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EXTRACRANIAL ARTERIOVENOUS MALFORMATIONS OF THE MAXILLOFACIAL REGION IN ENDOVASCULAR SURGERY. LITERATURE REVIEW

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Abstract

Arteriovenous malformations of the maxillofacial region are the most complex cases in prognostic, prophylactic and curative aspects in the context of extracranial angiodysplasias of other localizations. AVMs of the face and neck are quite common and cause significant discomfort, reduce mental and physical well-being, and worsen the quality of patients' life. With such localization, this disease in a large number of its manifestations can cause a huge variety of negative consequences in patients: from discomfort and cosmetic defect, up to death as a result of bleeding or heart failure. AVMs of the maxillofacial region have their own characteristics in the clinical course, classification and surgical tactics. Many retrospective studies have shown disappointing treatment outcomes in many cases due to ineffectiveness of available treatments, high recurrent rates, poor long-term outcomes, and low cure rate. This problem, as well as the lack of a universal treatment method of choice in such patients, is due to a poor understanding of the mechanisms of occurrence and prevalence of this pathology, and often due to incorrect or untimely diagnosis and incorrect tactics. The true epidemiology of arteriovenous malformations is still unknown and needs further retrospective research. The issues of etiology and pathogenesis are also unclear at the present time, this is an actively studied area in leading clinics around the world. The choice of treatment tactics in favor of surgical resection, interventional interventions or their combination is still the subject of controversy and discussion at international conferences and guidelines. Search for new and improvement of existing methods of treatment of angiodysplasias are an urgent problem and are being actively studied worldwide.

Thus, treatment of patients with AVMs of maxillofacial region should be provided by multidisciplinary team of specialists experienced in management of such cases.

Keywords: *vascular anomalies, angiodysplasias, extracranial arteriovenous malformations, maxillofacial region, endovascular surgery, embolization, sclerotherapy, Onyx, PVA, NBCA.*

Arteriovenous malformation (AVM) is a congenital vascular defect characterized by a defect in the development of the arterial and venous systems during ontogenesis with the formation of direct communications between vessels of various diameters with or without formation of a capillary network - nidus.

This lesion is one of the 4 types of vascular malformations according to ISSVA and is characterized by shunting of blood from the arterial to the venous bed through fistulas of various calibers.

The true incidence of vascular malformations in the population, in particular AVMs, is unknown. The clinical manifestation of AVM in the population is quite stable and, according to various researchers, is 0.94-1.2 cases per 100,000 population per year. The sex and age characteristics of AVM are nonspecific: the ratio of men and women, according to various sources, ranges from 1.09:1 to 1.91:1, and averages at 1.4:1 [*Kirilenko AN, Zyablova EI, 2019; Usman R et al., 2021*]. In this case, vascular malformations occur in 51% of cases in the head and neck region [*Persky MS, 1986*].

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Kohout M and co-authors found that in patients with diagnosed AVM, the disease is detected in 59% of cases at birth, in 10% in childhood, in 10% in adolescence, and in 21% in adults [*Kohout MP et al., 1998*].

The etiology of extracranial AVMs, like all vascular malformations, has not been reliably established, but recently there has been active research of genetic and hormonal factors in the development of these pathologies [*Utami AM et al., 2021*]. In a number of scientific researches, it was found that the cause of angiogenesis disturbance is the occurrence of mutations in the genes encoding the synthesis of vascular growth factors, such as: vascular endothelial growth factor, β-fibroblast growth factor, angiopoietin-2 [*Hashimoto T et al., 2001; Gerhardt H et al., 2003; Pavlov KA et al., 2011*]. Mutations in tumor suppressor genes such as the phosphatase and tensin homologue also play a role in the formation of vascular malformations [*Tan WH et al., 2007; Ota T, Komiyama M, 2020*].

Relatively recently, several studies have revealed a number of genetic mutations in extracranial AVMs. It is assumed that mutation of the mitogen-activated protein kinase 1 gene on endothelial cells affects their function and initiates pathological arteriovenous shunting through signaling activation of RAS / mitogen-activated protein kinase. It is assumed that this aberration is the main trigger factor for AVM formation in soft tissues [*Couto J et al., 2017; Smits PJ et al., 2020; Schimmel K et al., 2021*].

