Vascular Malformations and Tumours

David A. Koppel and Jaime Grant

R. M. Touyz, C. Delles (eds.), *Textbook of Vascular Medicine*,
https://doi.org/10.1007/978-3-030-16481-2_45

45

Key Concepts

- Nomenclature and classification are critical in understanding the different pathologies and communicating with colleagues.
- The pathogenesis of the majority of the vascular tumours and malformations is poorly understood.
- As a result of the poor understanding of the basic pathogenesis of these conditions, the management of the majority of these lesions is relatively crude with non-specific endovascular procedures (embolization, sclerotherapy) or surgical (excision, debulking) forming the mainstay of management options.

45.1 Introduction

When considering the pathogenesis, presentation, investigation and management of vascular tumours and anomalies, the use of accurate terminology and of a classification system is critical. Any classification system should be continually reviewed and renewed to ensure that it remains appropriate and fit for purpose. An ideal classification takes into account the pathogenesis and clinical presentation and then acts as a guide to the clinical management of conditions. Historically the classification and nomenclature used for these conditions have caused significant confusion, with different specialists using different names for the same condition and conversely the same name for different conditions [1]. This proliferation of names also gives the erroneous impression that the conditions they describe are fully understood and that there is a vast knowledge base underpinning the nomenclature. In 1998 a more rational and clinical approach was taken by the International Society for the Study of Vascular Anomalies [2]. This classification system divides vascular malformations into tumours and vascular malformations – the key pathophysiological feature differentiation between the two categories being that the tumours have abnormal endothelial cell turnover and the malformations have normal rates of cell turnover (in the undisturbed state).

The most common vascular tumour is the infantile haemangioma – in fact it is the commonest tumour of childhood. All other vascular tumours are rare by comparison.

Vascular malformations are subclassified by their primary tissue of origin (capillary, venous, arterial, lymphatic or mixed) and by the rate of blood flow through the lesion into low flow or high flow [3].

45.2 Infantile Haemangiomas

Infantile haemangiomas are the most common childhood tumours with an incidence reported to range from 1% to 10% [4–6]. There is an association between low birth weight and haemangioma [5].

Most studies show that head and neck lesions predominate; however an excellent well-powered study of a Dutch population suggests that truncal lesions are more common [6].

45.2.1 Natural History

Whilst the majority of tumours are cutaneous (Fig. 45.1), they can occur at any site or depth of tissue. The deeply placed lesions may remain occult or only be discovered incidentally but may present (particularly if they are large) with complications associated with or caused by the tumour [7]. It is unusual for an infant to present with visceral lesions in the absence of cutaneous lesions, and likewise the presence of five or more cutaneous lesions should prompt examination and investigation for deep lesions [8].

With regard to cutaneous infantile haemangiomas, around 30–40% are obvious at birth [9]. A small herald lesion – a blanched area – or other precursor lesions may be apparent at birth or soon after, and the majority become apparent by the 3rd and 4th week [6]. After its initial appearance, the lesion enters a proliferative phase of rapid neonatal growth reaching 80% of its maximum size by 5 months with growth levelling off between 10 and 12 months [10].

It is during the proliferative phase that most complications occur. Depending on size and site, ulceration, bleeding, obstruction (airway, eye, ear canal), skeletal disproportion and high-output cardiac failure can all occur. Once the proliferative phase has reached its maximum, the lesion enters a second, slower, involuting phase. Whilst they are considered as two distinct phases, there

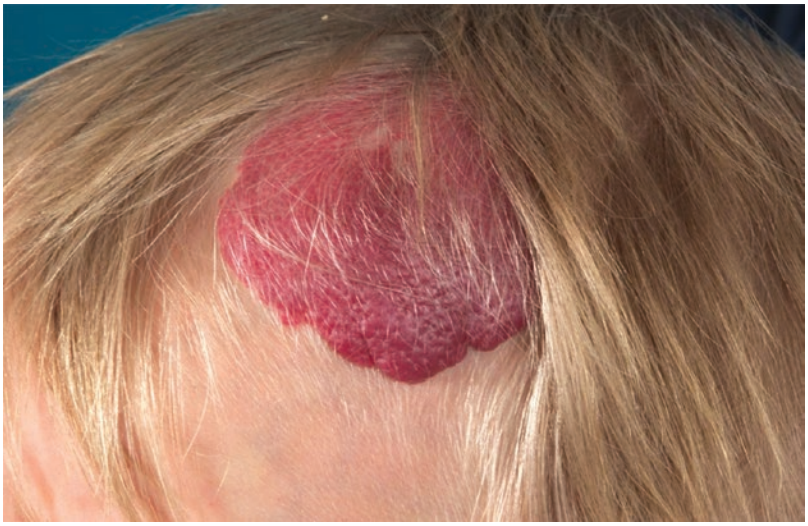

Fig. 45.1 Typical haemangioma just beginning to involute with grey flecks visible in the centre of lesion

is, in actuality, a gradual change from one to the other with a degree of overlap. This second phase lasts, on average, until around the age of 7 years with 70% having completely resolved by this point [11]. There is no correlation between the size of the original lesion or the age of onset and the degree of resolution [10]. Classification: The straightforward infantile haemangiomas are probably best classified as solitary (focal), multiple (multifocal) or territorial (regional).

Management: Diagnosis is usually made on clinical grounds, but if there is doubt, biopsy can be useful (though excessive bleeding is a risk). Histopathologically, infantile haemangiomas are characterised during the proliferative and involuting phases by the presence of the GLUT1 marker (erythrocyte-type glucose transporter enzyme 1) [12].

Active intervention is rarely indicated but may be required in cases presenting with (1) high-output cardiac failure; (2) airway obstruction in cases of tracheal, laryngeal tongue base, oral or nasal tumours and obstruction of vision (to prevent the development of amblyopia); and (3) ulcerated, painful and bleeding lesions and in some cases for cosmetic reasons [13].

Interestingly, it has been found that haemangiomas produce an enzyme (3 iodothyronine deiodinase) that breaks down normal thyroxine and can therefore lead to hypothyroidism. This is only reaches significance in large lesions, and for this reason routine measurement of TSH and thyroxine levels is suggested for patients with large lesions [13].

If active treatment is indicated, primarily for functional problems, there are a number of systemic and local interventions that are helpful. Systemic treatments with corticosteroids, beta blockers, interferon or vincristine have been used. Generally different centres will use either steroids or propranolol (with propranolol being most efficacious if administered in the 1st year of life) as a first-line treatment reserving interferon and interferon for nonresponders [14].

