

Vascular anomalies: review and current therapy

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Congenital vascular anomalies have been the subject of much controversy and confusion over the years. Since 1982, hemangiomas and vascular malformations have been recognized as distinct diseases exhibiting unique properties and behavior that demand an appropriately tailored treatment plan. This article will briefly review the characteristics of these vascular anomalies, including epidemiology, classification, and clinical presentation, and will then focus on the current therapeutic options available. The past decade has witnessed a revolution in the understanding and treatment of vascular lesions, marked by more advanced laser therapy, earlier intervention, and an increased sensitivity to the psychosocial dynamics of the disease. *Curr Opin Otolaryngol Head Neck Surg* 2002, 10:309–315 © 2002 Lippincott Williams & Wilkins, Inc.

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Abbreviations

PWS port wine stain
VM vascular malformation

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Much confusion and controversy have shrouded the classification and treatment of benign, congenital vascular anomalies. Hemangiomas and vascular malformations share the common attribute that they exhibit an abnormal abundance of blood vessels. Beyond this similarity, these vascular lesions differ fundamentally in histology and physiology. Early practitioners failed to distinguish between these two types of vascular anomalies, leading to inappropriate and at times harmful care of afflicted children. In 1982, the seminal treatise by Mulliken and Glowacki [1] proposed that hemangiomas and vascular malformations represent unique disease processes, with the former constituting a true neoplasm by virtue of an increased endothelial turnover.

The past decade has witnessed a revolution of thought and practice in the treatment of congenital vascular diseases and has seen a further refinement of the concepts originally developed by Mulliken and Glowacki [1]. A better understanding of the natural history of hemangiomas has resulted in a more effective treatment algorithm that may in turn diminish the damaging psychological repercussions of the disease on the child and family [2]. Genetic loci [3,4], related syndromes [5,6], and cellular markers [7] have also been discovered that have shed new light on the clinical behavior of these vascular anomalies. Laser technology continues to evolve and can now achieve outstanding results with minimal morbidity. Many therapeutic modalities have been introduced—including interferon therapy [8–10] and interventional radiology techniques [11]—that have met with varying success in the treatment of these disparate vascular disorders.

In order to provide a meaningful review of hemangiomas and vascular malformations, this article is divided into sections on these two types of vascular anomalies.

Hemangiomas Epidemiology

Hemangiomas are the most common neoplasm of infancy and childhood, with an estimated prevalence of 1 to 3% of all neonates [12,13] and 10% of infants by 1 year of age [14,15]. Most hemangiomas arise in the head and neck region (60%), and 20% of patients may suffer from more than one lesion [16]. Prematurity is a well-identified risk factor, especially in those neonates that fall below 1500 g in weight [17]. A predilection for the female sex has also been reported, with a ratio of 3 to 1 [18]. Most hemangiomas tend to arise *de novo* without

an antecedent family history, but a few studies have determined an autosomal-dominant pattern of inheritance in a select group of patients [18]. Chorionic villus sampling has also been found to predispose one's progeny to the development of a hemangioma [19].

Classification

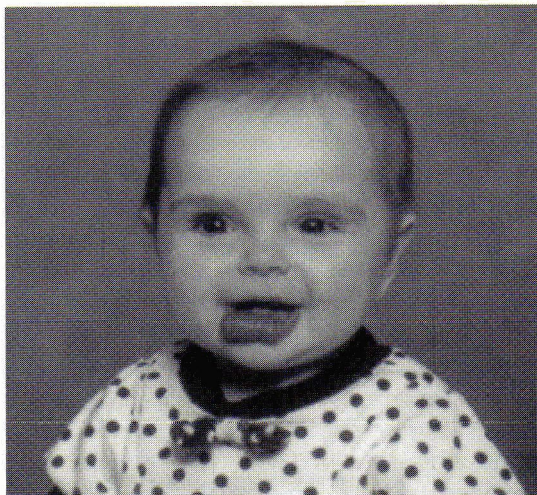
Prior to the work of Mulliken and Glowacki [1], terminology that described hemangioma types was mired in inconsistency and confusion. A plethora of words abounded to describe various hemangioma morphologies that at times overlapped with descriptions of vascular malformations such as *strawberry nevus* and *cavernous hemangioma*. These ill-defined terms have been largely replaced by a systematic nomenclature that seeks to delineate the anatomic dimensions of the lesion. Hemangiomas that arise only on the surface of the skin and immediate subjacent tissue may be accurately referred to as superficial (formerly known as capillary). Conversely, a lesion that is situated only in the deeper subcutaneous tissue may be considered a deep hemangioma (formerly known as cavernous). If both superficial and deep components are present, the hemangioma may be categorized as compound or mixed. Field hemangiomas represent multiple hemangiomas that rapidly enlarge and coalesce into a more singular entity. Visceral hemangiomas are derived within the internal organs such as the liver, colon, and brain. Diffuse neonatal hemangiomatosis is a highly lethal condition in which the newborn is covered with hundreds of hemangiomas that may involve the viscera as well, leading eventually to cardiac failure and ultimately to death within weeks [20]. Hemangiomas may also be part of a syndrome known as PHACE(S) (posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, eye abnormalities [and sternal clefting and supra-umbilical raphae]) [21].

