Diagnosis and treatment of pediatric vascular anomalies

BY PATRICIA BURROWS, MD, AND DAWN SIEGEL, MD

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Vascular anomalies are a diverse group of related conditions that include vascular tumors (hemangiomas) and vascular malformations (capillary malformations, venous malformations, lymphatic malformations and arteriovenous malformations). In the past decade or so, research has revealed the genetic or molecular basis for some of these lesions. We now know that a number of hereditary vascular malformations are caused by specific mutations (e.g., hereditary hemorrhagic telangiectasia, capillary malformation-arteriovenous malformation and CLOVES syndrome), and somatic mutations are either known or suspected to cause aberrant vascular development leading to other vascular malformations.

In general, hemangiomas are treated pharmacologically, typically monitored by our pediatric dermatologists. Symptomatic vascular malformations require a more mechanical approach, often managed by interventional radiology procedures, surgical removal or a combination. Extensive research suggests that patients with these complex vascular lesions do best when managed by an experienced multidisciplinary vascular anomalies team. The Birthmarks and Vascular Anomalies Program at Children’s provides a comprehensive multidisciplinary approach...
for these patients. We offer specialized diagnostic and therapeutic procedures, including pathology, diagnostic imaging, all of the surgical specialties, dermatology, interventional radiology, pharmacotherapy (hematology/oncology), laser treatment and compression/lymphedema treatment.

Patients with complex conditions are often discussed and examined at the multidisciplinary patient conference and clinic, where various subspecialists work together to formulate a treatment plan. Other, less complicated patients are evaluated and treated in the appropriate sub-specialty clinics, including the dermatology, plastic surgery, otolaryngology and interventional radiology clinics.

The clinical characteristics of vascular malformations
Vascular malformations are generally present at birth, although they may not become clinically evident until early childhood. They generally grow in proportion to the child and are present throughout life. Alternatively, infantile hemangiomas proliferate in infancy, then slowly undergo involution over several years. The diagnosis of vascular malformation is based both on the clinical appearance and behavior and the imaging features.

Capillary malformations appear at birth as a flat pink patch and can occur anywhere on the body, although the face and limbs are most common (Figure 1). Most capillary malformations, also called port wine stains, will thicken and darken throughout life. A subset of capillary malformations on the central face (nevus simplex) will fade during early childhood. When the CM is located in the trigeminal distribution on the face, there is a risk for seizures and leptomeningeal vascular anomalies (Sturge-Weber syndrome).

Capillary malformation-arteriovenous malformation syndrome is an autosomal dominant condition caused by mutations in the RASA1 gene. In this condition, the patient presents with multiple small, round to oval pink-tan capillary malformations that increase in number over time. These can sometimes be confused with café au lait macules. Increased flow can be detected with a hand-held Doppler. These patients are at risk for Vein of Galen aneurysm and intracranial arteriovenous fistulas as well as arteriovenous malformations and at other sites. Researchers at Children’s are working to determine the molecular mechanism responsible for the various manifestations.

Venous malformations are slow-flow lesions in which the affected veins have abnormal wall structure and gradually expand. They can be localized or diffuse, involving any anatomical area or tissue plane. In the skin they appear as blue ectatic venous channels (Figure 2). These malformations can expand when the patient places the affected area in a dependent position, and they can develop microthrombi and phleboliths, which can cause pain. This cycle of thrombosis and thrombolysis leads to elevated D-dimer levels and low fibrinogen. Venous malformations become progressively symptomatic as they expand. In the head and neck, they lead to deformity or airway obstruction, and in the lower limbs, they often cause pain with activity and standing. VMs of the joint can be complicated by chronic hemarthrosis, leading to degenerative joint disease. MR imaging shows these as T2 hyperintense, slowly enhancing lesions containing clots or phleboliths.
Lymphatic malformations are slow-flow vascular malformations made up of vesicles or cysts filled with lymphatic fluid. They can be localized to one area, such as the neck, or diffusely involve an entire limb or the thorax. There are three forms of LM: microcystic, macrocystic and malformations of the conducting lymphatic channels (e.g. lymphedema). The microcystic lesions (also known as lymphangioma circumscriptum) may involve the skin as a plaque with overlying superficial vesicles, which easily burst and drain clear or hemorrhagic fluid, or sometimes chyle (Figure 3). Macrocystic lymphatic malformations (previously known as cystic hygromas) are soft multilobular subcutaneous masses, often with a blue hue caused by intralesional bleeding.

