Updated classification and therapy of vascular malformations in pediatric patients

Bin Zhang | Lin Ma

Department of Dermatology, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing, China

Correspondence
Lin Ma, Department of Dermatology, Beijing Children’s Hospital, Capital Medical University, National Center for Children’s Health, Beijing, China.
Email: bch_maleen@aliyun.com.

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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. In 1982, Mulliken and Glowacki 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.

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. Radiological imaging is useful to evaluate the

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

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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. 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.

### 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. In SWS, impairment of the meningeal microvasculature affects the normal development of the brain, which is visible on magnetic resonance imaging soon after birth. Neurologic consequences can include contralateral seizures, neurological deficits, and hemiparesis or hemiplegia.

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. 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/cm²), and cryogen spray cooling can improve fading and minimize adverse effects.

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. Frequency-doubled neodymium-doped yttrium aluminium garnet (Nd:YAG) and potassium titanyl phosphate lasers producing 532 nm green light are also used to treat capillary malformations. 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. 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%
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. 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. Intervention treatment should be performed under ultrasound guidance, which should reduce radiation exposure for patients undergoing repeated treatments. 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 phlebothrombosis 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%). Patients with BRBNS experience pain and sometimes spontaneous rupture and hemorrhage leading to intralesional consumptive coagulopathy with low fibrinogen and high D-dimer levels. 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. 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. Salloum et al 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/m² 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.

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 macrocystic, microcystic, and mixed cystic lymphatic malformations. 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), Klippel-Trénaunay-Weber syndrome and CLOVES syndrome (PIK3CA).

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. Microcystic and mixed cystic lymphatic malformations are treated by intralesional injection of sclerofibrosing agents, such as bleomycin, plyingmycin, OK-423 (a killed strain of group A Streptococcus pyogenes), doxycycline, or absolute ethanol. 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.\textsuperscript{35–37} Successful use of radiofrequency ablation, also known as coblation, has been reported to reduce mucosal lymphangiomatous lesions.\textsuperscript{38} Lymphatic malformations that cause airway compromise require primary emergent surgical intervention, including endoscopic techniques, to fully evaluate the extent of the lesions.\textsuperscript{39} Sildenafil and propranolol are two new oral therapies that are reportedly effective in decreasing the size of lymphatic malformations and alleviating associated symptoms, although not all patients respond to the treatment.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{47}

**CONFLICT OF INTEREST**

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

**REFERENCES**

1. Azizkhan RG. Complex vascular anomalies. Pediatr Surg Int. 2013;29:1023-1038.
2. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg. 1982;69:412-422.
3. ISSVA, Classification of Vascular Anomalies 2014 International Society for the Study of Vascular Anomalies Available at "issva.org/classification" Accessed [2017-03-20], http://issva.org/classification.
4. Kolilpara R, Odhav A, Rentas KE, Rivard DC, Lowe LH, Dinnene L. Lymphatic anomalies in pediatric patients: updated classification, imaging, and therapy. Radiol Clin North Am. 2013;51:659-672.
5. Dubois J, Garel L. Imaging and therapeutic approach of hemangiomas and vascular malformations in the pediatric age group. Pediatr Radiol. 1999;29:879-893.
6. North PE, Waner M, Mizeracki A, Mihm MC Jr. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol. 2000;31:11-22.
7. Jagtap S, Srinivas G, Harsha KJ, Radhakrishnan N, Radhakrishnan A. Sturge-Weber syndrome: clinical spectrum, disease course, and outcome of 30 patients. J Child Neurol. 2013;28:725-731.
8. Sinawat S, Auvichayapat N, Auvichayapat P, Yospaiboon Y, Sinawat S. 12-year retrospective study of Sturge-Weber syndrome and literature review. J Med Assoc Thai. 2014;97:742-750.
9. Vidaurri-de la Cruz H, Tamayo-Sánchez L, Durán-McKinster C, Orozco-Covarrubias Mde L, Ruiz-Maldonado R. Phakomatosis pigmentovascularis II A and II B: clinical findings in 24 patients. J Dermatol. 2003;30:381-388.
10. Portilla P1, Husson B, Lasjaunias P, Landrieu P. Sturge-Weber disease with repercussion on the prenatal development of the cerebral hemisphere. AJNR Am J Neuroradiol. 2002;23:490-492.
11. Comi AM. Sturge-Weber syndrome. Handb Clin Neurol. 2015;132:157-168.
12. Brightman LA, Geronemus RG, Reddy KK. Laser treatment of port-wine stains. Clin Cosmet Investig Dermatol. 2015;12:27-33.
13. Chen JK, Ghasri P, Aguilar G, et al. An overview of clinical and experimental treatment modalities for port wine stains. J...
14. Astner S, Anderson RR. Treating vascular lesions. *Dermatol Ther*. 2005;18:267-281.

