VASCULAR ANOMALIES: A CHALLENGING DIFFERENTIAL DIAGNOSIS

ANOMALII VASCULARE: UN DIAGNOSTIC DIFERENȚIAL PROVOCATOR

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Rezumat

Anomaliile vasculare sunt tulburări complexe, frecvente care apar la sugari și copii. Clasificarea lor în două grupe majore, tumori și malformații, ajută la înțelegerea principalelor caracteristici ale ambelor tipuri. Cu toate acestea, ambele grupuri conțin mai multe alte tipuri care trebuie, de asemenea să fie diferențiate, iar acest lucru poate fi realizat clinic, imagistic sau prin abordare histopatologică. Tumorile sunt bazate pe proliferarea celulară, în timp ce malformațiile sunt reprezentate de modificări ale vaselor de sânge. În scopul de a diferenția, RMN și MRA sunt resursele de imagistică cele mai utilizate, dar biopsia este forma cea mai precisă pentru diagnostic și se realizează atunci când sunt dubii. În ceea ce privește tratamentul, tumorile sunt în mare parte tratate medical și malformațiile beneficiază de scleroterapie în majoritatea cazurilor. Laserterapia, radioterapia și chirurgia sunt opțiunile luate în considerare în câteva situații specifice.

Acest articol are ca scop să sublinieze cele mai importante caracteristici clinice ale fiecărei anomalii, cele mai utilizate diagnostice imagistice, și nu în ultimul rând, prezintă pe scurt abordarea cardinală de tratament a ambelor grupuri.

Cuvinte cheie: *Anomalii vasculare, diagnostic diferențial.*

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Summary

Vascular anomalies are frequent complex disorders that appear in infants and children. Their classification in two major groups, tumors and malformations, helps understanding the main characteristics of both types. However, both groups contain several other types that need as well to be differentiated, and this can be done by clinical, imaging or histopathological approach. Tumors are based on cellular proliferation, while malformations are represented by aberrant vessels. In order to differentiate MRI and MRA are the most used imaging resources, but the biopsy is the most accurate form of diagnosis and is realized when in doubt. Regarding the treatment, tumors are mostly medically treated and malformations benefit of sclerotherapy in the majority of cases. Lasertherapy, radiotherapy and surgery are options taken into account in a few specific situations.

This review has the aim to underline the most important clinical characteristics of each anomaly, the most used imaging diagnosis and, last but not least, it briefly presents the cardinal treatment approach of both groups.

Key words: *Vascular anomalies, differential diagnosis.*

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Introduction

Vascular anomalies are frequently seen in infants and children, and are of utmost importance to differentiate. Based on their pathological characteristics vascular anomalies are classified in 2 types: tumors and malformations.[1]

Vascular tumors are distinguished by cellular proliferation and vascular malformations by dysplastic vessels, or aberrations in vascular genesis[2, 3]. Both forms are under-classified in several types, taking into account clinical aspects, histopathology, physiopathology, evolution and prognosis. Diagnosing the exact type of anomaly is highly important, especially because of the therapy approach.

Vascular tumors appear solitary, such as in congenital or infantile hemangiomas, tufted hemangiomas, kaposiform hemangioendothelioma; or as part of associated malformations in several types of syndromes, such as Kassabach Meritt syndrome, PHACE syndrome and Lumbar syndrome (PELVIS, SACRAL syndrome).

Vascular malformations are under-classified after their flow characteristics[3] in low-flow malformations, such as venous and lymphatic malformations, Sturge Weber syndrome or Klippel Trenaunay syndrome; and high-flow malformations, such as arteriovenous malformations. Most of them are present at birth, but there are situations in which they are only discovered after a few weeks.[3] They tend to grow more rapidly with trauma, infection or hormonal changes[4], becoming locally or systemically aggressive.[4]

Clinical aspects and diagnosis

1. VASCULAR TUMORS

Congenital hemangiomas

This type of hemangioma is present at birth [5], but can be already found at 12 weeks of gestation.[1,3,6] They grow in utero and at birth they have their final dimension.[3] They can be seen in any area of the body, but have a head-neck predilection, and are frequently seen near joints. [3] Depending on their postnatal involution they are under-classified in RICH (rapidly involuting congenital hemangioma) and NICH (non-involuting congenital hemangioma). [7]

