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Vascular anomalies of the upper limb

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ABSTRACT

Vascular anomalies are common in the upper extremity, but there continues to be a relative paucity of information about them in the hand and upper limb surgical literature. The wide spectrum of pathology and an inconsistent use of terminology make vascular anomalies susceptible to incorrect diagnosis and as a result to misdirected management. This article aims to provide an update on vascular anomalies relevant to the upper limb, focusing on significant advances in pathogenesis and genetics, classification systems, diagnosis, and treatment.

Level of Evidence: V
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ABSTRACT

Vascular anomalies are common in the upper extremity, but there continues to be a relative paucity of information about them in publications dealing with surgery in the hand and upper limb. The wide spectrum of pathology and an inconsistent use of terminology make vascular anomalies susceptible to incorrect diagnosis and as a result, to misdirected management. This article aims to provide an update on vascular anomalies relevant to the upper limb, focusing on significant advances in pathogenesis and genetics, classification systems, diagnosis, and treatment.
INTRODUCTION

Vascular anomalies account for 2-6% of all tumours in the upper extremity (Jacobs et al., 2010; McClinton, 1993; Mendel and Louis, 1997). However, there is a relative paucity of information about them in publications concerning surgery of the hand and upper limb. The wide spectrum of pathology ranging from minor "birthmarks" to complex life-threatening conditions (Wassef et al., 2015), as well as an inconsistent use of terminology make vascular anomalies susceptible to incorrect diagnosis and as a result, to misdirected management. This article aims to provide an update on vascular anomalies relevant to the upper limb by reviewing recent significant advances in pathogenesis and genetics, and to assess their influence on the evolution of classification systems, diagnosis, and treatment.

VASCULAR DEVELOPMENT AND PATHOGENESIS OF VASCULAR ANOMALIES

The upper limbs of the developing human embryo form from around day 26 post-fertilization and are fully formed by around day 56 (DeSesso, 2017; Vargesson and Hootnick, 2017). Vascular development is central to the normal formation and outgrowth of the limb, and occurs through the process of angiogenesis whereby existing vessels produce new vessels by the proliferation and migration of endothelial cells into new, previously avascular areas (usually induced through cellular hypoxia). Intersegmental arteries (that run in between the somites from the aorta) vascularize the limb bud by forming a capillary vascular plexus throughout the developing limb.
bud and immediately after limb bud formation. (Vargesson, 2019 In Press) Rapidly (within a day) one of the intersegmental vessels, the subclavian artery, becomes dominant and from then on solely supplies the outgrowing limb vascular plexus (Vargesson and Hootnick, 2017). As outgrowth of the limb bud continues, the vascular plexus starts to differentiate (with regression of some areas) in a proximal to distal manner, into distinctive arterial and venous patterns, which, owing to molecular differences, are prevented from fusing to maintain normal blood flow (Vargesson, 2003). For example, the vascular plexus of the upper limb begins to differentiate so that the subclavian artery feeds into the axillary artery, which then feeds into the brachial artery (supplying parts of the humerus and upper arm). Subsequently, further differentiation of the vascular plexus occurs by splitting into the radial and ulnar arteries, which will ultimately lead into the arteries (e.g. the anterior interosseous) supplying the digital plate (DeSesso, 2017; Rodríguez-Niedenführ et al., 2001; Vargesson and Hootnick, 2017; Vargesson, 2019 In Press). This process, whereby the embryonic vascular plexuses develop into the adult vascular patterns, is also known as the vascular transition and occurs between week 5 and 7 (Levinsohn et al., 1991; Vargesson and Hootnick, 2017). The vascular transition accompanies and is intimately linked to the appearance of cartilage precursors of the bony elements, also in a proximal to distal fashion (Vargesson and Hootnick, 2017). For example, the humerus forms before the radius and ulna, which form before the digits – and as the elements form, they require vascularization to maintain outgrowth (Vargesson, 2003; Vargesson and Hootnick, 2017). Failure of the vascular transition or an inhibition into the correct vascular patterns causes vessels to be in the wrong position and can result in bony elements with reduced or no vascularization, which then results in malformed or missing bony elements (Levinsohn et al., 1991; Vargesson and Hootnick, 2017).
Consequently, this mechanism has been proposed as an explanation for some congenital limb reduction syndromes (such as radial dysplasia) as well as for teratogen-induced limb differences (Levinsohn et al., 1991; Vargesson, 2015; Vargesson and Hootnick, 2017; Vargesson, 2019 In Press).

