Angiogenesis and Vascular Malformations

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In the process of vasculogenesis, blood and lymphatic channels form in the embryo from clusters of angioblasts that differentiate into endothelium and other mesenchymal cells that form the vessel wall [smooth muscle cells, fibroblasts] and surrounding mesenchyme. Early vascular channels form the primary vascular plexus and vascular remodeling leads to development of arteries, veins, and capillaries. Subsequently, new blood vessels form from sprouting, intussusceptive vascular growth, and splitting of vessels from preexisting channels. Specification is believed to be related to expression of Efrin B2 in arterial and EphB2 in venous endothelium. Lymphatic channels form from veins. Defects in any of the proteins involved in the regulation of vasculogenesis and angiogenesis can result in abnormal channels that can subsequently expand and cause symptoms. After birth, abnormal regulation of angiogenesis can lead to increased cell proliferation or reduced apoptosis, thrombosis, and other changes that contribute to the clinical manifestations of a vascular malformation. Congenital vascular malformations, in general, enlarge in proportion to the growth of the affected child, but it is well known that they may expand episodically, especially during periods of accelerated somatic growth and increased hormonal stimulation. The recent finding that endothelial cells in vascular malformations have increased receptors to human growth hormone and somatostatin compared with those in normal tissue explains the increased growth and symptomatology of vascular malformations that is seen during growth spurts as well as at puberty and during pregnancy [1, 2]. In addition, animal models have confirmed the responsiveness of vascular malformations to angiogenic growth factors [3].

Venous Malformations

Familial mucocutaneous venous malformations and 50 % of sporadic VM are caused by mutations in the tyrosine kinase receptor TIE2. Experiments show that in human endothelial cells, mutant tie2 and its ligands, angiopoietins 1 and 2, cause increased activation of AKT signaling and reduced production of platelet-derived growth factor-B, which is important in mural cell recruitment. These molecular changes, both in the lab setting and in humans, cause VMs characterized by a defective endothelial cell monolayer, deficient smooth muscle in the vessel wall, and defects in thrombospondin function, while abnormalities result in formation of enlarged, disfigured, and fragile venous channels, as well as intralesional thrombosis and clotting protein consumption [4]. The cause and effect of TIE2

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mutation in the etiology of VM is supported by the observation that treatment of patients with sirolimus, which suppresses AKT, appears to control the growth and improve the consumption coagulopathy of extensive VM [5]. Rapid recurrence of symptomatic VM after partial resection is common, presumably due to stimulation of venous angiogenesis. In a similar fashion, even after effective endovascular ablation of malformed venous channels, similarly abnormal channels, presumably collaterals, can develop in the adjacent soft tissue. Intralesional thrombi created by sclerotherapy can be recanalized by circulating endothelial progenitor cells, leading to new abnormal channels. This is the reason that sclerotherapy should be repeated until the vessel is occluded permanently by fibrosis.

Abnormal angiogenesis can also occur in veins without TIE2 mutation. Angiogenesis in a partly thrombosed vein can lead to development of a focal vascular mass termed Masson's tumor. Arteriovenous shunts can develop in the walls of partly occluded veins after venous thrombosis, or after incomplete endovascular ablation (Fig. 3.1). In fact, dural sinus thrombosis is believed to be the trigger for development of acquired dural AVMs in adults.

Arteriovenous Malformations [AVMs]

AVMs are also caused by abnormal regulation of blood vessel development. More than 860 genes are known to be upregulated or downregulated in cerebral AVMs [6]. The study of familial forms of AVM has revealed a number of causative genetic mutations, including ENDOGLIN (ENG), ACTIVIN RECEPTOR-LIKE KINASE 1 [ALK1], and SMAD4 in patients with hereditary hemorrhagic telangiectasia [HHT], RASA1 in patients with capillary malformation-arteriovenous