The RICH type is a violaceous tumor, usually devolves by 12-14 months[1, 3, 6] often leaving a cutaneous and subcutaneous tissue defect. The NICH type does not follow the process of involution at all. Moreover, it tends to grow along with the child[1, 3, 6]. Both can be diagnosed as fast-flow lesions by ultrasound or MRI [1], and, bioptically, they are both GLUT-1 negative tumors.[6]

Infantile hemangiomas

Infantile hemangiomas usually develop in the first few weeks after birth, and undergo three stages of evolution. The first one consists of endothelial cell proliferation and is known as the proliferative phase. The phase is followed by an involution phase, and afterwards by an involuted phase.[7] They present themselves as tumors of variable sizes, forms and locations, ranging from 1 to 25 cm dimension[8]. Taking into account their dermal infiltration, they are classified in superficial, deep and mixed infantile hemangiomas[9]. The presence of GLUT-1 (glucose transporter 1) is pathognomonic for this type of anomaly, being present in each stage of evolution, and absent in all other types of vascular tumors or malformations.[1]

In most situations infantile hemangiomas come as solitary tumors, but up to 30% have multiple lesions[1]. The presence of multiple hemangiomas raises the question of other organs involvement, especially hepatic.[1]

MRI is useful in the diagnosis and in appreciating adjacent tissue damage.[10] CT has not proved its utility and angiography is more important in therapy than in diagnosis[8]. Moreover, biopsy puts the diagnosis of GLUT-1 positive tumor.[5]

Tufted hemangiomas. Kaposiform hemangioendothelioma. Kassabach Meritt syndrome

The most common types of hemangioma associated to the Kassabach Meritt syndrome are the kaposiform hemangioendothelioma (KHE) and the tufted angioma[11], [1], [4], but it can come as well with infantile hemangiomas.

The tufted hemangiomas are small round, erythematous lesions built of capillaries and pericytes into nodules or tufts[1], with the aspect of

"cannonballs"[3]. They affect mostly children under 5 years and are localized especially on the neck[3], trunk and the extremities[1]. Bioptically, they are CD31 and CD34 immunopositive, and are thought to be a gentler form of KHE.[3]

The kaposiform hemangioendothelioma comes as a solitary tumor of the extremities, trunk or retroperitoneum in children under 1 year[1]. They are red-purple masses, with infiltration into the subcutaneous tissue, with local aggression and risks of metastasis[1] and a high mortality rate.[5] Histologically, they are, as well, CD31 and CD 34 immunopositive, and they appear as fascicles of spindled endothelial cells.[3]

Trombocytopenia, microangiopathic haemolytic anemia and consumptive coagulopathy associated to hemangiomas are the most important aspects of the Kassabach Meritt syndrome[12]. Even if it's a rare disorder, affecting <1%[12] of infants with vascular tumors, its high-risk morbidity and mortality (30%[12]) underline the urgency of treatment. The localization of hemangiomas is extremely important, because their growth can lead to the compression of vital structures[13] and this needs immediate attention. Histopathologically, the cause of the syndrome is the trapping of thrombocytes in the hemangioma, which raises the risk of bleeding, hemolytic anemia and DIC (disseminated intravascular coagulation). Clinically, the tumor becomes more firm and changes its color.[3]

Diagnosis is put on coagulation tests for the KM syndrome and imaging studies, such as MRI[5], are required to study the tumors.