15. Becher GL, Cameron H, Moseley H. Treatment of superficial vascular lesions with the KTP 532-nm laser: experience with 647 patients. *Lasers Med Sci*. 2014;29:267-271.

16. McGill DJ, MacLaren W, Mackay IR. A direct comparison of pulsed dye, alexandrite, KTP and Nd:YAG lasers and IPL in patients with previously treated capillary malformations. *Lasers Surg Med*. 2008;40:390-398.

17. Zhang B, Zhang TH, Huang Z, Li Q, Yuan KH, Hu ZQ. Comparison of pulsed dye laser (PDL) and photodynamic therapy (PDT) for treatment of facial port-wine stain (PWS) birthmarks in pediatric patients. *Photodiagnosis Photodyn Ther*. 2014;11:491-497.

18. Crabb M, Chan WO, Taranath D, Huilig SC. Intense pulsed light therapy (IPL) induced iritis following treatment for a medial canthal capillary malformation. *Australas J Dermatol*. 2014;55:289-291.

19. Marquès L, Núñez-Córdoba JM, Aguado L, et al. Topical rapamycin combined with pulsed dye laser in the treatment of capillary vascular malformations in Sturge-Weber syndrome: phase II, randomized, double-blind, intraindividual placebo-controlled clinical trial. *J Am Acad Dermatol*. 2015;72:151-158.

20. Kang GB, Bae YC, Nam SB, Bae SH, Sung JY. The usefulness of Surgical Treatment in Slow-Flow Vascular Malformation Patients. *Arch Plast Surg*. 2017;44:301-307.

21. McRae MY, Adams S, Pereira J, Parsi K, Wargon O. Venous malformations: Clinical course and management of vascular birthmark clinic cases. *Australas J Dermatol*. 2013;54:22-30.

22. Burrows PE, Mason KP. Percutaneous treatment of low flow vascular malformations. *J Vasc Interv Radiol*. 2004;15:431-445.

23. Lee BB, Bergan J, Gioviczki P, et al. Diagnosis and treatment of venous malformations. Consensus document of the International Union of Phlebology (IUP)-2009. *Int Angiol*. 2009;28:434-451.

24. Jin XL, Wang ZH, Xiao XB, Huang LS, Zhao XY. Blue rubber bleb nevus syndrome: a case report and literature review. *World J Gastroenterol*. 2014;20:17254-17259.

25. Choi KK, Kim JY, Kim MJ, et al. Radical resection of intestinal blue rubber bleb nevus syndrome. *J Korean Surg Soc*. 2012;83:316-320.

26. Hamlil AM, Wentzel M, Gupta A, et al. Sclerotherapy for the treatment of complicated vascular anomalies in children. *Pediatr Blood Cancer*. 2011;57:1018-1024.

27. Lackner H, Karastaneva A, Schwinger W, et al. Sclerotherapy for the treatment of children with various complicated vascular anomalies. *Eur J Pediatr*. 2015;174:1579-1584.

28. Salloum R, Fox CE, Alvarez-Allende CR, et al. Response of Blue Rubber Bleb Nevus syndrome to sirolimus treatment. *Pediatr Blood Cancer*. 2016;63:1911-1914.

