REVIEW

Updated classification and therapy of vascular malformations in pediatric patients

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ABSTRACT
Vascular malformations (VMs) comprise a diverse group of diagnoses. They are classified by the type of vessel involved, including capillaries, veins, arteries, lymphatic vessels, or combinations of these. Complex VMs, although benign, can impair vital structures, cause deformations, or even threaten the child's life. Although multimodal treatment of VMs in children with disease include a wide variety of options such as observation, laser therapy, sclerotherapy, surgical resection, radiofrequency ablation, and medical therapy, the management of VMs necessitates a multifocal and multidisciplinary method with the patient's quality of life as the priority.

KEYWORDS
Children, Therapy, Vascular malformations

INTRODUCTION

Vascular malformations (VMs) are a heterogeneous group of disorders that result from alterations in blood and lymphatic channels and can involve multiple systems and organs. The vast majority of VMs follow a benign course, however, complex VMs can cause severe complications and result in disfigurement, chronic pain, thrombosis, organ dysfunction, and even death.[1] In 1982, Mulliken and Glowacki[2] proposed a biologic classification system to describe two types of vascular anomalies: hemangiomas and VMs. The most recent classification system adopted by the International Society for the Study of Vascular Anomalies in 2014, defines VMs in more detail, proposes more causal genes of vascular anomalies, and includes more complex syndromes with other abnormalities, as illustrated in Table 1.[3]

Compared with vascular tumors, VMs are anomalies involving malformed vessels without endothelial cell proliferation and occur during the morphological development of the vascular system. They are always present at birth; some become obvious later. Some VMs are stable, and others can be exacerbated by trauma, infection, or fluctuation of hormonal levels as the child growth. The most recent classification divided VMs into capillary malformations, venous malformations, arteries malformations, lymphatic malformations, and combinations of these. Typically, the diagnosis of VMs is made clinically. However, noninvasive imaging modalities such as ultrasonography, magnetic resonance imaging, and computed tomography, and sometimes even histological methods, may be needed to determine the type and extent of the lesions in patients with atypical disorders.[4] Radiological imaging is useful to evaluate the

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TABLE 1 Classification of vascular anomalies

Vascular Tumors	Vascular Malformations		
	Simple	Combined	Of major named vessels
Benign vascular tumors	Capillary malformations	CVM	Klippel-Trenaunay syndrome
Infantile hemangioma	Lymphatic malformations	CLM	Parkes Weber syndrome
Congenital hemangioma	Venous malformations	CAVM	Servelle-Martorell syndrome
Tufted angioma	Arteriovenous malformations	LVM	Sturge-Weber syndrome
Spindle-cell hemangioma	Arteriovenous fistula	CLVM	Limb CM + congenital non-progressive limb hypertrophy
Epithelioid hemangioma		CLAVM	Maffucci syndrome
Pyogenic granuloma		CVAVM	Macrocephaly - CM (M-CM / MCAP)
Locally aggressive vascular tumors		CLVAVM	Microcephaly - CM (MICCAP)
Kaposiform hemangioendothelioma		others	CLOVES syndrome
Retiform hemangioendothelioma			Proteus syndrome
PILA, Dabska tumor			Bannayan-Riley-Ruvalcaba sd
Composite hemangioendothelioma			others
Kaposi sarcoma			
Malignant vascular tumors			
Angiosarcoma			
Epithelioid hemangioendothelioma			

CVM: capillary venous malformation; CLM: capillary lymphatic malformation; CAVM: capillary arteriovenous malformation; LVM: lymphatic venous malformation; CLVM: capillary lymphatic venous malformation; CLAVM: capillary lymphatic arteriovenous malformation; CVAVM: capillary venous arteriovenous malformation; CLVAVM: capillary lymphatic venous arteriovenous malformation.

extent of large lesions and their relationships to adjacent structures before treatment; such imaging can also reflect the histopathology of the VMs, which could differentiate hemangiomas from malformations.[5] Histologically, VMs show slow endothelial turnover and are negative for glucose transporter-1 protein (GLUT-1), whereas vascular tumors (especially hemangiomas) show endothelial hyperplasia and are GLUT-1-positive.[6]

CAPILLARY MALFORMATIONS

Capillary malformations are present at birth and persist throughout life. A port-wine stain (PWS) is one of the most common types of capillary malformations. Most capillary malformations are cosmetic problems, but unlike nevus simplex, a PWS does not fade in early ages of childhood; instead the skin thickens and raised gradually with multiple nodular fibrovascular lesions due to underlying soft tissue hypertrophy during puberty. Sturge-Weber syndrome (SWS) typically involves one or more trigeminal distributions (V1, V2, V3), and it often extends unilaterally or bilaterally over more of the face and neck. Periocular cutaneous lesions of SWS, especially those involving the V1 region, may be associated with glaucoma in 30% to 50% of patients.[7-9] In SWS, impairment of the meningeal microvasculature affects the normal development of the brain,[10] which is visible on magnetic resonance imaging soon after birth. Neurologic consequences can include contralateral seizures, neurological deficits, and hemiparesis or hemiplegia.[11]