Local interventions include topical beta blockers (Timolol) and high-dose topical corticosteroids; intralesional treatments include steroids and bleomycin.

In refractory cases with limited response, embolisation and surgery may be considered [15].

Subtypes: There are two forms of congenital haemangioma – rapidly involuting congenital haemangioma (RICH) and non-involuting congenital haemangioma (NICH). There are also additional rarer lesions that form part of a syndrome [3].

45.3 Vascular Tumours

Other than infantile haemangiomas, vascular tumours are rare, may be benign or malignant and may also have systemic effects such as a consumptive coagulopathy (Kasabach-Merritt phenomenon [16]). Examples include pyogenic granuloma, Kaposiform haemangioendothelioma, Tufted angioma and angiosarcoma. Management: Pyogenic granulomas can usually be treated with limited surgical intervention with either shaving or local

excision although satellite lesions may form following excision (rarely). The more aggressive tumours are usually treated with a combination of surgery and chemotherapy.

45.4 Vascular Malformations

45.4.1 Capillary Malformations (and Other Superficial Lesions)

This collection of conditions, variously known previously as port wine stains, capillary haemangiomas and/or naevus flammeus, are relatively common. For practical purposes they can be divided into:

1. Common (cutaneous) types, Sturge-Weber syndrome, megalencephaly-capillary malformation
2. Hyperkeratotic lesions (e.g. verrucous haemangioma, angiokeratoma)
3. Telangiectasias (spider angioma, Campbell De Morgan spots, hereditary haemorrhagic telangiectasia (HHT)) [3]

45.4.1.1 Epidemiology

The published incidence rates for common cutaneous capillary malformations vary from 0.1% to 2% of newborns. Sex distribution is equal [17].

45.4.1.2 Natural History

The common cutaneous lesions are usually seen at birth though they may be less obvious because of anaemia or skin pallor. Whilst some lightening may occur during the 1st year of life, the majority do not significantly change in colour with development. In adulthood they often darken, and the overlying skin may thicken and take on a cobblestone appearance. This can lead to significant progressive disfigurement [17].

45.4.1.3 Classification

The common cutaneous lesions can occur at any site. When they occur in the head and neck, they may follow one or more of the dermatomes supplied by the three sensory divisions of the trigeminal nerve and can be associated with overgrowth of the underlying skeleton and soft tissues [18].

Sturge-Weber syndrome is probably the best known syndromic form of a capillary malformation. This is a triad of a capillary malformation affecting the upper face (usually unilateral), vascular anomalies of the meninges and ocular choroid. Two of these features are necessary to make the diagnosis. As the lesions progress with age, bony overgrowth, coupled with the darkening and thickening of the cutaneous lesions, can result in significant facial disfigurement. The meningeal vessels are enlarged and tortious, whilst the cortical vessels are hypoplastic. This leads to cerebral atrophy with subcortical calcifications. The calvarium can become thickened as part of the overall overgrowth phenomenon. Seizure activity is common, and whilst neurological impairment is not an inevitable result of the syndrome, where seizures are severe or intractable, impairment can occur [19]. The ocular lesions include ectatic vessels in the sclera, conjunctiva, retina or choroid, and glaucoma can ensue in around 60% of cases [20].

Megalencephaly-capillary malformation is a condition with capillary malformations typically affecting the midline of the face (forehead or upper lip) in association with megalencephaly. Hemihypertrophy may also occur and there is an associated increase in risk of Wilms tumour [21].

A proportion of capillary lesions are thickened and are thought to be of a different subtype – this subtype has not been fully studied or classified, and they can be termed verrucous haemangiomas. They often start as dark capillary stains but begin to thicken and roughen in early childhood with a well demarcated but irregular margin [22].

Telangiectasias are common lesions of the mucous membranes or skin. They are linear, punctate or stellate dilated small vessels.

Spider Telangiectasias: Characterised by a central arteriole with radiating small vessel in a starburst akin to the legs of a spider (hence spider naevus). These lesions usually appear in infants and the majority disappear after puberty. Acquired lesions are seen in pregnancy and hepatic failure. This points to the role of oestrogen in the genesis of these lesions – liver failure leads to the reduced breakdown of oestrogen and thus its increase in the systemic circulation as happens naturally in pregnancy. Diagnosis can be confirmed by central compression and then

release – this leads to initial blanching followed by radial blushing [23].

Campbell De Morgan spots are common lesions seen in the ageing population and are thought to be harmless. Whilst there are reports of their association with systemic disease, there is no convincing supporting evidence for this. The lesions themselves are 2–5 mm in diameter, smooth and elevated from the underlying skin, and they may become pedunculated. They are non-pulsatile and there is typically a surrounding halo of pallor [23].

Hereditary haemorrhagic telangiectasia (HHT) is a more serious condition with the potential for significant, life-threatening bleeding. It is inherited in an autosomal dominant pattern and a number of mutations have been identified. The telangiectasia may occur at any site; commonly in the mucous membranes, GI tract, cutaneous, visceral or cerebrally. The lesions are arteriovenous malformations, and the condition is also known as Rendu-Osler-Weber syndrome. The presentation and symptomatology are highly variable, and the diagnosis is confirmed clinically with three out of four features – multiple telangiectasias, spontaneous recurrent epistaxis, visceral lesions and an affected first-degree relative [24].

45.4.1.4 Management

The management of this diverse group of conditions is highly dependent on the condition, and its effects and an accurate diagnosis are necessary to minimise the adverse effects of the condition.

Simple, non-syndromic capillary malformations are managed to minimise the resultant deformity. The available treatment options include laser treatment and/or surgery. Surgical excision is reserved for small lesions where primary closure would be achievable or in more severe cases where there is a necessity the lesion can be excised and the skin resurfaced utilising skin grafts or free tissue transfer techniques [25]. Laser treatment is the most common form of treatment, and a pulsed dye laser is the first-line choice of device. The principle of treatment is to cause photocoagulation whilst minimising surrounding tissue damage and hence reducing scarring. Laser treatment necessitates a trial patch to evaluate the response; multiple treatments are usually necessary, and whilst lightening of the lesion is common, complete elimination is not the norm, and other types of laser are often tried to improve the result [26]. Where overgrowth occurs, particularly of the facial skeleton, corrective orthognathic surgery can be performed in a conventional way; however, if the cutaneous lesion remains, it is probable that the skeletal overgrowth will recur, even in adulthood after the completion of normal growth [27].