Mutations in the MAPK-ERK pathways, which can occur in arteriovenous malformations of the skin and soft tissues of the facial region, neck region, and other anatomical sites, can serve as targets for therapy using currently available MEK inhibitors, trametinib, or cobimetinib [*Redondo P et al., 2007; Lekwuttikarn R et al., 2019; Schimmel K et al., 2021*]. Thus, Lekwuttikarn R. et al. reports the successful treatment of patients with trametinib for a 6-month course, with a significant decrease in AVM volume [*Lekwuttikarn R et al., 2019*].

There are several inherited genetic mutations that predispose to the development of vascular lesions in subsequent generations. Osler-Weber-Rendu syndrome (congenital hemorrhagic telangiectasia), Bean syndrome ("blue bladder nevus" syndrome), phosphatase and tensin homologue mutations have a genetic basis for subsequently manifested vascular lesions [*Tan WH et al., 2007; Bockeria LA et al., 2015*].

Most often, patients with AVM pass to a more severe Schobinger stage in adolescence, which suggests an important role of hormonal levels in the pathogenesis of this disease. Thus, somatotropin (GH) acts as a pro-angiogenic factor inducing endothelial cell proliferation, migration, and capillary formation in vitro [*Clapp C et al., 2009; Bockeria LA et al., 2015*]. Several studies by Clapp C. et al. showed an increased concentration of follicle-stimulating hormone and somatotropin in AVM cells in comparison with control samples of healthy tissues.

Normally, angiogenesis is regulated by the balance of pro- and anti-angiogenic factors. Violation of this balance leads to the proliferation of blood vessels in the focus of the formed malformation. Traumatization and ischimization of vessels and tissues involved in the pathological process in AVM leads to release of pro-angiogenic factors, stimulating the growth of malformations and formation of new shunts. This mechanism explains the high recurrence rate after subtotal resection and partial embolization of arteriovenous malformations and the deterioration of the clinical course in the long-term observation *[Liu AS et al., 2010; Schimmel K et al., 2021*]. It is known that disease progression is also reliably stimulated by a number of events such as trauma, puberty, and pregnancy. Women suffering from this pathology often report a significant deterioration in the course of the disease during pregnancy [*De Lima CF et al., 2017; Utami AM et al., 2021*].

Arteriovenous malformations of the maxillofacial and neck areas, due to their delicate localization, manifest at the earliest stages of development, and, unlike peripheral AVMs, often affect the mucous membranes of the lips, eyelids, mouth, and

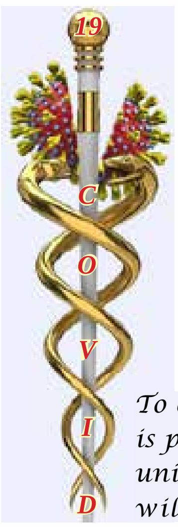

Table 1.

SSVA classification for vascular anomalies, 2018 (review version)

Vascular anomalies				
Vascular tumors	Vascular malformations (VM)			
	Simple	Combined *	VM of major named vessels	VM associated with other anomalies
Benign	Capillary (C) malformations	CVM	truncular VM	Klippel-Trenaunay syndrome
Locally aggressive or borderline	Lymphatic (L) malformations	CLM		Parkes Weber syndrome
	Venous (V) malformations	CAVM		Servelle-Martorel syndrome
Malignant	Arteriovenous malformations malformations** (AVM)	CLAVM		CLAPO syndrome
	Arteriovenous fistula ** (AVF)	others		Others

Notes: ** - defined as 2 or more simple forms of CM in one lesion*
*** - lesions with high velocity blood flow*

nasal cavities, causing significant bleeding [*Kim JB et al., 2017*]. The treatment of extracranial malformations is a complex task that requires more careful planning and application of the most modern techniques of endovascular interventions in combination with plastic and reconstructive surgery [*Bockeria LA et al., 2015; Shchehlov D et al., 2020*]. In view of the large number of clinical manifestations of this pathology and various options for endovascular interventions developed for the treatment of AVMs, the choice of tactics for such lesions largely depends on the accurate classification [*Lam K et al., 2017*].

The founders of the modern classification of vascular anomalies are Mulliken J. and Glowacki J., who proposed to fundamentally divide all vascular anomalies by morphological type into hemangiomas - true endothelial tumors and proper vascular malformations [*Mulliken JB, Glowacki J, 1982*]. Founded by Mulliken J. and co-authors the International Society for the Study of Vascular Anomalies, as a result of many congresses and debates, has developed the modern ISSVA classification (table 1)[*ISSVA classification for vascular anomalies, 2018*].

The clinical picture of extracranial AVMs is extremely variable and depends on the type of malformation, its volume, velocity characteristics and localization. The formation of malformations leads to disruption of the normal angioarchitecture of blood vessels in the affected area, which, in turn, causes disorders of general and local hemodynamics.