29. Lee BB, Baumgartner I, Berlien P, et al. Diagnosis and Treatment of Venous Malformations. Consensus Document of the International Union of Phlebology (IUP): updated 2013. *Int Angiol*. 2015;34:97-149.

30. Defnet AM, Bagrodia N1, Hernandez SL, Gwilliam N, kandel JJ. Pediatric lymphatic malformations: evolving understanding and therapeutic options. *Pediatr Surg Int*. 2016;32:425-433.

31. Lindhurst MJ, Sapp JC, Teer JF, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. *N Engl J Med*. 2011;365:611-619.

32. Kurek KC, Luks VL, Ayturk UM, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. *Am J Hum Genet*. 2012;90:1108-1115.

33. Farnoosh S, Don D, Koempen J, Panosian A, Anselmo D, Stanley P. Efficacy of doxycycline and sodium tetracycl sulfate sclerotherapy in pediatric head and neck lymphatic malformations. *Int J Pediatr Otorhinolaryngol*. 2015;79:883-887.

34. Leung M, Leung L, Fung D, et al. Management of the low-flow head and neck vascular malformations in children: the sclerotherapy protocol. *Eur J Pediatr Surg*. 2014;24:97-101.

35. França K, Chacon A, Ledon J, Savas J, Izkovic J, Nouri K. Lasers for cutaneous congenital vascular lesions: a comprehensive overview and update. *Lasers Med Sci*. 2013;28:1197-1204.

36. Shumaker PR, Dela Rosa KM, Krakowski AC. Treatment of lymphangioma circumscriptum using fractional carbon dioxide laser ablation. *Pediatr Dermatol*. 2013;30:584-586.

37. Torezan LA, Careta MF, Osorio N. Intra-oral lymphangioma successfully treated using fractional carbon dioxide laser. *Dermatol Surg*. 2013;39:816-817.

38. Colletti G, Valassina D, Ber tossi D, et al. Contemporary management of vascular malformations. *J Oral Maxillofac Surg*. 2014;72:510-528.

39. Eivazi B, Teymoortash A, Wiegand S, et al. Intralosomal endoscopy of advanced lymphatic malformations of the head and neck: a new diagnostic approach and a potential therapeutic tool. *Arch Otolaryngol Head Neck Surg*. 2010;136:790-795.

40. Swetman GL, Berk DR, Vasana wala SS, Feinstein JA, Lane AT, Bruckner AL. Sildenafil for severe lymphatic malformations. *N Engl J Med*. 2012;366:384-386.

41. Ozeki M, Kanda K, Kawamoto N, et al. Propranolol as an alternative treatment option for pediatric lymphatic malformation. *Tohoku J Exp Med*. 2013;229:61-66.

42. Akyüz C, Ataş E, Varan A. Treatment of a tongue lymphangioma with sirolimus after failure of surgical resection and propranolol. *Pediatr Blood Cancer*. 2014;61:931-932.

43. Yesil S, Tanyildiz HG, Bozkurt C, Cakmakci E, Sahin G. Single-center experience with sirolimus therapy for vascular malformations. *Pediatr Hematol Oncol*. 2016;33:219-225.

44. Francis CS, Rommer EA, Kane JT, Iwata K, Panossian A. Limited-incision surgical debulking of lymphatic malformations using ultrasound-assisted liposuction. *Plast Reconstr Surg*. 2012;130:920-922.

45. Galich SP, Dabizha AIu, Gindich OA, et al. Combined treatment of arteriovenous malformations of the head and neck. *Angiol Sosud Khir*. 2015;21:170-177.

46. Johnson CM, Navarro OM. Clinical and sonographic features of pediatric soft-tissue vascular anomalies part 2: vascular malformations. *Pediatr Radiol*. 2017;47:1196-1208.

47. Balakrishnan K, Edwards TC, Perkins JA. Functional and symptom impacts of pediatric head and neck lymphatic malformations. *Pediatr Invest*. 2018;2:119-123. https://doi.org/10.1002/ped.12043