45.4.2 Lymphatic Malformations

The commonest form of lymphatic malformation is a disorder of lymphatic vessels or nodes leading to the accumulation of extravascular (extralymphatic) fluid known as lymphoedema. Abnormalities of the central lymphatic system (primarily the thoracic duct and its tributaries) are rare but can occur [28]. The formation of mass lesions of lymphatic vessels coalescing into larger fluid-filled cavities (macrocysts) or smaller microcysts leads to the lesions variously known as lymphatic malformations, lymphangioma and cystic hygroma (seen in the neck). The most apt term for these lesions is lymphatic malformation with division into macrocystic, microcystic or mixed, where both microcysts and macrocysts can occur together. The division between the two types is rather arbitrary, but cysts that can be aspirated are termed macrocystic – those too small for this are termed microcystic [3]. This pragmatic approach is useful as the macrocystic lesions are more amenable to treatment with sclerotherapy.

Lymphatic malformations can occur anywhere with the exception of the central nervous system where there is no lymphatic tissue. They occur most commonly in the neck and other sites where there are major lymphatic vessels such as the groin and retroperitoneal region.

Epidemiology: The exact incidence of lymphatic malformations is not known, but the literature estimates it to be around 1–5/10,000 live births [29].

45.4.2.1 Natural History

Larger lesions are often diagnosed antenatally; however others may not manifest until later on in life. Rarely the lesions are so large as to present airway or other obstructive symptoms, but

the majority are asymptomatic [30]. Gradual growth in step with the child's growth is the norm; however superimposed on this are relatively rapid fluctuations in size that can be caused by posture, constriction and concomitant infections.

45.4.2.2 Management

Lymphatic malformations causing airway embarrassment need early intervention, and emergency tracheostomy may be necessary (for instance, in large cervical lesions). Once the diagnosis has been made, usually on MRI scanning [31], the options are for surgical debulking and/or sclerotherapy. The macrocystic lesions respond better to sclerotherapy than the microcystic lesions, but sclerotherapy can be tried for both types. Sclerotherapy involves the direct puncture of the lesion, aspiration of the lymphatic fluid and then instillation of the sclerosant agent usually under ultrasound or x-ray control. The sclerosant agent then causes an inflammatory response leading to fibrosis and scarring, hence reducing the size of the lesion. Surgery is reserved for debulking large lesions or those causing other adverse effects [28]. The timing of surgery is determined by the problems that the lesion is causing and the risks of intervention must be balanced against the potential benefits. The use of surgical coblation techniques is useful in reducing the complications of surgery [32].

In later life as the child grows, lymphatic malformations often become swollen and tense with concomitant infections, and this enlargement may lead to complications; these acute inflammatory episodes may require urgent treatment that can include respiratory support, antibiotics and/or steroids. In the longer term, it is thought that these infective episodes create an inflammatory response and can act as a form of sclerotherapy, shrinking the lesion [33].

In the vast majority of cases, cure is not possible and would only be accomplished with a complete surgical resection which often necessitates extensive damage to surrounding tissues. This collateral damage, particularly in the head and neck, would be debilitating or disfiguring. Furthermore, the margins between normal and affected tissues are not clearly defined increasing the risk of incomplete excision [34].

For these reasons the management of all but the smallest lymphatic malformations is in the main, supportive with active interventions targeted at specific symptoms with clear and well-defined objectives. A staging system proposed by de Serres et al. suggests a guide to when intervention is indicated [30]. Sclerotherapy with bleomycin, sodium tetradecyl sulphate or OK432 (Picibanil, lyophilized mixture of Group A *streptococcus pyogenes*) as well as other agents have been utilised [28].

45.4.3 Venous Malformations

Classification: Venous malformations may be either (i) anomalous anatomic veins or (ii) venous anomalies that are separate from named venous branches [3]. This chapter will only discuss the second category.

45.4.3.1 Epidemiology

These lesions are relatively common with 1–4% of the population. There is equal sex distribution [29].

45.4.3.2 Natural History

Slow-flow venous malformations are present at birth, but not all of them are clinically apparent. They tend to grow in proportion as the child grows; however they can respond to hormonal changes such as puberty or pregnancy, and growth may be accelerated during these periods [35]. In addition the lesions expand when venous pressure is increased such as during a Valsalva manoeuvre or when the lesion is dependent. Recurrent episodes of increased venous pressure can lead to stretching of the walls of the venous cavities, and this can also result in enlargement [36]. Calcification of stagnant blood within the venous cavities results in the formation of phleboliths; these can vary in size and are often palpable and visible on radiological investigations [37].

Symptoms can vary – most are painless – but some discomfort or pain can occur particularly after interventions that may cause a consumptive coagulopathy. If pain is a significant symptom, low-dose aspirin may be of use [38]. Troublesome bleeding is not usually an issue; even after significant traumatic injuries, haemorrhage can be

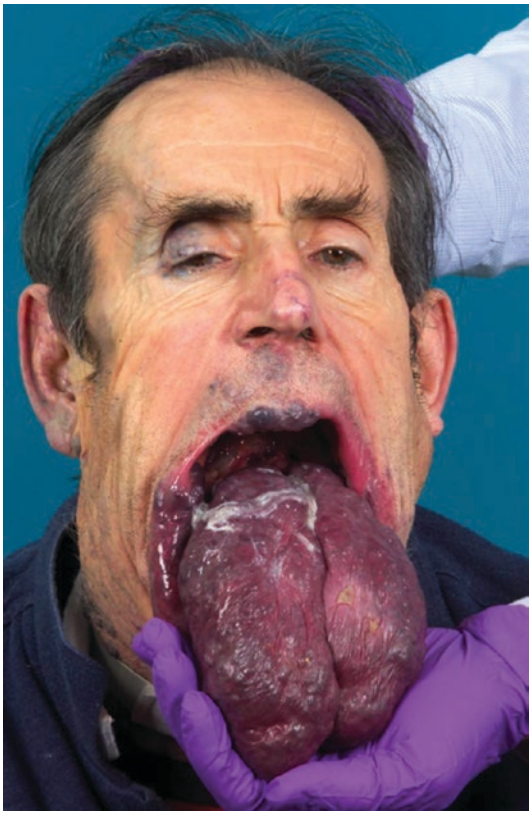

Fig. 45.2 Large multiple venous slow-flow vascular malformations affecting the tongue, lips and right orbit

controlled easily with pressure, reflecting the slow-flow nature of the lesions. The lesions can occur in any organ or location, but cutaneous sites are the most common (Figs. 45.1 and 45.2). These lesions, similar to capillary malformations, can cause overgrowth of the underlying tissues, including the bone. This can result in limb and extremity size discrepancies as well as skeletal and occlusal abnormalities in the head and neck region [39].