The local stealing-syndrome of tissues distal to the blood shunting zone leads to a decrease in perfusion, causes ischemia and ulceration. Pathological communication between the high-velocity arterial and slow venous beds leads to the appearance of blood flow turbulence, which, in addition to severe trauma to the vascular wall, causes a decrease in the pressure gradient in the shunting zone. Both of these factors create favorable conditions for further stretching of the walls of the draining veins and cause a decrease of systemic vascular resistance. The volume of circulating blood, being inversely proportional to the systemic vascular resistance, increases as the disease progresses and ultimately leads to the development of heart failure.

These mechanisms determine the clinical course of arteriovenous malformations and

Table 2.

Schobinger classification of arteriovenous malformations.

Stage I – quiescence	Hyperemia, hyperthermia, arteriovenous shunting with Doppler examination. AVM can hide behind the mask of capillary malformation or hemangioma in the stage of regression.
Stage II – expansion	Stage I + increase in the size of blood vessels, trembling, increased pulsation, dilatation and tortuosity of veins.
Stage III – destruction	Stage II + trophic disorders, ulcers, bleeding. Bone tissue lysis is possible.
Stage IV – decompensation	Stage III + manifestations of heart failure with increased cardiac output

make it possible to distinguish 4 stages described by Schobinger in his classification (table 2) [*Schobinger RA, 1971*].

As a rule, only local manifestations, as hyperemia, hyperthermia of the skin of the affected area, are noted in the early stages. Over time, the lesion involves soft tissue and bone structures, causing their hypertrophy. Arteriovenous malformations usually manifest on their own in the form of excessive pulsation of soft tissues with edema of the surrounding structures, and increasement in the diameter of the arteries and veins.

AVMs with limb involvement can be represented by hypertrophy of soft tissues and bone structures. Hypertrophy of soft tissues most often affects muscles and subcutaneous fat. AVMs with bone lesions can cause significant pain, but overgrowth of bones, associated with stimulation of the pineal gland, is more often observed, which ultimately leads to a difference in limb length and gait disturbance due to pelvic tilt [*Madani H et al., 2014; Bockeria LA et al., 2015*].

Extracranial arteriovenous malformations of the facial area are characterized by the involvement of the mucous membranes of the lips, eyelids, mouth, nose in the pathological process, in which bleeding is observed in the vast majority of cases [*Mathew L et al., 2020*].

The examination of patients with vascular malformations should initially include anamnesis, general examination and a combination of basic non-invasive or minimally invasive research methods, which include:

- ultrasound dopplerography;
- duplex scanning (arterial and venous vessels);
- MRI with T1 or T2-weighted image; MRA with dynamic contrast enhancement (DCE);
- CT-angiography with contrast enhancement, with 3D reconstruction;

Ultrasound research methods are the first line in the diagnosis of extracranial AVMs, and allow to clarify the localization of the process, the number and caliber of shunts, as well as velocity characteristics of blood flow in the studying area. Minimally invasive diagnostic radiology techniques, in particular MRA with DCE and CT-angiography, allow a more detailed assessment of the angioarchitecture of the lesion in the preoperative period, especially in patients with AVMs of large volumes and difficult localizations, such as the maxillofacial region and neck [*Kostrova OYu et al., 2020*]. Superselective angiography is the gold standard in the diagnosis of vascular anomalies. This procedure is performed immediately before the treatment stage and provides information that determines the tactics of treatment.

Yakes W. and co-authors developed and introduced into clinical practice their classification of arteriovenous malformation angioarchitecture, based on the angiographic views [*Yakes WF et al., 2017*]. A feature of this classification is the differentiation of AVMs into 4 types of angioarchitecture, taking into account the velocity characteristics of the blood flow. This approach made it possible to develop a universal strategy for the treatment of peripheral AVMs at various stages and localization. The tactics proposed by the author for each type of lesion showed good results in the treatment of patients with AVMs with a significant reduction in intra- and postoperative complications [*Yakes WF et al., 2017*].

Angioarchitectonics of arteriovenous malformation by Yakes (Fig.1):

- type I - direct arteriovenous fistula;
- type IIa - typical arteriovenous nidus;
- type IIb - typical nidus with shunting into an aneurysmically dilated vein;
- type IIIa - nidus is represented by aneurysmically dilated vein itself, draining blood;
- type IIIb - nidus is represented by an aneurysmically dilated vein with outflow through several vessels;
- type IV - infiltrative form of AVM with involvement of the capillary network.