PHACE syndrome

The syndrome is an association of several malformations of the superior part of the body, with infantile hemangiomas. The acronym comes from **P**osterior fossa, **H**emangiomas of the head and neck, **A**rterial and **C**ardiovascular, **E**ye anomalies[1, 14]. Incidence of cardiovascular anomalies, varies from 21% to 67% in several studies[15, 16], being both the most common extracutaneous disorder[17] and the most poten-tially injurious. The coarctation of the aorta in PHACE syndrome is different from the ordinary congenital one, being characterized by multiple narrowing segments of the transverse aortic arch without left-heart involvement[18]. Vessel anomalies consist

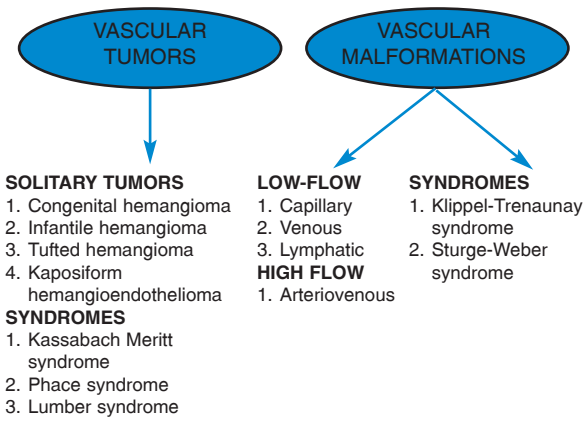

Fig. 1. Classification of vascular anomalies

of dysplastic arteries, and the cerebral involvement is emphasized by dysplastic, narrowed or primitive embryonic carotid-vertebrobasilar connections of the cerebral arteries.[18] Internal carotid artery stenosis has the highest risk for stroke.[17] The eye matter is either primary, or secondary to the cerebro-vascular disorders[17].

The lesions have an up to 18 months [1] proliferative phase and do not devolve completely. Complications are frequent, cutaneous ones imply scarring and ulceration[1] and systemic ones imply seizures, stroke or developmental delay[1] in up to 50% of affected patients.

The diagnosis is multidisciplinary and is based on MRI, an ophthalmologic, neurologic and cardiologic consult.[1, 14]

Lumbar syndrome

The syndrome comprises hemangiomas in the lower part of the body with anomalies of other organs of the area. It is, as well, under-classified in the PELVIC syndrome and the SACRAL syndrome. The PELVIC syndrome is characterized by perineal hemangiomas with genital malformations, lipomyelomeningocele, vesicorenal anomalies or anal anomalies[4]. The SACRAL syndrome associates cutaneous, renal, urologic anomalies, spinal disrafism with lombosacral hemangioma.[4] Rarely, it can be life-threatening, symptoms can vary from very subtle to severe ones.[17] The diagnosis is based on multiple approaches, imaging for both hemangiomas and congenital anomalies.[17]

2. VASCULAR MALFORMATIONS

Capillary malformations

Capillary malformations are the most frequent vascular malformations in children and are composed of numerous dilated capillaries or venules[19, 20]. They appear at birth and involute quickly, facial ones tend to become violaceous and trunk and limb stains tend to fade.[3] They are maculas localized on different sites, mostly on the cephalic extremity.[1] Port-wine stains occur in 0,3% of infants, typically along the branches of the trigeminal nerve.[3] Association to other malformations or vascular anomalies are assigned in reference to the capillary localization. Eyelid capillary malformations raise the question of concurrent opthalmological involvement, e.g. Wyburn Mason syndrome. Trunk or extremity capillary involvement associated to venous or lymphatic malformations suggest a Klippel Trenaunay syndrome[1]. Lumbar capillary malformations implicate possible CNS anomalies[1], and association to congenital CNS malformations raises the question of Sturge Weber syndrome.[3]

Diagnosis comprises clinical evaluation; Doppler ultrasound[20] and MRI/CT scan for the evaluation of associated congenital anomalies. [1]

Sturge-Weber syndrome

The diagnosis of Sturge Weber syndrome is based on three important criteria: 1. Capillary malformations[21], most often a port-wine stain present at birth, seen commonly in the distribution of the ophthalmic branch of the trigeminal nerve[22, 1]. 2. A high-intraocular pressure (glaucoma) ipsilaterally[21, 22] 3. An ipsilateral leptomeningial angiomatose[22] with contralateral focal seizures[21].