In summary, the development of a functional and controlled vasculature is essential for normal limb development. Vascular failure, inhibition or disruption can result in congenital limb differences. Teratogens such as thalidomide can cause vessel failure and are linked with causation of limb differences through vascular loss (Therapontos et al., 2009; Vargesson, 2015). Other processes, such as thrombi from the maternal placenta as well as constriction bands have also been linked to the causation of limb differences (Holmes et al., 2018).

**CLASSIFICATION**

**Clinical classification**

The 1996 International Society for the Study of Vascular Anomalies (ISSVA) divided vascular lesions into proliferative vascular lesions or tumours (Enjolras, 1997) or vascular malformations. Vascular malformations were further subdivided on the basis of their predominant vessel type into capillary (CM), venous (VM), lymphatic (LM), arterial (AM), arterio-venous (AVM), or combined malformations (CVM). Additional disease entities have been identified and a more detailed understanding of the histopathology and genetics has led to the 2014 updated ISSVA classification (Table 1). Vascular malformations can be further categorized based on their flow...
characteristics, as determined by Doppler ultrasound, into low/no-flow (CM, LM, VM) and high-flow anomalies (AVM, arterio-venous Fistulas, AVF) (Mulliken et al., 2000; Mulliken and Glowacki, 1982).

Genetic classification

More recently, modern genetic sequencing techniques have enabled the reclassification of vascular anomalies based on causative genetic mutations rather than on phenotypic subdivisions. Somatic mosaic mutations in the Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) gene, which encodes the catalytic subunit of the enzyme Phosphatidylinositol 3-kinase (PI3K), have been found in malformation/overgrowth syndromes (Figure 1). This led to the designation of the term “PIK3CA-Related Overgrowth Spectrum” of disorders (PROS), ranging from isolated anomalies to more complex segmental overgrowth disorders (Keppler-Noreuil et al., 2015). These recent genetic findings are likely to have significant impact on the understanding of vascular anomalies and their classification and medical treatments.

CLINICAL PRESENTATIONS AND MANAGEMENT OF SPECIFIC VASCULAR TUMOURS

Benign vascular tumours

Infantile haemangioma (IH) is the most common tumour of infancy (Kilcline and Frieden, 2008) with an incidence within the limbs of around 15%. Most IHs appear
during the neonatal period within the first two weeks of life, but about one-third would already be present at birth, usually in the form of telangiectasia or a pink macular stain (Mulliken et al., 2000). Classically, IHs appear cherry red and lie in the papillary dermis (Figure 2). IHs are characterized by a typical pattern of initial rapid proliferative growth during the first 6 to 12 months, followed by a period of slow involution or regression over several years. In 50% of infants, involution is complete by five years, in 70% by seven years and the remainder by 10 years of age. After regression, 50% of affected children present with normal skin in the area of the former lesion, but larger lesions tend to leave an area of wrinkled skin overlying fibro-fatty tissue.

As opposed to IHs, congenital haemangiomas (CH) are characterized by a distinct clinical course and histopathology. They form in utero, can be detected as early as in the second trimester of pregnancy, and are fully formed at birth (Boon et al., 1996; Bronshtein et al., 1992). CHs can be further divided into rapidly involuting (RICH), partly involuting (PICH), and non-involuting (NICH) types. Regression in RICH begins early, with full involution by 9 to 14 months. NICHs persist as the child grows (Boon et al., 1996; Enjolras et al., 2001). Unlike IHs, their endothelial cells do not express Glut-1 (Wassef et al., 2015).

Most haemangiomas on the upper limbs are small and regress following a predictable pattern without the need for intervention. Hence, they should be allowed to proliferate and involute under careful observation (Fevurly and Fishman, 2012). In cases of larger, more functionally incapacitating lesions, systemic propranolol might be considered as a first-line treatment (Holland et al., 2010). Topical Beta-blockers are...
occasionally used but have so far shown only modest results (Pope and Chakkittakandiyl, 2010).

Most commonly, decisions about surgery are delayed until complete involution has taken place. Early surgical intervention during the proliferative phase may be indicated in cases of recurrent infection, ulceration, or bleeding, especially when the haemangioma is well-localized. Early excision may also be considered in cases where removal is very likely to be required, even after involution, and the same optimal cosmetic result can be achieved (Fevurly and Fishman, 2012).

Locally aggressive or borderline vascular tumours

More invasive, benign, or locally aggressive and borderline vascular tumours of clinical significance are tufted angiomas (TA) and kaposiform hemangioendotheliomas (KHE). TA and KHE can be present at birth and are probably more of a spectrum of lesions than distinct entities although both lesions show distinct histopathological features. Clinically, they present with erythematous or brown plaques with surrounding ecchymosis and occasionally generalized petechiae (Figure 3).