In type I AVMs, direct mechanical occlusion with spirals, plugs, etc. is indicated.

In type IIa AVMs, transcatheter and direct embolization with particles of PVA, Onyx, NBCA, ethanol is indicated.

In type IIb AVMs, transcatheter and direct embolization with the introduction of coils into the draining vein is indicated.

In type IIIa AVMs, occlusion of the draining vein with spirals is indicated.

In type IIIb AVMs, spiral occlusion of each draining vein is indicated.

In type IV AVMs, transcatheter and direct

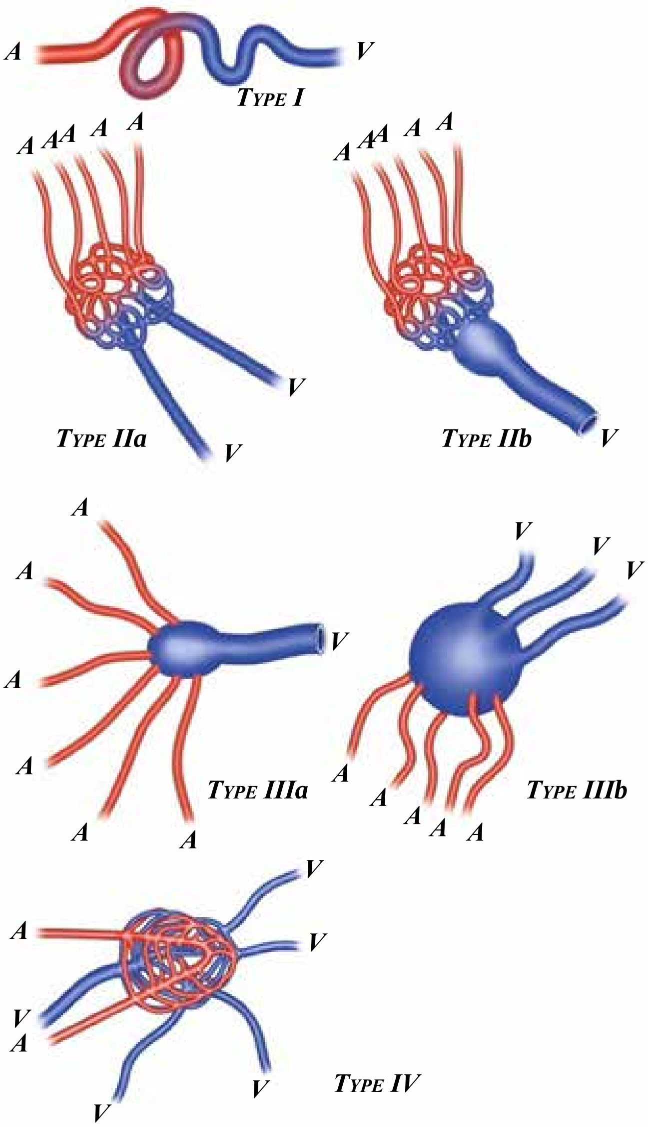

FIGURE 1. Classification and angioarchitectonics of arteriovenous malformations by Yakes

ethanol scleroembolization is indicated [*Yakes WF et al., 2017*].

Endovascular methods of treatment in the volume of embolization in combination with sclerotherapy, or in isolation, are currently considered the most preferred tactics in the treatment of extracranial arteriovenous malformations [*Bockeria LA et al., 2015; Lam K et al., 2017; Shchehlov D et al., 2020*]. X-ray guided endovascular occlusion and/or scleroembolization are the method of choice for diffuse infiltrative forms of AVM, as well as for localization of the process in the maxillofacial and neck areas, due to the less invasiveness and radicality of such interventions and a significantly better cosmetic effect [*Sufianov AA et al., 2019; Kim R et al., 2021*].

Embolization is a minimally invasive intravascular surgical treatment representing selective occlusion of the affected blood vessels using special embolizing materials.

According to the available data, the first embolization was performed in 1904 by R. Dawbarn, who occluded the arteries of the neck tumor with paraffin and petrolatum through the puncture of the external carotid artery [*Dawbarn R, 1904*]. For the first time transcatheter embolization of the right gastroepiploic artery in 1970 was performed by Dotter Ch. in order to stop acute gastric bleeding He used autologous blood clots as an embolizing material [*Dick R, 1977*]. In 1974, Tadavarthy et al. reported the first use of a synthetic polymer, polyvinyl alcohol (PVA), as an embolizing agent [*Tadavarthy SM et al., 1974*]. In 1975, Gianturco C. and co-authors reported the development and use of the first coils: a cotton-tail device consisting of cotton threads on a steel rod, and a wool-tail device of wool fibers attached to a steel guidewire [*Gianturco C et al., 1975*].