Clinical presentation

At birth, a child may exhibit various manifestations of the incipient hemangioma, including an erythematous macule, a telangiectatic mark, a faded area, or no identifiable lesion at all. Although most hemangiomas are present within the first month of life, it is rare that they are recognizable as such at the time of birth. Superficial hemangiomas are bright red and noncompressible and may assume a raised or flat contour. Deep hemangiomas are situated in the subcutaneous tissue and may be well below the skin so that a raised mound provides the only clue to the underlying lesion. At times, a bluish hue may be visible through the skin as a hint of a deep hemangioma that approaches the skin's surface more closely. In addition, telangiectasias or prominent veins may pepper the skin overlying a deep hemangioma (Figs. 1,2).

The natural history of hemangiomas is characterized by a marked proliferative phase during the first few months of

Figure 1. A child who underwent oral steroid therapy and three pulsed-dye laser treatments for a rapidly expanding hemangioma of the lower lip and surgery at 2 years of age due to the late involuting nature of the lesion



The child at 9 months of age after oral steroid therapy and immediately prior to laser therapy. Published with permission.

life that usually is sustained to the end of the first year but rarely persists beyond that time. During this period, the hemangioma may risk ulceration or frank hemorrhage. The former condition may lead to infection and scarring, and the latter usually ceases with simple application of pressure. The greatest concern with rapid growth of the hemangioma lies in its obstructive potential: in the subglottic airway, resulting in stridor or further compromise; near the eye, leading to amblyopia; or in the external auditory canal, causing a conductive hearing loss. The psychological impact of the expanding heman-

Figure 2. A child who underwent oral steroid therapy and three pulsed-dye laser treatments for a rapidly expanding hemangioma of the lower lip and surgery at 2 years of age due to the late involuting nature of the lesion



The child at 3 years of age, 1 year after surgery. Published with permission.

gioma should not be underestimated and may cause considerable alarm in parents, leading them to seek medical counsel during this time. After the first year of life, the hemangioma may begin to involute slowly, or it may remain stable, then slowly diminish in size over the next several years. If the hemangioma should resolve slowly (a late involuter), the child may suffer considerable psychological damage during the school years and still be left with a marked cosmetic deformity. The classification of hemangiomas into early and late involuting types has shaped a newer treatment algorithm.

Current therapy

Since the work of Lister and Camb [22], management of hemangiomas has been plagued with the prevailing dictum of benign neglect. Many practitioners have advocated no therapy at all with the prescription that all hemangiomas will ultimately resolve. Recent studies have determined that late involuting hemangiomas only incompletely regress and leave behind an often significant residuum [23,24]. Neonates and infants may remain unaware of their disfiguring condition, but children 3 years and older are subjected to a burgeoning self-identity and the attendant social stigma that being different bears [25,26]. A policy of watchful waiting in a slowly involuting hemangioma may prove detrimental to a child's psyche and may lead to ostracism from peers.

Williams *et al.* [2] have proposed a new treatment strategy based on the proliferative and involuting characteristics of a hemangioma to treat select patients on a timely basis and to preclude the potential psychological sequelae of a longstanding hemangioma. A proliferative hemangioma that risks ulceration or bleeding or that is rapidly expanding in a cosmetically sensitive area is a candidate for early intervention. Pulsed-dye laser therapy with adjunctive intralesional steroid application has proven to be effective to retard the rate of growth. A trial of oral steroids may be mandated for a hemangioma that shows signs of impending obstruction, eg, by encroaching on the airway or vision. Most hemangiomas begin to involute early, albeit slowly, and should be left to regress spontaneously. However, a hemangioma that tends toward late involution should receive therapy to remove the disease that would most likely fail to involute completely and that would impair the child's favorable psychosocial maturation. At this stage, surgical debulking with adjunctive laser therapy is the preferred method of intervention, as steroids have no beneficial role during the involutorial phase.