Arteriovenous malformations occur when there is a direct connection between arteries and veins leading to a venous hypertension, swelling, pain and tissue destruction, with the potential for life-threatening bleeding and cardiac volume overload. They appear as a pink or red stain with an underlying subcutaneous component and are warm or hot to the touch. They may feel pulsatile. A palpable thrill indicates a significant shunt. AVMs are usually progressive as defined by the Schobinger staging system (Table 1).

Table 1: The Schobinger staging system for arteriovenous malformations

<table>
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<tr>
<th>Stage I: Quiescent</th>
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<tr>
<td>Stage II: Progressive phase</td>
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<td>Stage III: Destructive phase with pain, bleeding and ulceration</td>
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<td>Stage IV: Cardiac decompensation and congestive heart failure</td>
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Current interventional radiology treatment for vascular malformations

At Children’s, we initially assess patients either in the multidisciplinary vascular anomalies clinic or the IR clinic using physical examination and diagnostic imaging studies, such as MRI. Clinic ultrasound provides an extension of the physical examination to assess flow characteristics. We explain the diagnosis in detail to the patient and family and discuss potential treatment, if indicated.

Children’s has truly state-of-the-art IR procedure suites, fully staffed with pediatric anesthesiologists, nurses and technologists. Procedures performed for vascular malformations include:

- diagnostic angiography
- venography and lymphangiography
- embolization of arteriovenous malformations
- sclerotherapy of lymphatic and venous malformations
- endovenous, interstitial and surface laser treatments

Our IR physicians aim to provide the most effective treatment available with the smallest number of procedures and the lowest risk. For example, sclerotherapy is a procedure in which sclerosing solutions are injected percutaneously, using ultrasound and fluoroscopic guidance, into low-flow
malformations such as VM and LM, to induce shrinkage and fibrosis. Simple macrocystic LMs respond extremely well to sclerotherapy using doxycycline or OK-432, with complete obliteration in approximately 80 percent of patients, usually in one or two outpatient procedures. OK-432 (Picibanil) is an investigational agent that can be administered in selected patients, under the direction of Robert Chun, MD, in the Otolaryngology department. Complex or diffuse LMs are more difficult to treat, but sclerotherapy often results in improved symptoms and reduced rates of cellulitis.

For patients with VMs, sclerotherapy is highly effective in improving symptoms. Optimal treatment of an extensive lesion typically involves repeated sessions every few months until the abnormal channels are effectively closed. In the past, absolute ethanol was used for sclerotherapy of VMs. Ethanol is an effective sclerosant, but it causes significant swelling and discomfort during recovery, with risk of injury to skin and peripheral nerves. Techniques developed by Dr. Burrows incorporate adjunctive methods such as endovenous laser therapy or injection of tissue adhesive to induce outflow occlusion in venous malformations, and then injecting a combination of milder sclerosing agents with different, symbiotic mechanisms of action. We feel that these techniques result in shrinkage of the VMs with fewer procedures, fewer complications and an easier recovery (due to decreased swelling). Intralesional bleomycin injection is effective in areas where swelling must be avoided, such as the orbit or airway.