Over time, various liquid adhesive and non-adhesive synthetic embolizing agents have been developed and introduced into clinical practice, such as N-butyl-2-cyanoacrylate, Onyx. Liquid adhesive and non-adhesive embolizing agents are widely used in endovascular treatment of extracranial arteriovenous malformations [*Lamanna A et al., 2021; Albuquerque TV et al., 2021*]. At the moment, technologies of intravascular catheter embolization are becoming more widespread in clinical practice due to a low traumatization, a low incidence of complications quick recovery and the possibility of staged treatment compared to open operations. An embolization can be performed either as an independent method of treatment, or as a preparation for the immediate surgical resection of pathologically altered tissues in order to reduce operational risks and improve long-term outcomes [*Bockeria LA et al., 2015; Shchehlov D et al., 2020*].

The occlusion of extracranial vascular malformations is aimed at eliminating pathological shunts, and, depending on the type and location of the lesion, can be performed using various embolizing agents.

Based on the ability to resorption, mechanisms of influence on the vascular wall, physical and chemical properties, Bolomatov N. proposed the following classification of embolizing materials (EM):

1. Resorbable EM:
- autologous blood clots;
- denatured collagen (hemostatic gelatin sponge, Gelfoam);
- oxycellulose (Oxycel, Surgicel, Becton Dickinson, Franklin Lakes);
- oily substances (lipiodol ultra-fluid, petrolatum).

2. Non-resorbable EM:

A. Particular (related to particles):
- auto muscle;
- microparticles or microspheres (PVA, triacryl gelatin and hydrogel spheres, microparticles with hydrogel);
- microparticles with drugs;
- microparticles with ferromagnets;
- metal balls;

B. Nonparticular (nonparticulate):
- spirals;
- medical felt (EM made of 4-fluoroplastic polymer).
- suture material;
- detachable balloon catheters;
- occluders;
- stent grafts and stents.

C. Liquid:
- adhesive composites (EMs containing n-butyl-2-cyanoacrylate);
- non-adhesive composites (EMs containing ethyl vinyl alcohol polymer: Onyx, Squid; or polymers of poly-lactide-glycogen and polyhydroxyethyl methacrylate compounds: Phil);
- ethyblock.

3. Sclerosing EM:
- ethyl alcohol 96%;
- sodium tetradecyl sulfate (Sotradekol, Trombovar, Obliterol, Tergitol-4);
- polidocapol (Ethoxysclerol);
- glucose 40% and higher concentration.
- bleomycin

4. Advanced EM. (This group of EM includes substances, compositions, devices, technologies that are under development, preclinical tests).

The proposed classification includes the maximum number of EMs, both rarely used and recently developed [*Bolomatov NV, 2020*].

The use of one or another EM is determined either by its type, presence in hospital and localization and stage of AVM, as well as the patient's individual tolerance to a particular drug.

The selection of a suitable embolizing agent or their combination, its size or concentration is made individually in each case, and, along with the experience of a multidisciplinary team of specialists, is the main predictor of successful endovascular treatment of facial AVMs [*Nassiri N et al., 2015; Sufianov AA et al., 2019; Shchehlov D et al., 2020; Bolomatov NV, 2020*].

An embolizing agent or sclerosant should be injected directly into the shunting site. The approaches that ensure compliance with this principle can be transarterial, transvenous, direct puncture, or their combinations [*Bockeria LA et al., 2015*]. Treatment, in order to minimize the risk of possible complications, should be carried out fractionally in several stages, however, the simultaneous exclusion of low-velocity AVMs of moderate volume from the bloodstream also gives a good effect in the long-term period.

The progression of arteriovenous malformations in the maxillofacial region can have detrimental consequences for both the physical and mental well-being of patients, and reduce the quality of life. This disease in a large number of its manifestations can cause a huge variety of negative consequences in patients: from discomfort and cosmetic defect to death as a result of bleeding or heart failure. Since the developed methods of treatment at the present stage have a high percentage of recurrence in the long-term period and in many cases remain ineffective, further research is needed to study angiogenic microproliferative processes in AVM with the prospect of developing etiotropic treatment. It is also necessary to develop and improve existing technologies of endovascular interventions.

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