These 3 aspects explain the symptoms of the disorder. Cutaneous involvement is, as mentioned, characterized by port-wine stains with flat or elevated border, uni- or bilaterally, in the area of the trigeminal nerve[22]. Some studies suggest that the port-wine stains follow rather the embryonic vasculature of the face, than the trigeminal nerve branches.[21] Glaucoma occurs in up to 60%[22, 23] of affected patients, and underlines the importance of multidisciplinary approach. Retinal detachment and choroidal hemorrhage are possible complications of ocular involvement.[21] CNS symptoms are the most upsetting ones, with contralateral seizures (83%[22]), headaches[1, 22] developmental delay[1], hemiparesis [1] and learning and attention deficit.[22] Seizures are thought to be a consequence of the chronic hypoxemia and decreased perfusion of the cortex[21], and are the most frequent neurologic complication.[23] At birth children appear to be normal, with physiological development in the first months. Symptoms appear later, and are more or less severe depending on the case.[1, 22]

Diagnosis is based on imaging, MRI being of better reliance.[1, 22] Brain atrophy can only be seen after 2-3 years of life[22]. Moreover, calcification of the brain, absence of superficial cortical veins, dilatation of deep veins and choroid plexus malformations can, as well, be noted in this syndrome.[21]

Venous malformations(VM):

Superficial or deep lesions present at birth, represented by bluish, localized or diffuse veins are known as venous malformations.[1] They can be sporadic or intra-familial, with an autosomal –dominant pattern[3, 20] Superficial lesions are at risk for thrombosis[1], phlebolits are often[5, 20] and cause pain and successively functional impotence. Deep lesions are at risk for affecting proximal structures, such as bones or muscles.[1, 24] Coagulopathy is a disorder, that appears especially with large VM[20, 24] and occurs as a result of venous stasis and vein anomalies.[1] Multiple injuries question possible syndromatic disorders, such as Maffucci syndrome or blue rubber bleb nevus syndrome.[3, 25]

Clinical examination, plane radiographs, ultrasound or MRI evaluate the lesion[24]. Blood tests, including coagulation are important to determine risk factors for clotting complications.[1]

Lymphatic malformations

Lymphatic malformations are slow-flow lesions that appear either solitary or in association with other anomalies in a variety of syndromes. The predominant localizations imply the neck, head and the axillae[3, 20]. Cystic lymphatic lesions come as macro- , microcystic or as mixed forms.[26, 27] Mixed forms are the most frequent and comprise lesions of the other two types. Macrocystic lesions are characterized as lymphatic anomalies of more than 2 cm, with or without compression of adjacent structures.

Microcystic lesions are small vesicles with infiltration into fatty tissue or muscles.[1]

Some of the lesions can be diagnosed prenatally, but most of them are visible after 2 years of age.[28] Ultrasound can put the diagnosis, but cannot determine their infiltration into adjacent tissues. MRI is the gold-standard for the diagnosis and for the diagnosis of the local extension.[1, 20, 26, 29]

The rupture of these malformations can lead to bacterial superinfection, situation that imposes antibiotic therapy.[1]

Klippel-Trenaunay syndrome

The syndrome is characterized by the classic triad: 1. Port-wine stains 2. Bone hypertrophy or soft tissue hypertrophy 3. Venous malformations (varicosities)[23 ,30, 31]

The capillary malformations are limited by the midline of the body[30], most often on the same side with the affected limb. They do not disappear, but can involute with time.[30] The bone or soft tissue hypertrophy can affect one or more sites, enlarging the limb or increasing its length[23, 32]. Yet, 80-85% of patients have only one affected limb.[31] Other deformities are, as well possible, such as macro- or syndactyly, dislocation of hip joint or split hand deformity.[30, 31] Varicosities occur most often on the lateral side of the limb[30, 32], the vein of Servelle has been noted in 68-80%[31] of cases. Lympathic malformations can, as well, be associated.[30, 31]

The diagnosis is mostly clinical, but imaging helps characterizing the exact form. X-rays, venography, CT and MRI are useful in describing the exact features of each case. [31, 32]

Arterio-venous malformations

This rare[33] malformations are fast-flow lesions, warm, with a palpable thrill and an audible bruit [1] that can appear in every part of the body, but are mostly seen in head-neck region[33] or the trunk[1]. They are arterial-venous communications without normal capillary beds [3, 20, 24], with an incidence of 40-60% present at birth[3]. They grow more rapidly in puberty, pregnancy, traumatic situations[5, 27] or when surgery is incorrectly applied.[1] Their growth is based on the enlargement of already malformed vessels, and not on cellular proliferation[33]. Histoligically, there are capillaries, thick veins, large arteries and arterioles with random distribution in a fibrous dermis.[3]