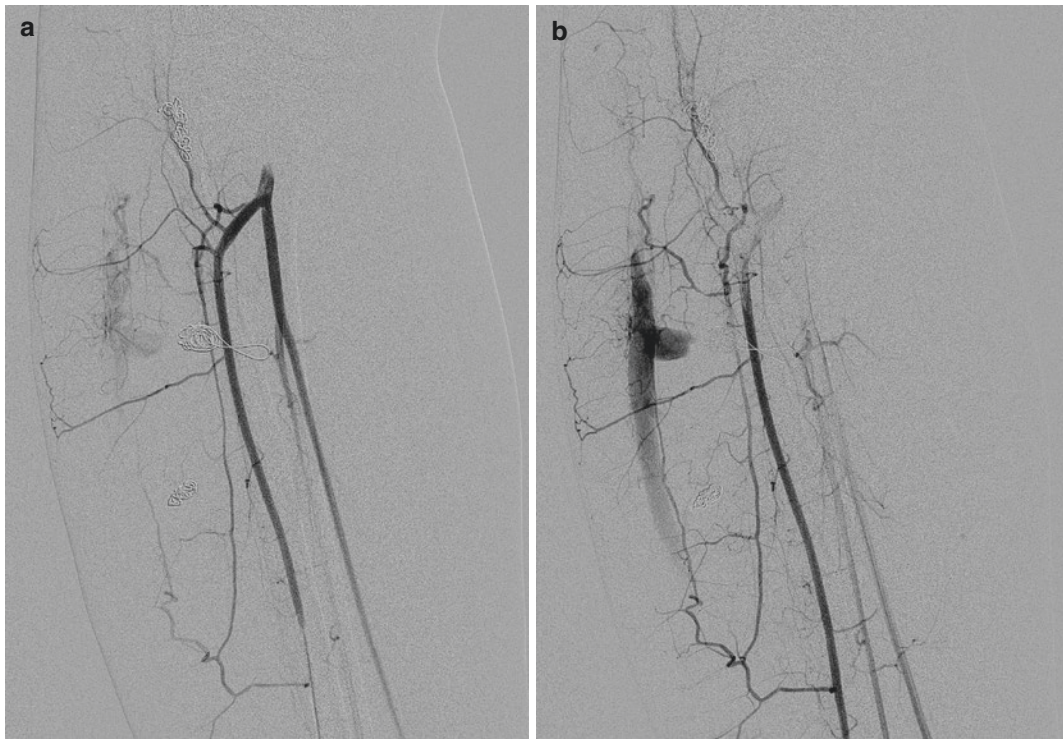

Fig. 3.1 Angiogenesis causing acquired arteriovenous fistulae in the wall of a marginal vein after unsuccessful endovenous laser treatment. Probable triggers: injury and hypoxia. (**a**, **b**) Sequential images from a right anterior tibial angiogram showing tiny arteriovenous shunts into the distal segment of the partly occluded vein

malformation [CM-AVM], and PTEN in patients with AVM associated with Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome. A number of animal models have been developed, mainly by creating mutations in endoglin (eng), activin receptor-like kinase 1 [Alk1], RASA1, and notch pathways [7–9]. In the lab setting, angiogenesis in normal and abnormal endothelial cell models can be stimulated by vascular endothelial growth factors (VEGF). In the Alk1 mouse model, AVMs establish from newly formed arteries and veins, rather than from remodeling of a preexistent capillary network. Creation of a wound or stimulation with VEGF is needed to create the AVM in ALK1-deficient adult mice. In this model, VEGF blockade can prevent the formation of AVM and arrest the progression of AVM development [10]. Clinically, most AVMs evolve over time, and it has been known for many years that quiescent lesions can become more active [increased shunting, swelling, pain] during periods of active somatic growth and as a result of conditions that are known to upregulate vascular growth factors, such as surgery, embolization, trauma, inflammation, puberty, and pregnancy (Figs. 3.2 and 3.3). Histochemistry of resected AVM tissue has revealed increased numbers of endothelial cell receptors for human growth factor and somatostatin, as well as upregulation of MMP9, inflammatory markers, and VEGF [11]. Recently, it has been found that suppression of VEGF pharmacologically [bevacizumab and thalidomide] can result in decreased arteriovenous shunting and improved symptomatology in some patients with HHT [12]. Doxycycline appears to decrease cerebral MMP-nine activity and angiogenesis induced by VEGF. Endothelial cells from resected AVMs respond to doxycycline and minocycline in cell culture, but clinical response in patients with symptomatic AVMs has not been well documented. One child with sporadic AVM had an excellent, dose-dependent, sustained response to treatment with marimastat, a preclinical broad-spectrum MMP inhibitor. Other patients with AVMs have been treated with angiogenesis inhibitors anecdotally, but, aside from a small trial of minocycline in patients with cerebral AVMs, there have not been any prospective clinical trials.