Central nervous system lesions can also occur, and their effect at these critical sites can range from being entirely asymptomatic to devastating should haemorrhage occur [40].

45.4.3.3 Management

The management of each particular lesion depends on its site and effects, but in general if the lesion is small and accessible, complete excision will result in cure. This approach is rarely possible as most lesions are too large, with indistinct margins to allow for reliable excision without extensive disfigurement or debilitating damage to surrounding structures. The main objectives in treatment are to mitigate the effects of the lesion and achieve this with as little collateral damage as possible. The mainstay of treatment is sclerotherapy with one or more of a variety of different agents including bleomycin, sodium tetradecyl sulphate and absolute alcohol. These interventional radiology techniques may be augmented with surgical manoeuvres to maximise the effect of the irritant agent by compressing or compartmentalising the lesion; this also has the effect of minimising the rapid systemic distribution of the sclerosant agent [41]. Surgical resection of anatomically amenable lesions has a role; however these procedures often are debulking procedures rather than truly curative resections. Nonetheless, debulking can often lead to significant improvement in symptoms, deformity and quality of life and should not be discounted completely.

45.4.4 Arterial Malformations

In these lesions an abnormal communication forms between arteries and veins. These may be congenital or acquired, either in accidental trauma or intentionally as a surgical procedure (for venous access in dialysis patients). In congenital lesions, there are often multiple connections between the arterial and venous system. Whatever the cause of the abnormal connection(s), the effects are similar. The flow through the arteriovenous malformation (AVM) increases. This shunting from high pressure to low pressure has several effects – the blood flow distant to the lesion reduces as more blood is diverted to the low resistance system, a proximal collateral arterial supply develops, and then this can lead to reverse flow in the artery immediately distant to the AVM. This in turn reduces the flow to the distal portion and can lead to ischaemia. The veins are thus subjected to abnormal high pressures and respond by becoming thickened and "arterialised". The abnormal flow results in

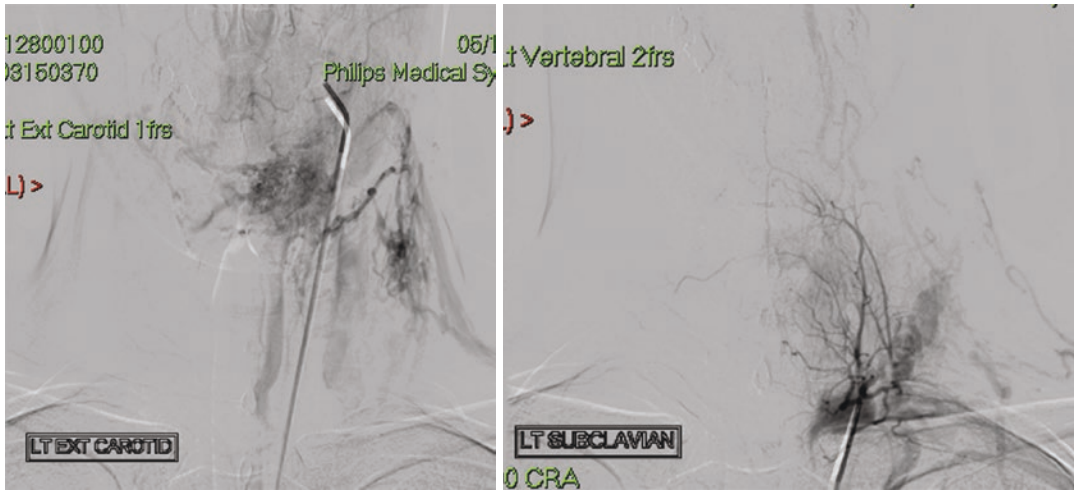

Fig. 45.3 Angiogram showing extensive fast-flow arteriovenous malformation in the left neck and upper thorax primarily supplied by left external carotid artery and left subclavian arteries

high turbulence, and hence a bruit is often heard and thrill palpated [42]. In very large AVMs, the increased blood flow can result in high-output cardiac failure [43].

45.4.4.1 Natural History

The AVMs usually inextricably enlarge with time, and many seem very sensitive to hormonal changes. Schobinger has staged the progression of AVMs (though it was Mulliken who published this classification): Stage I, Stage II, Stage III and Stage IV.

Stage I: Quiescent – cutaneous warmth and blush, Stage II: Expansion – bruit, pain, Stage III: Destruction – ulceration, bleeding, infection, Stage IV: Decompensation – hight output cardiac failure [43].

Bleeding from AVMs due to ulceration, infection or trauma can be torrential and life threatening. As the lesions enlarge, the recruitment of additional feeding vessels and draining veins increases the local damage they incur, and their adverse systemic effects progress [43].

45.4.4.2 Epidemiology

There is very little reliable data on the incidence or prevalence of extracranial AVMs. But in case series of all vascular malformations, they represent a small proportion (approximately 5%) of cases seen [44].

45.4.4.3 Classification

AVMs may be solitary, multiple and/or part of a syndrome. Intracranial AVMs are discussed below.

45.4.4.4 Management

As a result of the potentially serious consequences of progressive growth and worsening of AVMs, active intervention is recommended for virtually all lesions. The most successful treatments usually follow complete resection of the lesion; this is often difficult without the use of preoperative embolization techniques and intraoperative bleeding and in their absence can often be catastrophic. Embolisation techniques can be utilised in isolation, but this approach, without excision of the nidus, risks the development of additional supplying arteries that may not be amenable to further embolisation [45]. Some lesions because of their location or size are not resectable, and treatment with repeated embolisation procedures may be necessary to palliate the effects of inoperable lesions (Fig. 45.3). In terms of surgery, it is often helpful to consider their resection akin to the resection of a malignant tumour. In many cases resection leads to both functional and cosmetic deformities that present significant ongoing challenges.

