RANTES, and TGFβ1 decreases in patients with progressive IH growth and can be used as a predictor of hemangioma growth and be a point of application of immunotherapy as a new treatment approach [55]. It should be taken into account that the sample in this study was not representative and consisted of three patients.

The results of scientific works devoted to the role of VEGF in the process of hemangioma growth are rather contradictory. Most authors come to the conclusion that VEGF level determines the clinical course of IH [56, 57], while others point to the absence of significant changes in VEGF level depending on the stage of the disease, which casts doubt on its use as a predictor of a response to therapy [50]. VEGF is known to be a potent mediator of angiogenesis and vasculogenesis in fetuses, children, and adults. During embryogenesis, it regulates proliferation, migration, and growth of endothelial cells, thereby determining the density and size of blood vessels. After birth, VEGF maintains the integrity of endothelial cells and acts as a mitogen for micro- and macrovascular endothelial cells [58].

Structural features of the tumor detected by instrumental diagnostic methods may also be a prognostic factor for successful treatment with propranolol in IH. Hypervascularization of the tumor according to the results of color Doppler imaging before therapy and reduction of vascularization in the early period of treatment may be a harbinger of a good response. This is probably due to the fact that propranolol induces vasoconstriction and has an antiangiogenic effect, resulting in decreased vascularization of hemangioma. The prominent fatty component of hemangioma detected on magnetic resonance imaging before treatment was more common in patients with a poor response to therapy thereafter [24].

CONCLUSION

Infantile hemangioma is a significant and widespread problem of interdisciplinary nature in the pediatric population, represented by clinical forms ranging from superficial masses prone to self-resolution to extensive tumors leading to local complications or impairment of vital functions. The etiology of this disease is not fully understood. The leading role in the pathogenesis is attributed to the hypoxic state of the fetus. For a timely and correct choice of a treatment strategy for patients, it is important to differentiate this disease with other

vascular malformations. Diagnosis is usually made on the basis of anamnestic and clinical data. The choice of a treatment method should be based on clinical evaluation, including individual patient characteristics, localization and size of the lesion, taking into account possible risks and complications of the chosen approach. Monitoring the effectiveness of therapy, especially in complex cases, should be based not only on subjective clinical assessment, but also on objective imaging and laboratory control methods. Laboratory control may include monitoring of biomarkers related to tumor activity and the body's response to therapy. An integrated approach to the assessment of treatment dynamics facilitates timely correction of therapy, reducing the risk of complications and improving overall efficacy.

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