Pulsed dye laser (PDL) therapy, which is based on selective photothermolysis of the affected vessels, is the most commonly used laser therapy for capillary malformations.[12] This treatment is also frequently effective for PWS, more so for lesions on the face and trunk than for those involving the distal extremities because of the potential to decrease potential psychosocial distress and avoid lesion thickening. Modified PDL therapy using a longer wavelength (595 or 585 nm), increased pulse duration (0.45–20 ms), higher fluence (8–15 J/cm^2), and cryogen spray cooling can improve fading and minimize adverse effects.[13] Because the dermal thickness increases with age and the adult dermis allows for less optimal targeting of vessels, more improved fading is visualized and earlier treatment is begun during childhood.[14] Frequency-doubled neodymium-doped yttrium aluminum garnet (Nd:YAG) and potassium titanyl phosphate lasers producing 532 nm green light are also used to treat capillary malformations.[15] Because of the limited penetration depth due to the shorter wavelength, the use of such laser therapy is limited to the treatment of superficial vascular lesions, and the most common adverse effect is hyperpigmentation. Nd:YAG laser with a wavelength of 1064 nm are always used to treat thicker lesions, but the rates of the pigmentary changes and scarring are higher than those in PDL therapy.[16] Photodynamic therapy (PDT) is an advanced treatment option for pediatric PWS. One study of 3 to 10 years old patients with PWS showed that the rate of an excellent response in the PDT group was significantly higher than that in the PDL group (25.0%

vs. 10.9%, respectively).[17] As a chemical photosensitizer typically administered via intravenous injection, PDT is chosen as second-line therapy. The second-generation intense pulsed light therapy produces non-coherent, broadband light with improved selectivity and has been increasingly used for the treatment of capillary malformations.[18] A recent study demonstrated that PDL treatment in combination with topical sirolimus for PWS of patients with SWS is more effective than laser treatment alone.[19] The timing and patient selection are important considerations for surgical therapy, which is also an important treatment option for some patients, especially those with slow-flow VMs. Surgical treatment include direct suturing, partial skin flaps, skin grafting, and tissue expansion.[20]

VENOUS MALFORMATIONS

Venous malformations are developmental abnormalities of veins, which are thin-walled, dilated channels of variable size, and are characterized by mural thickness with a normal endothelial lining and deficient smooth muscle. Venous malformations may infiltrate any structure of the body including the skin, mucous membrane, bones, joints, and even viscera.[21] Affected patients experience swelling or pain. Venous malformations are solitary in 90% of patients, and multifocal forms should raise suspicion for hereditary-based syndromes (eg. familial venous malformations, cutaneous-mucosal, blue rubber bleb nevus syndrome, glomuvenous malformation, and cerebral cavernous malformation).

The first-line treatment of venous malformations is sclerotherapy. Although absolute ethanol is the most efficient sclerosing agent, the concentration of the sclerosant is important to the success of the sclerotherapy. Foam is more effective than liquid in displacing blood from the abnormal veins and prolonging contact time with the vascular wall.[22] Intervention treatment should be performed under ultrasound guidance, which should reduce radiation exposure for patients undergoing repeated treatments.[23] Surgical excision is particularly effective for smaller, more well-circumscribed lesions. A long-wavelength laser (eg. long-pulsed Nd:YAG laser), may be used for superficial lesions. Low-molecular-weight heparin treatment is also useful for venous malformations in patients with elevated D-dimer levels, or before and after surgical procedure to prevent phlebolith formation and decrease pain. Blue rubber bleb nevus syndrome (BRBNS), also eponymously known as “bean syndrome”, is a rare venous malformations that is commonly present at birth or in early childhood. The syndrome comprises multifocal lesions affecting the skin (93%), viscera and gastrointestinal tract (76%), or central nervous system (13%).[24] Patients with BRBNS experience pain and sometimes spontaneous rupture and hemorrhage leading to intralesional consumptive coagulopathy with low fibrinogen and high D-dimer levels.[25] Several treatment can be modalities utilized, such as corticosteroids, interferon-α, thalidomide, sclerotherapy, and surgical interventions. Mammalian target of rapamycin (mTOR) is a serine/threonine kinase regulated by phosphoinositide-3-kinase. When signals are transferred through Akt/protein kinase B to mTOR, protein synthesis is activated to proliferate cells and increase angiogenesis.[26] Sirolimus (also known as rapamycin) is a specific inhibitor of mTOR that is commonly used to prevent graft rejection after organ transplantation. In recent years, sirolimus has shown a favorable therapeutic effect on complex VMs.[27] Salloum et al[28] showed that all four children with BRBNS who received sirolimus treatment showed clinical improvement. The adverse effects of the drug in the cohort only consisted of mucositis in three patients and neutropenia in one patient. In our clinical experience, the most common dosage of sirolimus for BRBNS is 1.5 to 2.0 mg/m^2 per day, the therapeutic range of the drug is 5 to 10 ng/mL based on the usual effective range in the treatment of patients undergoing kidney transplantation, and the most common adverse effects are grade I to II mucositis and hematological (neutropenia) and metabolic (hypercholesterolemia) changes. Complex venous malformations require a multidisciplinary approach to management, usually including a combination of interventional radiology, physiotherapy, laser therapy, hematologic therapy, mTOR administration and pediatric surgical resection.[29]