Embolisation can be achieved with a variety of intravascular techniques and materials. These

techniques include intravascular access either to the arterial or venous side of the lesion (or both) and or direct puncture of the lesion. The materials used for embolization can be aimed at occluding the vessel by causing the blood to clot or by mechanically obstructing the vessel, and the effect may be temporary (used pre-surgically) or permanent. Alternatives include absorbable materials such as Gelfoam, nonabsorbable materials such as gelatin-acrylic spheres, liquid agents that solidify such as cyanoacrylate (Superglue), Onyx (ethylene vinyl copolymer dissolved in dimethyl sulfoxide) and PHIL (precipitating hydrophobic injectable liquid). A variety of mechanical devices are also used, coils, detachable balloons and coated metal coils (to induce thrombosis), and the use of combinations of devices and agents is common [46]. Ethanol can also be used to act as a sclerosant in AVMs.

45.5 Intracranial Vascular Malformations

Vascular malformations of the central nervous system are a heterogenous group of disorders and occur from morphogenetic areas affecting arteries veins or a combination of vessels. There may be classified histopathologically into arteriovenous malformations venous angioma, capillary telangiectasia and cavernous malformation. They may also be classified functionally into those with AV shunting (AVM, dural AV fistula and vein of Galen VOG malformation) and those without AV shunting (venous angioma, capillary telangiectasia, cavernous malformation and sinus pericranii). They may occur in isolation or be associated with syndromes.

45.5.1 Arteriovenous Malformation

Most arteriovenous malformations are parenchymal lesions (pial AVM); they are usually congenital and supratentorial in 85%. It is unusual for them to be multiple (<2%), but this may be the case when they are associated with syndromes such as HHT, Sturge-Weber or Woburn-Mason [47, 48].

Pathologically the surrounding brain parenchyma shows signs of haemorrhage with gliosis and ischaemic changes. Typically they present in the second to fourth decade of life and may present with haemorrhage, seizures or focal neurological deficit due to steal from adjacent areas or mass affect. They are associated with a cumulative lifelong risk of haemorrhage of 2–4% every year. Spontaneous regression of these lesions does occur but is exceptionally rare [49]. As in the management of cutaneous avms in order to effect a cure, complete obliteration of the nidus is required. Treatment options include endovascular embolisation followed by surgery or stereotactic radiosurgery. All but the smallest AVMs require multiple modality treatment, and the more complex may be incurable [50, 51].

45.5.2 Dural AV Fistula

Thought to occur after sinus thrombosis due to increased angiogenesis, dAVFs may vary vastly in size although multiple lesions are uncommon. They mostly affect adults (4060), and their presenting complaint depends on the sinus affected, e.g. transverse sinus/sigmoid sinus will result in a bruit and tinnitus and cavernous sinus (carotid cavernous fistula) results in pulsatile proptosis, chemosis and orbital pain. Lesions which have cortical venous drainage result in seizures dementia and progressive neurological deficit. The majority (>90%) follow a benign course; however malignant dAVFs have an aggressive clinical course with haemorrhage and neurological deficit as do multiple dAVFs. If the patient is not at risk of immediate haemorrhage, treatment may be conservative with observation with or without carotid compression. If they are at risk of haemorrhage, treatment is with embolisation of the arterial components or surgical resection of the involved dural venous sinus. In addition stereotactic radiosurgery can be used for these lesions [52].

45.5.3 Vein of Galen Aneurysmal Malformation

The embryonic precursor of the vein of Galen is a single transient midline vein known as the median prosencephalic vein and if this persists can result

in a direct AV fistula between the deep choroidal arteries and its remnant. It is rare in adults; however in symptomatic children, it may present in the neonatal period with high-output cardiac failure and a cranial bruit. In older children with macrocrania, hydrocephalus, developmental delay and seizures to headaches. If untreated, it may result in progressive brain damage, intractable cardiac failure and death. Treatment is aimed at control of the lesion in order to allow normal brain development; this is achieved with staged arterial embolisation at 4–5 months [53].

45.5.4 Cavernous Malformation

These lesions may be inherited or acquired and are formed of angiogenically immature blood-filled locules called caverns. They do not contain brain parenchyma; the adjacent parenchyma shows reactive changes. 2/3 are solitary, and they typically present at 40–60 years with seizure headache and focal neurological deficit. They have a haemorrhage risk of around 0.5% per year. If symptomatic, they may be resected microsurgically or steriotactically if surgically inaccessible [54].

45.5.5 Capillary Telangiectasia

These lesions are usually asymptomatic and discovered incidentally on brain imaging. They represent a collection of engorged thin-walled vessels surrounded by normal brain parenchyma; they are most likely congenital and do not generally require treatment [55].

45.5.6 Sinus Pericranii

Transcalvarial communication between the intra and extracranial venous drainage systems is mostly congenital. These are rare and typically present in children and young adults with a non-tender, non-pulsatile, blue, compressible scalp mass which increases in size on Valsalva manoeuvre and reduce in size on standing up. The extracranial component may be removed for cosmesis [56].

45.6 Genetics of Vascular Malformations

As the understanding of genetics increases, the number of vascular lesions that have their genetic causes grows. When considering Mendelian inheritance, there are examples of each type – sporadic, X-linked, autosomal dominant, recessive – and as the relevant molecular pathway is identified, the opportunity for targeted therapeutic interventions becomes possible. This would allow a move away from mechanical and surgical interventions to targeted drug therapies. Taking hereditary haemorrhagic telangiectasia (HTT) as an example, this is an autosomal dominant condition, the locus of the mutation is 9q33–34, and the transforming growth factor β (TGFβ) receptor is the abnormal protein. This opens up the possibility of understanding the abnormality and testing candidate therapeutic interventions in an animal model [57].

Conclusions and Clinical Perspectives

Vascular tumours and malformations are a diverse and complex group of conditions that can have major life limiting or altering effects on a wide group of patients and their families. These patients present to specialists of many disciplines and management often involves multidisciplinary care. At present surgery still has a significant role in the treatment, but its role is diminishing, and interventional radiology techniques and novel pharmacological interventions are increasing in importance. ◘ Table 45.1 outlines some of the more recent developments in the understanding of the biochemical basis of many of the conditions, their significance and potential therapeutic interventions.

Table 45.1 Table showing some recent developments in the understanding of infatile haemangioma, and vascular malformations linking the findings to explanations and possible therapeuric interventions.