While it has been widely believed that AVMs are congenital, there is increasing evidence that AVMs can be acquired [13]. Triggers for postnatal development of AVM include venous thrombosis [deep vein thrombosis in the lower extremities and dural sinus thrombosis resulting in dural AVM], ischemia [e.g., cerebral infarct], and trauma [e.g., chronic posttraumatic AV fistula, uterine AVMs]. While the mechanisms leading to acquired AVM have not been studied in detail, the presence of increased numbers of endothelial progenitor cells in thrombosed blood vessels as well as higher grade AVMs suggests a role for these cells, likely in response to upregulation of vascular growth factors [11, 14].

Summary

Vasculogenesis, normal and aberrant angiogenesis, and pathological angiogenesis stimulated by extrinsic factors are all involved in development and progression of vascular malformations. Antiangiogenic drug treatment appears to be effective in controlling the development and progression of AVM in animal models as well as in patients with HHT, who have mutations in ALK1 and ENG. Further study of patients with sporadic AVM and patients with VM will hopefully lead to effective pharmacotherapy in the future.

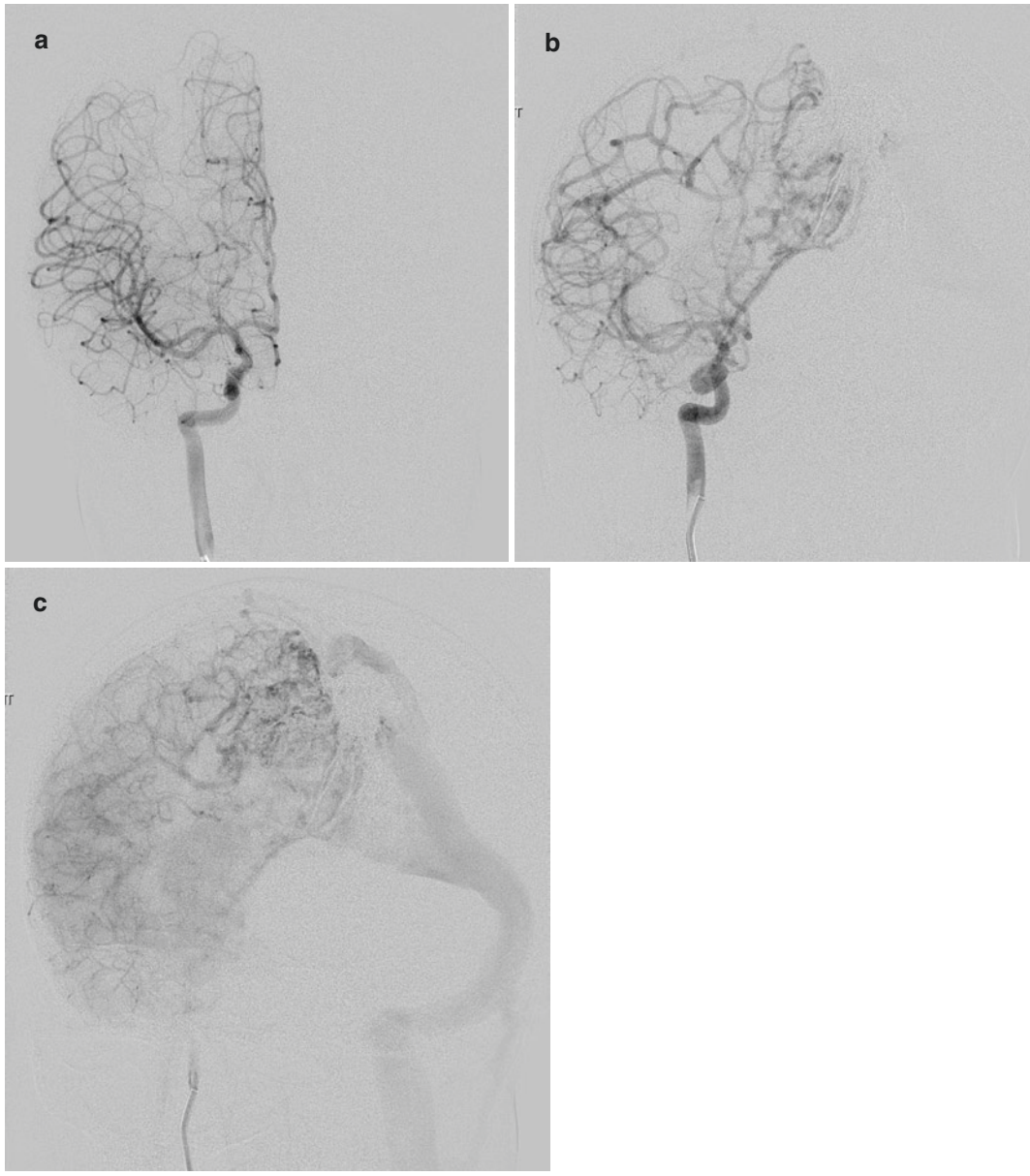