Arteriovenous malformations are notoriously difficult to treat due to their tendency to recruit new blood supply after partial treatment and to progress, often causing tissue destruction, bleeding and other complications. Previously, patients with AVM were often observed without treatment until they became extremely symptomatic, and then treated with preoperative embolization and surgery. It is now known that embolization of feeding arteries using coils or temporary embolic agents, as well as partial resection, are ineffective in slowing the progression of AVMs. The goal of primary embolization is to cure or palliate the AVM, rather than to decrease blood flow to the lesion. This is done by meticulously embolizing only the nidus, or arteriovenous connections, using a permanent ablative material such as absolute ethanol. In selected patients, staged ethanol embolization can result in complete occlusion of the AVM in about 40 percent of patients. In the future, we expect that pharmacotherapy will become more important as a primary treatment or in conjunction with endovascular treatment. At Children’s, the IR department is collaborating with Ramani Ramchandran, PhD, director of Vascular Biology at the Medical College of Wisconsin, to identify biomarkers and potential drug treatments for AVMs and other vascular malformations.

Neonatal AVMs present a special problem, as they are often associated with life-threatening cardiac failure. Endovascular treatment is hampered by the small size of the patient’s blood vessels, limited fluid capacity and physiological fragility. Fortunately, microcatheters and vascular occlusion devices appropriate for use in these small patients are improving rapidly. New micro-ballon occlusion catheters facilitate flow control, allowing accurate deposition of liquid embolic agents. Detachable micro-coils are now available in a huge range of diameters and lengths, approved and suitable for treating infants with Vein of Galen, dural, pial and peripheral arteriovenous fistulae. Children’s, with its superb neonatal care, cardiac anesthesia and experienced interventional radiologists, is well-positioned to treat these patients with good outcomes.
Sclerotherapy of a predominantly macrocystic lymphatic malformation in an infant with a left facial mass. The MRI (A) shows multiple cysts predominantly in the subcutaneous tissue. The cysts were cannulated (B) with needles, placed under ultrasound guidance and the fluid was aspirated. For the first procedure, Picibinal was used. Doxycycline was later injected into smaller cysts. The posttreatment MRI (C) shows complete resolution of the macrocysts. There is still some enlargement of the left parotid gland due to microcystic disease.

Sclerotherapy of a symptomatic facial venous malformation in a 10-year-old girl (A). MRI (B) shows a fairly extensive lesion in the deep and superficial soft tissues of the right cheek. Low-dose digital subtraction imaging of a contrast injection into the deep part of the malformation (C) shows large dysplastic spaces draining to the transverse facial veins. A small amount of tissue adhesive (n-BCA) was injected to close the communication with the draining vein. The lesion was thrombosed with sodium tetradecyl foam and then bleomycin was injected. MRI (D) and clinical exam (E) four months after one procedure showed an excellent response.

Preoperative embolization and resection of a cerebellar AVM that had bled (A). MR angiography (B) led to the diagnosis of AVM. Left vertebral angiography (C and D) showed the AVM supplied by a superior cerebellar arteries. Two feeding arteries were categorized with a microcatheter (C) and embolized with Onyx, significantly reducing the flow through the AVM (F). The patient underwent resection on the following day and postop angiography (G) showed no residual AVM.
Staged embolization of a severely symptomatic AVM of the left medial quadriceps muscle in a 15-year-old boy. MR angiography (A) confirmed the diagnosis of AVM. The patient is undergoing staged angiography (A and B) with intranidal ethanol embolization. After two procedures (D), his pain had resolved. He will undergo additional embolizations until the lesion is completely closed.

Staged ethanol embolization was carried out in a young man with a progressively enlarging AVM of his left hand. Angiography shows extensive disease with dysplastic changes of the main arterial trunks (A and B). After five intranidal ethanol embolizations, the AVM is reduced but not completely eliminated.

Embolization of a massive midline posterior dural AVM in a neonate. MRA (A) and post contrast sagittal MRI (B) as well as subsequent right common carotid angiography (C and D) show a varix of the torcular supplied by a large number of severely dilated external carotid artery branches. Because the varix drained the cerebral veins as well as the AVM, it could not be completely occluded in one session. Six embolization procedures, closing the arterial connections as well as coiling the torcular varix in stages (E) resulted in control of the high output cardiac failure and hydrocephalus. Follow-up angiography and MRI (H) at 18 months (F and G) shows occlusion of the varix, most of the arteriovenous shunts, and excellent cerebral venous drainage. A small shunt persists. Gavin (I) is developing and acting like a normal two-year-old.

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