	Finding	Importance	Explanation	Extrapolation
Infantile haemangioma	Tissue-specific markers (Lewis Y, merosin, FcyRII and GLUT-1) [58, 59]	Coexpression by placental microvessels	1. Embolism of placental endothelial cells via right to left shunt	High levels of VEGF produced by the placenta (and also IH). sFlt-1 produced in maternal serum and amniotic fluid binds to VEGF preventing uncontrolled growth – post-party's lack of sFlt-1 results in uncontrolled response to VEGF by IH – explaining the possible role for VEGF inhibitors
			2. Abnormal (endothelial phenotype) angioblastic colonisation of mesenchyme	
	Mesodermal-like stem cells present in IH [60]	Regulated by RAS	1. Inherent response to systemic RAS	1. Explains action of β-blockers (decrease renin levels) and ACEI/AT2RB
			2. Independent production of angiotensin 2	2. Explains incompleteness of effect and variability of response
	Hypoxia-induced mediators of progenitor cell trafficking present in IH (VEGF-A HIF-1a, MMP-9, oestrogen) [61]	Tissue hypoxia leading to angiogenesis (via hypoxia-induced mediators)	Results in endothelial progenitor cell (blood vessel precursors) mobilisation and thus neovascularisation	Explains precursor white patch
				Potential further targets for treatment (role of oestrogen esp.)
Capillary malformation	Decreased density of perivascular nervous tissue [62, 63]	Decreased vascular tone leading to progressive dilatation	Inverse correlation between nerve density and blood vessel diameter	Poorer response to laser therapy in low-density nerve high-density blood vessel lesions
				Supports a neural role in progression of CM
	Increased VEGF-A and VEGF-R2 [64]	Known to be involved in vascular tissue proliferation	Could be involved in proliferation or vast dilatation	Possible role for VEGF blockers
	Specific mutation	Found in lesional skin of both syndromic and non-syndromic CMs and also in affected brain tissue of patients with Sturge-Weber	Timing of mutation possibly explains severity and defines the tissues involved	Potential target for gene therapy
	Somatic activating mutation encoding a p.Arg183Gln amino acid substitution in GNAQ) [65]			

(continued)

Table 45.1 (continued)

	Finding	Importance	Explanation	Extrapolation
Lymphatic malformations	VEGF-C [66]	Present in high levels in LMs esp. in proliferative phase	Rapamycin reduces cell proliferation via mTOR in VEGF-C driven growth in the proliferative phase	Rapamycin could be used for some cases (either in the proliferative phase or in cases where cell proliferation continues)
				VEGF-C could potentially be used as a marker for proliferation
	Genetic abnormalities in thePI3K/AKT/mTOR pathway [67]	Present in CLOVES, proteus, Klippel–Trénaunay syndrome	PI3K inhibitors reduce proliferation in individuals with these genetic abnormalities	PI3K inhibitors reduce proliferation in individuals with these genetic abnormalities
Venous malformations	Endothelial receptor on ch9 [68]	Autosomal dominant inheritance of a gene in families with VMs	The EC-specific receptor tyrosine kinase TIE2 gene had been mapped previously to 9p21 by in situ hybridization	Explains familial VM
				Genetic screening for affected individuals
				Extrapolation of mechanism leading to new targets for therapy
	Tyrosine kinase receptor deficiency [69]	Thought to cause abnormal interaction between smooth muscle and endothelial cells leading to fewer muscle cells surrounding dilated venous channels	Tie-2 receptor TK has a specific kinase-activating mutation which leads to an increase in receptor autophosphorylation and altered signalling thereafter	Specific points on the signalling pathway could provide targets for therapy
Arteriovenous malformations	TGFβ signalling pathway	A number of targets on the TGF signalling pathway are implicated in the formation of AVMs	Alk-1, Eng, SMAD 4-deficient mouse models all exhibit increased AVM formation	These could represent important targets in themselves for future therapies or be used a study models for future therapies as root cause an effect become clear with further research
	Alk-1			
	Eng			
	SMAD 4 [70]			
	NOTCH receptor [71, 72]	NOTCH 4 activity is increased in AVMs unknown role	Notch receptors are transmembrane proteins that promote arterial endothelial cell (EC) specification by enhancing expression of arterial molecular markers and suppression of venous marker expression. Abnormal signalling induces enlarged AV connections and shunting (venolisation of arteries)	A potential target for future therapies
		NOTCH 1- and 3-deficient mouse models exhibit increased rates of AVMs		

Gaps in Knowledge

There are still huge chasms in our understanding of how the identified genetic changes, receptor differences, protein expression and environmental factors interact to form and allow these conditions to progress; however this is an extremely exciting time as the surface is beginning to be scratched in unravelling some of the complexities involved.

- Pathogenesis of vascular tumours
- Pathogenesis of vascular malformations
- Full mechanism of action of propranolol in the management of infantile haemangiomas
- The interactions and relationships between the genotype and phenotypes