Depending on their clinical severity they are classified in 4 stages: 1. Quiescent maculas; 2. High-flow state with palpable thrill and throbbing; 3. Necrosis, ulceration or hemorrhage (even bone deformities); 4.Cardiac decompensation.[3,7]

CT, MRI[33] and MRA are useful for diagnosis of the lesion and its extension, helping therapy approach.[1] Angiography can be used as a diagnostic tool in this kind of malformations.[27]

Treatment

The most important aspect of the therapy of vascular anomalies is whether treatment is necessary or not. In both situations, either tumors or malformations, benignity is more often than malignancy. Localization and subsequent complications are considerable elements to be taken into account in the decision of treating. Each type of tumor or malformation, with its individualized characteristics, has its own therapy indications, but there are specific group-targeted treatment regimens.

Treatment for vascular tumors

Corticotherapy has been a first-line treatment for a long time, using mostly Prednisolone in doses ranging from 2 to 5 mg/kg/day, for 4-8 weeks.[34] If after 4 weeks a hemangioma doesn't improve under steroids, it is considered corticoresistant.[34] Topical steroids, such as Bethamethasone are an option too, and nonetheless they avoid systemic steroids side effects.

Since 2008, Propranolol has been used in all types of hemangioma with good responses and few side effects.[1, 35, 36] Doses range from 0,5 up to 2 mg/kg/day[10]. Topical beta-blockers are also an option; moreover they raise the compliance and avoid systemic adverse reactions.[37]

Vincristine, an antineoplastic agent, with antiangiogenic effects [34] is used in corticoresistant and beta-blocker resistant hemangiomas, or in case of contraindications for other treatment options .[1]

Lasertherapy is a useful method for small, superficial vascular tumors or for residual teleangiectasis after involution of hemangiomas.[1, 25, 37] Embolization can be used in

hepatic hemangiomas, but need special attention due to its risks, like hepatic rupture or heart-failure.[38]

Surgery is indicated in situations where tumors cause dysfunction, cosmetic impairment or when they are medication-resistant.[39]

Treatment for vascular malformations

- Treatment for low-flow vascular malformations

In most situations sclerotherapy is the first option, and is used predominantly in venous [40] and macrocystic lymphatic malformations, complicated with recurrent swelling or phlebolits, functional impairment, deformity or infection.[26, 40]. Sclerosant options are based on etiology, venous malformations are mostly treated with ethanol [20], while lymphatic ones with Doxycycline [28]. Complications of sclerotherapy are caused frequently by the extravasation of sclerosant; ulceration, blistering are seen often, while nerve injury and compartment syndrome are less frequent[24, 26, 40]. Hemoglobinuria comes with large VM, and is transitory[24, 26]. Laser photocoagulation, resection or multiple-therapy approaches are other choices of treatment.[24]

Surgery is a second option in treating low-flow malformations, and it is used in cases where endovascular therapy, like sclerotherapy, has no results.[39]

- Treatment for high-flow vascular malformations

Embolization is the first option for treating such malformative disorders and is individualized depending on the localization of the malformation.[33] It is applied either transarterially or transvenously[24] with several types of sclerosants[33].

Surgery is another choice[39] and is indicated in 2 main situations, one in which lesions are resectable and another one in which embolization has no chance of curing.[33] Combination of these two therapies is used successfully in more complicated types of AVM[33, 39] .

Monoclonal antibodies, such as Bevacizumab, have been studied as AVM therapy and were shown to be efficient.[35] Important side effects are thrombembolic events, parasthesias and bleeding.[35]

Conclusions

To conclude, the differential diagnosis of vascular anomalies is extremely important for the medical approach. Complications, prognosis and treatment differ in each situation, and it is essential to handle the cases based on their specific features.

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Conflict de interese
NEDECLARATE

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NONE DECLARED

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