It should be emphasized that most hemangiomas do not require therapy, and only a select minority coincide with the enumerated criteria for intervention. Parents suffer significant psychological distress from the presence of a vascular birthmark [27]. However, the timing and rationale for intervention should never be dictated by paren-

tal coercion, as this injudicious policy would do a disservice to both the child and the insurance carrier or other third-party payer to whom the physician is responsible.

Throughout the history of hemangioma management, many therapeutic options have been advocated or tried with mixed success. Compression therapy was popular when few options were available [28–30]. However, some authors still rely on this low-risk method of treatment. Cryosurgery was popular in the past but has lost some of its charm [31]. Many therapeutic modalities that carry a high morbidity profile were also once in vogue, including embolization, sclerosis, chemotherapy, and irradiation [32,33]. Embolizations of visceral hemangiomas [34] and intralesional chemotherapy [35] for refractory cases have still shown some clinical utility. Interferon therapy may also prove helpful in life-threatening or recalcitrant cases [8–10] but has been associated with neurotoxicity, including spastic diplegia [36], and should be used with great caution. The cornerstones of effective therapy for hemangioma today principally involve steroid therapy, laser therapy, and surgery.

Steroid therapy

Systemic steroid therapy has been a reliable method of treatment for over 30 years [37], but no controlled, prospective studies have been undertaken to evaluate the efficacy, proper dosing, duration of therapy, or tapering regimen. Steroid therapy, whether systemic (oral and intravenous) or local (intralesional and topical), is only effective during the proliferative phase of hemangioma development and should be used to treat a rapidly proliferating hemangioma in a cosmetically sensitive area that risks imminent ulceration or bleeding or that may lead to obstruction, eg, near the eye or in the airway. Usually, a rapidly proliferating hemangioma that may ulcerate or hemorrhage may be treated with the pulsed-dye laser and with concomitant intralesional triamcinolone acetonide 10 mg/ml injection. However, if an obstructive potential exists, oral steroids may be necessary.

A meta-analysis of systemic steroid therapy determined a response rate of 84% in 10 original case series that met inclusion and exclusion criteria (treatment of a problematic hemangioma, child younger than 2 years, more than five cases, no other simultaneous treatments, proper follow-up, and sufficient data) [38••]. The study concluded that administration of higher doses of prednisone (> 3 mg/kg/d) resulted in a higher response rate (94%) but a concomitantly higher side-effect profile, and that lesser doses (< 2 mg/kg/d) showed less response, fewer adverse effects, and a greater rebound rate (70%). Patients underwent a mean 2-month period of therapy and were maintained on oral steroids until cessation of growth or actual regression was evident. Tapering schedules were not delineated in most case series and varied considerably in the reported studies. In conclusion, oral steroid

therapy (2–3 mg/kg/d) can be effective in a select group of hemangioma patients who have obstructive or recalcitrant lesions and who demonstrate a response to steroids.

Laser therapy

The introduction of the pulsed-dye laser has proved nothing short of miraculous for the treatment of vascular lesions and has almost entirely replaced the argon laser. A large series (617 hemangiomas) treated with the pulsed-dye laser demonstrated a 96.6% arrest in further growth after a mean of 2.5 treatments (13.8% complete remission, 14.9% significant regression, 67.9% discontinuation of growth) [39••]. During rapid proliferation, hemangiomas may require several sessions of laser therapy 6 to 8 weeks apart to retard the growth rate. Intralésional steroid therapy may be a beneficial adjunct at the time of laser administration. The indication for laser therapy would include a rapidly proliferating lesion that may ulcerate, bleed, or obstruct. The pulsed-dye laser targets only the superficial component of the hemangioma. The ND:Yag and argon lasers have been applied interstitially for the treatment of deeper hemangiomas [40], but the authors strongly advise caution as the risk of scar formation may be considerable. During the involutorial period, the laser may remove residual dermal ectasias and telangiectasias, tighten the loosened skin overlying the hemangioma, and serve as a useful adjunct postsurgery to address residual deformities. Unlike late involuting hemangiomas, early involuters should be permitted to regress naturally and should not be subjected to unnecessary therapy.