LYMPHATIC MALFORMATIONS

Due to hyperplasia of the lymphatic network, lymphatic malformations are slow-flow vascular anomalies characterized by dilated lymphatic channels and cysts. The most common lymphatic malformations are subdivided into macrocytic, microcytic, and mixed cystic lymphatic malformations.[30] Lymphatic malformations are associated with various syndromes, and the genetic basis and molecular biology of these diseases have been reported; for example, they may be associated with Proteus syndrome (AKT1),[31] Klippel-Trènaunay-Weber syndrome and CLOVES syndrome (PIK3CA).[32]

In patients with lymphatic malformations, small lesions can be managed with a conservative “watch-and-wait” approach. If intralesional bleeding or infection causes sudden enlargement of lymphatic malformations, then nonsteroidal anti-inflammatory drugs or corticosteroids and antibiotics should be used. Sclerotherapy is the mainstay of treatment. Microcytic and mixed cystic lymphatic malformations are treated by intralesional injection of sclerofibrosing agents, such as bleomycin, pingyangmycin, OK-423 (a killed strain of group A *Streptococcus pyogenes*), doxycycline, or absolute ethanol.[33,34] Aspirating the cystic fluid before injecting the sclerosant is also helpful for diagnosis. Carbon dioxide

lasers, continuous-wave Nd:YAG lasers, fractionated erbium lasers, and pulsed dye lasers have been described as treatments of cutaneous and mucosal lymphatic malformations.[35-37] Successful use of radiofrequency ablation, also known as coblation, has been reported to reduce mucosal lymphangiomatous lesions.[38] Lymphatic malformations that cause airway compromise require primary emergent surgical intervention, including endoscopic techniques, to fully evaluate the extent of the lesions.[39] Sildenafil and propranolol are two new oral therapies that are reportedly effectivein decreasing the size of lymphatic malformations and alleviating associated symptoms, although not all patients respond to the treatment.[40-42] In a single-center study of sirolimus therapy for VMs in 2016, six pediatric patients (4 with capillary lymphaticovenous malformations, 1 with a lymphaticovenous malformation, and 1 with a venous malformation) were treated with sirolimus after they had undergone various unsuccessful treatments. The patients' age at the beginning of the treatment ranged from 3 years 8 months to 13 years, and the mean duration of the treatment was 13 months. Five of the six patients showed clinical and radiological responses to the drug, and no increase in the incidence of infection or treatment-related adverse effects was seen.[43] Some new surgical techniques have emerged for the treatment of lymphatic malformations. Ultrasound-guided liposuction was shown to reduce the limb size in patients with enlargement of the extremities due to microcystic lymphatic malformations.[44]

ARTERIOVENOUS MALFORMATIONS

Arteriovenous malformations form when veins are connected to arteries without an intervening capillary bed and are often mistaken for a hemangioma or PWS in children. These are fast-flow VMs, in which the blood flows directly from a high-pressure system to a low-pressure system.[45] Arteriovenous malformations can be categorized into four stages with increasing progression, each of which is associated with various clinical presentations, including heaviness, a pulsating mass, the sensation of heat, pain, intermittent bleeding, ulceration, and necrosis. Arteriovenous malformations may occur independently or as part of a syndrome, such as Bannayan-Riley-Ruvalcaba syndrome, Parkes-Weber syndrome, CLOVES syndrome, and Cobb syndrome.

In childhood, arteriovenous malformations are often clinically inconspicuous, but most are potentially harmful to the patients' health. The clinical management of pediatric arteriovenous malformations requires a detailed examination and long-term clinical observation. The most common treatments are surgical interventions and intravascular embolotherapy/sclerotherapy, and a combination of both may sometimes be effective especially in children.[46]

CONCLUSIONS

The goal of VM management and treatment is to maintain functionality, control associated symptoms, and preserve aesthetic integrity. Severe life-threatening functional impairment mandates early intervention. Therefore, to ensure optimal treatment, a multidisciplinary team including dermatologists, plastic surgeons, pediatricians, maxillofacial surgeons, interventional physicians, and psychologists is necessary.[47]

CONFLICT OF INTEREST

We declare that we have no conflict of interest in connection with the work submitted.

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