Fig. 3.2 Stimulated angiogenesis in an 11-year-old girl with dural AVM, most likely triggered by somatic growth, embolization, and onset of puberty. (**a**) *Right* internal carotid angiogram, frontal projection in 2008, showing no arteriovenous shunting. (**b**, **c**) *Right* internal carotid arteriogram, frontal oblique projection, shows multiple new arteriovenous fistulae between pial branches of the anterior and middle cerebral arteries and the superior sagittal sinus. In the interval, the patient had undergone additional embolization of the dural AVM and started her menstrual cycles

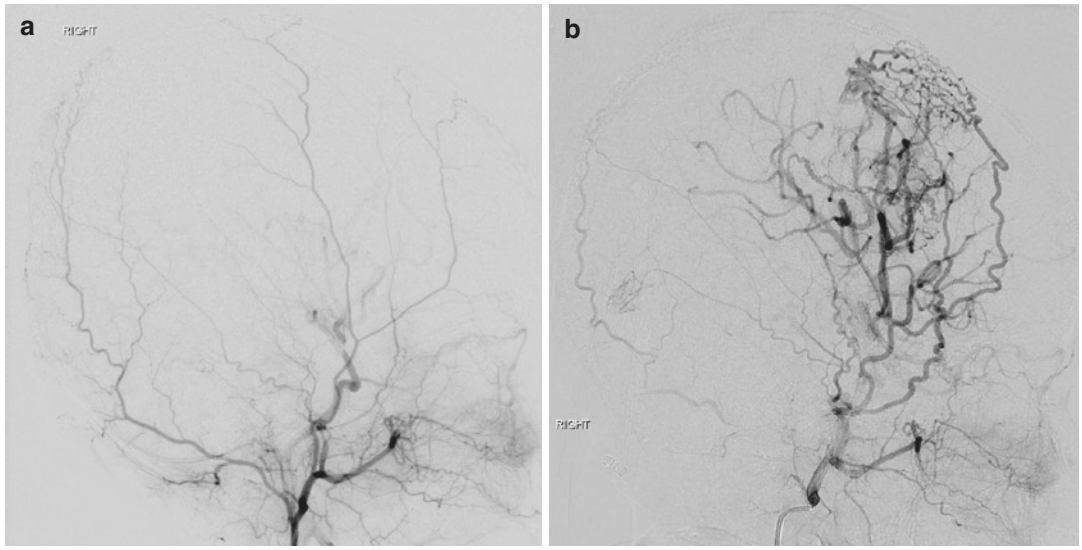

Fig. 3.3 Angiogenesis in a one-year-old girl with severe stenosis of the right internal carotid artery treated by synangiosis surgery. Probable stimuli: ischemia, hypoxia, surgical trauma, and somatic growth. (**a**) *Right* external carotid arteriogram, lateral projection prior to surgery shows normal size and distribution of the external carotid artery branches. (**b**) *Right* external carotid angiogram 1 year after synangiosis shows increased size and tortuosity of the superficial temporal artery with extensive anastomoses with the right middle cerebral artery branches

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