The carbon dioxide laser may play a useful role in the treatment of laryngeal hemangiomas that encroach on the airway, but it should be used conservatively to avoid tracheal stenosis [41]. Because the risk of scarring is high for large or circumferential lesions, tracheotomy and systemic steroid therapy may be beneficial in certain cases [42•]. Tracheotomy and systemic steroid therapy clearly have their own attendant risks and limitations, including delayed speech and swallowing problems for the former and the many well-known side effects of the latter. The physician is urged to apply clinical judgment when deciding on a particular course of therapy.

Surgery

Surgery remains a reliable technique of debulking hemangiomas in a rapid and definitive manner. During the proliferative phase, hemangiomas rarely require surgical intervention except to alleviate obstructive lesions that fail to respond to more conservative measures. Generally, surgery plays a more useful role during the involutorial phase to remove the unsightly residuum that may remain. A key surgical concept is removal of the bulk of the disease, leaving a small (10%) remainder of the lesion behind to accommodate any further regression that the

lesion may undergo in the future. Usually 6 to 8 weeks after surgery, the patient may benefit from pulsed-dye laser therapy to remove any superficial dermal ectasias or discolorations that are still present. By approaching the involuted hemangiomas conservatively, the surgeon may avoid larger, unnecessary incisions and prevent a depression due to overresection. Most residual hemangiomas may be removed in a straightforward fashion. However, infrequently, the surgeon may require tissue expanders or serial excisions to resect larger residual deformities that encompass a greater cutaneous surface. Although tissue expanders have been described with success in the literature [43], the authors believe that children tend not to tolerate these devices well psychologically or physically and may be better served with serial excisions for larger, more difficult hemangiomas.

Kasabach-Merritt syndrome

The current thinking on the Kasabach-Merritt syndrome must be addressed here. This syndrome, characterized by thrombocytopenic coagulopathy, has been recently found to be associated not with true hemangiomas but with two distinct vascular tumors known as the kaposiform hemangioendothelioma and tufted angioma [44]. These unique lesions exhibit a violaceous tone and nodular pattern, but each has its own particular histopathologic features. Kasabach-Merritt syndrome carries a high mortality rate, and treatment is often inadequate and inconsistent, relying on multimodality therapy of cytotoxic agents such as vincristine, cyclophosphamide, systemic prednisone, and interferon- α [45].

Vascular malformations

Epidemiology, classification, and clinical presentation

Vascular malformations (VMs) arise from an error in morphogenesis of any combination of the following vascular networks: arterial, venous, capillary, and lymphatic. Unlike hemangiomas, these vascular anomalies are present at birth, grow proportionally to the size of the child, and do not exhibit any tendency to involute spontaneously. Hormonal factors such as puberty or pregnancy may influence the growth of these vascular lesions, causing acceleration in size during these periods. Direct trauma or infection may also trigger a rapid expansion. The predominant vessel type (arterial, venous, capillary, or lymphatic) dictates the flow (slow or fast) and thereby the physical attributes of the lesion. Fast flow malformations usually have an arterial component and exhibit a propensity to expand, to achieve large volumes, and to pulsate. Slow flow lesions encompass capillary, venous, and lymphatic types and behave according to the primary vessel present.

By far the most common of the VMs, capillary malformations (port wine stains [PWSs]) occur in an estimated three children per 1000 births, with approximately 80% occurring in the head and neck region and with an equal

sex distribution [46]. PWS manifests as a flat lesion with a red to pink hue which may lighten during the first year but tends to darken throughout life, turning a deeper shade of red or blue and even becoming thicker or more nodular as the patient matures [47]. Two related syndromes have been linked with PWSs: Sturge-Weber syndrome and Klippel-Trenaunay syndrome. Sturge-Weber syndrome or encephalotrigeminal angiomatosis is characterized by a PWS that is distributed in the first trigeminal division (V1), with or without V2 or V3 involvement, and with central nervous system abnormalities. Central nervous system defects include cerebral atrophy, leptomeningeal angiomas, and cortical calcifications that may lead to seizures, mental retardation, and hemiparesis. MRI should be conducted after 6 months of age to screen the high-risk neonate, who, by the authors' experience, usually has V1 involvement that circumscribes the eyelid, and often V2 extension as well. In addition, ocular examinations should be undertaken to determine whether glaucoma is present with the syndrome. Klippel-Trenaunay syndrome or angio-osteohypertrophy is characterized by a PWS that usually involves a unilateral, lower extremity marked by hypertrophy, varicose veins, lymphedema, and phleboliths [48].