References

1. Nosher JL, Murillo PG, Liszewski M, et al. Vascular anomalies: a pictorial review of nomenclature, diagnosis and treatment. World J Radiol. 2014;28:677–92.
2. Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues). Adv Dermatol. 1998;12:375.
3. ISSVA Classification of Vascular Anomalies ©2018 International Society for the Study of Vascular Anomalies. Available at "issva.org/classification". Accessed [01/09/18].
4. Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. Pediatr Dermatol. 2008;25(2):168–73.
5. Drolet BA, Swanson EA, Frieden IJ, Hemangioma Investigator Group. Infantile hemangiomas: an emerging health issue linked to an increased rate of low birth weight infants. J Pediatr. 2008;153(5):712–5, 5 e1.
6. Hoornweg MJ, Smeulders MJ, Ubbink DT, van der Horst CM. The prevalence and risk factors of infantile haemangiomas: a case-control study in the Dutch population. Paediatr Perinat Epidemiol. 2012;26(2):156–62.
7. Tal R, Dotan M, Lorber A. Approach to haemangiomatosis causing congestive heart failure. Acta Paediatr. 2016;105:600.
8. Vradenborg AD, Janmohammed SR, de Laat PCJ, Madern GC, Oranje AP. Multiple cutaneous infantile haemangioma and the risk of internal hemangioma. Practical paediatric dermatology. Cham: Springer; 2016.
9. Finn MC, Glowacki J, Mulliken JB. Congenital vascular lesions: clinical application of a new classification. J Pediatr Surg. 1983;18:894–900.
10. Bauland CG, Lüning TH, Smit JM, et al. Untreated haemangiomas: growth patterns and residual lesions. Plast Reconstr Surg. 2011;127:1643.
11. Ronchese F. The spontaneous involution of cutaneous vascular tumours. Am J Surg. 1953;86(4):376–86.
12. North PE, Waner M, Mizeracki A, Mihm MC Jr. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. Hum Pathol. 2000;31(1):11–22.
13. Léauté-Labrèze C, Prey S, Ezzedine K. Infantile haemangioma: part II. Risks, complications and treatment. J Eur Acad Dermatol Venereol. 2011;25:1254–60.
14. Novosibirsk M, Baselga E, Beltran S, et al. Interventions for infantile haemangiomas of the skin. Cochrane Database Syst Rev. 2018;(4):CD006545.
15. Coulie J, Coyette M, Moniotte S, Bataille AC, Boon LM. Has propranolol eradicated the need for surgery in the management of infantile hemangioma? Plast Reconstr Surg. 2015;136(4 Suppl):154.
16. Kelly M. Kasabach-merritt phenomenon. Pediatr Clin N Am. 2010;57:1085–9.
17. Happle R. Capillary malformations: a classification using specific names for specific skin disorders. J Eur Acad Dermatol Venereol. 2015;29:2295–305.
18. Bioxeda P, de Misa RF, Arrazola JM, Perez B, Harto A, Ledo A. Facial angioma and the Sturge-Weber syndrome: a study of 121 cases. Med Clin (Barc). 1993;101:1–4.
19. Thomas-Sohl KA, Vaslow DF, Maria BL. Sturge-Weber syndrome: a review. Pediatr Neurol. 2004;30(5):303–10.
20. Sharan S, Swamy B, Taranath DA, et al. Port-wine vascular malformations and glaucoma risk in Sturgeon-Weber syndrome. J AAPOS. 2009;13(4):374–8.
21. Praticò A, et al. Megalencephaly capillary malformation syndrome. J Pediatr Neurol. 2018. https://doi.org/10.1055/s-0038-1667010.
22. Tennant LB, Mulliken JB, Perez-Atayde AR, Kozakewich HP. Verrucous hemangioma revisited. Pediatr Dermatol. 2006;23(3):208–15.
23. Rozas-Muñoz E, Frieden IJ, Roé E, Puig L, Baselga E. Vascular stains: proposal for a clinical classification to improve diagnosis and management. Pediatr Dermatol. 2016;33(6):570–84.
24. Shovlin CL, Guttmacher AE, Buscarini E, Faughnan ME, Hyland RH, Kjeldsen AD, et al. Diagnostic criteria for hereditary hemorrhagic telan- giectasia (Rendu-Osler-Weber syndrome). Am J Med Genet. 2000;91:65–6.
25. Clodius L. Surgery for the facial port wine stain: technique and results. Ann Plast Surg. 1986;16(6):457–71.
26. Faurschou A, Olesen AB, Leonardi-Bee J, et al. Lasers or light sources for treating portwine stains. Cochrane Database Syst Rev. 2011;(11):CD007152.
27. Enjolras O. Classification and management of the various superficial vascular anomalies: hemangioma and vascular malformation. J Dermatol. 1997;24:701–10.
28. Elluru RG, Balakrishnan K, Padua HM. Lymphatic malformations: diagnosis and management. Semin Pediatr Surg. 2014;23(4):178–85. WB Saunders.
29. Tasnadi G. Epidemiology and etiology of congenital vascular malformations. Semin Vasc Surg. 1993;6(4):200–3.
30. de Serres LM, Sie KC, Richardson MA. Lymphatic malformations of the head and neck. A proposal for staging. Arch Otolaryngol Head Neck Surg. 1995;121(5):577–82.
31. Partovi S, Vidal L, Nakamoto D, Lu Z, Buethe J, Coffey M, Patel I. Lymphatic malformation treatment in adult and pediatric populations using real-time MRI guided percutaneous sclerotherapy. J Vasc Interv Radiol. 2016;27(3):S221–2.