Venous malformations are characterized by a dark blue hue and may be situated in the skin, subcutaneous tissue, or mucosa. They tend to be compressible and may have nodular areas that constitute phleboliths scattered throughout. Lymphatic malformations, formerly known as lymphangiomas, typically arise in the head and neck. They may be deeply infiltrative above the hyoid and more circumscribed below the hyoid. Arteriovenous malformations are found principally in the cephalic region and show signs of rapid arterial flow, including warmth and the presence of a bruit or thrill. One of the most dreaded complications that may occur with this fast flow lesion is high-output cardiac failure.

Current therapy

Vascular malformations represent a dissimilar group of disorders that mandate a treatment plan predicated on the vessel type and related clinical manifestation. PWSs represent the most common form of VM, and the extent of literature concerning PWSs is commensurate with their prevalence. Accordingly, most of the current treatment options discussed here focus on management of PWSs.

Capillary malformations (port wine stains)

Prior to the introduction of laser therapy, the only method of treatment for PWSs was cosmetic camouflage. Initially, the argon laser showed promise in the treatment of vascular diseases, but the incidence of scarring and the advent of the pulsed-dye laser have largely relegated the argon to historical interest. With the pulsed-dye laser that selectively targets the vascular chromo-

phore in PWS, patients have now found a new hope in minimizing their deformity with little morbidity. However, patients should be properly informed that their lesion will fade but not completely vanish with the pulsed-dye laser. Numerous studies have documented the proven reliability of the pulsed-dye laser in treating PWSs [49•,50]. Some studies have investigated the role of a 532-nm KTP laser in the treatment of resistant PWSs and found clinical efficacy [51••], but scarring has been reported with this laser type [51••,52]. Intense pulsed light has also proven to be highly effective and safe for the treatment of PWSs, according to one study [53]. The authors recommend discretion in the use of lasers other than the pulsed dye, which is a proven and safe gold standard of therapy.

Recent studies have emphasized the psychological aspect as much as the efficacy of treatment [54–57]. Most studies have demonstrated the ostracizing effects of the PWS and the benefit of intervention to the psychological welfare of the afflicted individual. One small study contended that the patients in the series (N = 9) revealed no subjective benefit to treatment despite objective physical improvement [55]. As the children mature, they not only confront the psychosocial trauma of bearing the unsightly mark but also may develop a lesion that is more difficult to treat as age and hormonal factors darken and thicken the PWS. For all these reasons, it is imperative to institute early laser therapy to counteract the detrimental psychological and physical forces and to continue therapy based on the responsiveness to the treatment and the tolerance and desire of the patient and family to undergo further cycles of therapy.

Other vascular malformations

A comprehensive review of all the options that are available to cope with vascular malformations lies beyond the scope of this discussion. The mainstay of therapy for other types of vascular malformations remains complete surgical extirpation. Incomplete attempts only make future surgery both necessary and more difficult and can foil any successful pre-embolization efforts. Embolization for arteriovenous malformations should be seriously considered to minimize intraoperative blood loss as well as the extent and complexity of surgery [11••]. Patients should be counseled on the morbidity of embolization and surgery versus that of no intervention and should weigh the options intelligently.

Conclusions

Many advances have been made in the understanding and treatment of vascular anomalies, including improved laser therapy, increased knowledge of disease biophysiology, and sensitivity to the psychological repercussions on the child and family. This progress has informed the timing and technique with which caregivers have therapeutically intervened. More active and earlier therapy

has been administered to a select minority of hemangioma patients who demonstrate a rapidly proliferating hemangioma in a cosmetically sensitive area or an area that risks ulceration and hemorrhage or who show a late involuting lesion that may not completely resolve and may serve only to worsen the child's psychosocial integration. PWSs have been successfully treated with the pulsed-dye laser, and those afflicted with these lesions have been the favored subject of much psychological analysis. Advances on all fronts are expected in the management of vascular anomalies and should alleviate the considerable burden of disease carried by the child and family.

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