32. Koh LH, Tan HK. The successful use of bipolar radiofrequency ablation (coblation) in treatment of a lymphatic malformation affecting the upper airway. Int J Otorhinolaryngol Head Neck Surg. 2016;2(4):267–70.
33. Mirza B, Ijaz L, Saleem M, et al. Cystic hygroma: an overview. J Cutan Aesthet Surg. 2010;3:139–44.
34. Fliegelman LJ, Friedland D, Brandwein M, Rothschild M. Lymphatic malformation: predictive factors for recurrence. Otolaryngol Head Neck Surg. 2000;123(6):706–10.
35. Maclellan RA, Goss JA, Greene AK. Vascular malformation enlargement during menopause. J Craniofac Surg. 2018;29(5):1271–2.
36. Dompmartin A, Vikkula M, Boon LM. Venous malformation: update on aetiopathogenesis, diagnosis and management. Phlebology. 2010;25:224–35.
37. Politi M, Barbera L, Roth C, Papanagiotou P. Diagnosis and treatment of vascular malformations. Hell J Radiol. 2018;3(3):41–53.
38. Nguyen JT, Koerper MA, Hess CP, Dowd CF, Hoffman WY, Dickman M, Frieden IJ. Aspirin therapy in venous malformation: a retrospective cohort study of benefits, side effects, and patient experiences. Pediatr Dermatol. 2014;31(5):556–60.
39. Clemens RK, Pfammatter T, Meier TO, Alomari AI, Amann-Vesti BR. Vascular malformations revisited. Vasa. 2015;44(1):5–22.
40. Wilkins RH. Natural history of intracranial vascular malformations: a review. Neurosurgery. 1985;16(3):421–30.
41. Jackson IT, Keskin M, Yavuzer R, Kelly CP. Compartmentalization of massive vascular malformations. Plast Reconstr Surg. 2005;115(1):10–21.
42. Allen LS, Mulliken JB, Zurakowski D, Fishman S, Greene AK. Extracranial arteriovenous malformations: natural progression and recurrence after treatment. Plast Reconstr Surg. 2010;125:1185–94.
43. Kohout MP, Hansen M, Pribaz JJ, Mulliken JB. Arteriovenous malformations of the head and neck: natural history and management. Plast Reconstr Surg. 1998;102:643–54.
44. Lee BB, Lardeo J, Neville R. Arterio-venous malformation: how much do we know? Phlebology. 2009;24:193–200.
45. Lam K, Pillai A, Reddick M. Peripheral arteriovenous malformations: classification and endovascular treatment. Appl Radiol. 2017;46:15–21.
46. Nassiri N, Cirillo-Penn NC, Thomas J. Evaluation and management of congenital peripheral arteriovenous malformations. J Vasc Surg. 2015;62(6):1667–76.
47. Willinsky RA, Lasjaunias P, Terbrugge K, Burrows P. Multiple cerebral arteriovenous malformations (AVMs). Neuroradiology. 1990;32(3):207–10.
48. Morgan T, McDonald J, Anderson C, Ismail M, Miller F, Mao R, Madan A, Barnes P, Hudgins L, Manning M. Intracranial hemorrhage in infants and children with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome). Pediatrics. 2002;109(1):e12.
49. Pasqualin A, Vivenza C, Rosta L, Scienza R, Da Pian R, Colangeli M. Spontaneous disappearance of intracranial arterio-venous malformations. Acta Neurochir. 1985;76(1–2):50–7.
50. Simon CH, Chan MS, Lam JM, Tam PH, Poon WS. Complete obliteration of intracranial arteriovenous malformation with endovascular cyanoacrylate embolization: initial success and rate of permanent cure. Am J Neuroradiol. 2004;25(7):1139–43.
51. Flickinger JC, Kondziolka D, Lunsford LD, Pollock BE, Yamamoto M, Gorman DA, Schomberg PJ, Sneed P, Larson D, Smith V, McDermott MW. A multi-institutional analysis of complication outcomes after arteriovenous malformation radiosurgery. Int J Radiat Oncol Biol Phys. 1999;44(1):67–74.
52. Harrigan MR, Deveikis JP. Dural arteriovenous fistulas. In: Handbook of cerebrovascular disease and neurointerventional technique. 2013. p. 603–25.
53. Bhattacharya JJ, Thammaroj J. Vein of Galen malformations. J Neurol Neurosurg Psychiatry. 2003;74(Suppl 1):i42–4.
54. Bergametti F, Denier C, Labauge P, Arnoult M, Boetto S, Clanet M, Coubes P, Echenne B, Ibrahim R, Irthum B, Jacquet G. Mutations within the programmed cell death 10 gene cause cerebral cavernous malformations. Am J Hum Genet. 2005;76(1):42–51.
55. Ruzevick J, White-Dzuro G, Levitt M, Kim L, Ferreira M. Intracranial arteriovenous malformations. In: Evidence-based management of head and neck vascular anomalies. Cham: Springer; 2018. p. 179–191.
56. Manjila S, Bazil T, Thomas M, Mani S, Kay M, Udayasankar U. A review of extraaxial developmental venous anomalies of the brain involving dural venous flow or sinuses: persistent embryonic sinuses, sinus pericranii, venous varices or aneurysmal malformations, and enlarged emissary veins. Neurosurg Focus. 2018;45(1):E9.
57. Zarrabeitia R, Aurrecoechea E, Fariñas-Alvarez C, Fontalba A, Zarauza J, Ojeda L, Parra JA. In: Hereditary haemorrhagic telangiectasia pathological nailfold capillaroscopy is associated with pulmonary arteriovenous malformations.
58. Hornig C, Barleon B, Ahmad S, Vuorela P, Ahmed A, Weich HA. Release and complex formation of soluble VEGFR-1 from endothelial cells and biological fluids. Lab Investig. 2000;80(4):443–54.
59. Banks RE, Forbes MA, Searles J, et al. Evidence for the existence of a novel pregnancy-associated soluble variant of the vascular endothelial growth factor receptor, Flt-1. Mol Hum Reprod. 1998;4(4):377–86.
60. Bischoff J. Progenitor cells in infantile hemangioma. J Craniofac Surg. 2009;20(Suppl 1):695–7.
61. Kleinman ME, Greives MR, Churgin SS, et al. Hypoxia-induced mediators of stem/progenitor cell trafficking are increased in children with hemangioma. Arterioscler Thromb Vasc Biol. 2007;27(12):2664–70.
62. Chang CJ, Yu JS, Nelson JS. Confocal microscopy study of neurovascular distribution in facial port wine stains (capillary malformation). J Formos Med Assoc. 2008;107(7):559–66.
63. Smoller BR, Rosen S. Port-wine stains. A disease of altered neural modulation of blood vessels? Arch Dermatol. 1986;122(2):177–9.
64. Vural E, Ramakrishnan J, Cetin N, Buckmiller L, Suen JY, Fan CY. The expression of vascular endothelial growth factor and its receptors in port-wine stains. Otolaryngol Head Neck Surg. 2008;139(4):560–4.

65. Couto JA, Huang L, Vivero MP, Kamitaki N, Maclellan RA, Mulliken JB, et al. Endothelial cells from capillary malformations are enriched for somatic GNAQ mutations. Plast Reconstr Surg. 2016;137(1):77e–82e.
66. Baluk P, Yao LC, Flores JC, Choi D, Hong YK, McDonald DM. Rapamycin reversal of VEGF-C–driven lymphatic anomalies in the respiratory tract. JCI Insight. 2017;2(16).
67. Boscolo E, Coma S, Luks VL, et al. AKT hyperphosphorylation associated with PI3K mutations in lymphatic endothelial cells from a patient with lymphatic malformation. Angiogenesis. 2015;18:151–62.
68. Boon LM, Mulliken JB, Vikkula M, Watkins H, Seidman J, Olsen BR, Warman ML. Assignment of a locus for dominantly inherited venous malformations to chromosome 9p. Hum Mol Genet. 1994;3:1583–7.
69. Gallione CJ, Pasyk KA, Boon LM, Lennon F, Johnson DW, Helmbold EA, Markel DS, Vikkula M, Mulliken JB, Warman ML, et al. A gene for familial venous malformations maps to chromosome 9p in a second large kindred. J Med Genet. 1995;32:197–9.
70. Crist AM, Lee AR, Patel NR, Westhoff DE, Meadows SM. Vascular deficiency of Smad4 causes arteriovenous malformations: a mouse model of Hereditary Hemorrhagic Telangiectasia. Angiogenesis. 2018: 1–8.
71. Kofler NM, Cuervo H, Uh MK, Murtomäki A, Kitajewski J. Combined deficiency of Notch1 and Notch3 causes pericyte dysfunction, models CADASIL, and results in arteriovenous malformations. Sci Rep. 2015;5:16449.
72. Murphy PA, Kim TN, Huang L, Nielsen CM, Lawton MT, Adams RH, Schaffer CB, Wang RA. Constitutively active Notch4 receptor elicits brain arteriovenous malformations through enlargement of capillary-like vessels. Proc Natl Acad Sci. 2014;111(50):18007–12.