TA and KHE can be associated with profound thrombocytopenia (Kasabach-Merritt Phenomenon, KMP) (Enjolras et al., 1997), with a significant risk for intracranial, pleural-pulmonic, intraperitoneal, or gastro-intestinal haemorrhage with a mortality of up to 30% (Martinez-Perez et al., 1995). Sirolimus, an inhibitor of the PI3K/mTOR pathway, has now become a first-line treatment in KHE, and its use is rapidly
expanding in the treatment of other vascular malformations and overgrowth syndromes (Enjolras et al., 2000; Gruman et al., 2005).

Malignant vascular tumours

In atypical presentations, malignant vascular tumours, although rare, must be kept in mind within the differential diagnosis. In unclear cases, a biopsy and histopathological diagnostics should be obtained. Management depends on the aggressiveness of the subtype and includes surgery and chemotherapy (Board, 2002).

CLINICAL PRESENTATION AND MANAGEMENT OF SPECIFIC VASCULAR MALFORMATIONS

Low flow vascular malformations

Capillary malformations (CMs), often referred to as “port wine stains” are composed of dilated capillaries and post-capillary venules that are located within the superficial dermis (Smoller and Rosen, 1986). Present at birth, they are the commonest vascular malformations, occurring in 0.3% of all new-borns (Jacobs et al., 2010). CMs generally persist lifelong and may demonstrate thickening and darkening due to vessel dilatation. They can be associated with overgrowth, or may be indicative of the presence of other vascular malformations (LM, VM) or syndromes (combined vascular malformations, vascular malformations associated with other anomalies) (Wassef et al., 2015).
CMs on the upper extremity rarely require treatment other than for cosmetic reasons. The pulse-dye laser demonstrates good clinical response rates with a minimal complication risk. The optimal timing for laser treatment remains controversial, but early treatment appears beneficial (van der Horst et al., 1998).

Lymphatic malformations (LMs) are composed of dilated channels or cysts and can be classified into microcystic (cysts <1cm), macrocystic (cysts >1cm), or mixed type lesions, depending on the diameter of the cysts (Figure 4). In the upper limb, LMs are generally of mixed type, but tend to be microcystic below the elbow. On inspection, the overlying skin of larger cysts can have a bluish appearance. Involved skin can also be thickened or puckered and may develop vesicles that have a propensity to weep, which increases the risk of infection. In the upper limbs, LMs are often associated with fibro-fatty tissues, and are most often confined to the skin and subcutis without penetration into the deep fascia or muscle. Occasionally, LMs are associated with skeletal overgrowth and distortion (Boyd et al., 1984), although they do not typically infiltrate bone or joints (Upton and Marler, 2005).

Compression garments can be effective as a first line measure for some symptomatic lesions (Jacobs et al., 2010); however, a lack of compressibility and the sheer size of some lesions can render compression ineffective. Additional problems associated with LMs include weeping, infections, and intralesional bleeding. Intralesional bleeding usually presents as rapid painful enlargement within the LM with associated ecchymosis. These episodes typically resolve with rest and analgesia. Pain and swelling may also occur as a result of bacterial or viral infection, which can be transmitted from a systemic infection into a LM. Early broadband spectrum antibiotic
treatment is indicated, and prolonged intravenous therapy may be required in order to adequately treat infection in recalcitrant cases.

Sclerotherapy is a well-established treatment modality for LMs, especially those with a significant macrocystic component. Sclerotherapy is also used as an adjunct pre- and post-surgical debulking (Morgan et al., 2016). There is a growing body of evidence supporting the efficacy of sirolimus (Morgan et al., 2016), which has been shown to be effective in trial cases of LMs and mixed lympho-venous malformations (Ricci, 2017; Trenor, 2016).

Surgery for LMs can be complex, and careful planning is essential. Complete resection is often not possible, and recurrence rates of up to 30% have been reported (Morgan et al., 2016). The resection is often best done in a staged manner (Upton and Marler, 2005) with the use of manoeuvres such as the administration of tranexamic acid, tourniquet control and diathermy assisted dissection to help minimize intra-operative blood loss (Ghadimi et al., 2016). Pre-operative D-Dimer and fibrinogen levels can be useful predictors of the degree of vascularity in cases of mixed lymphovenous lesions. Incisions across joints and extensions into the axilla should be zigzagged to prevent joint contractures and allow for future growth. For each side of a digit, hand, or forearm, separate procedures should be used, and combined dorsal and palmar dissections should be avoided (Upton and Marler, 2005). Mid-lateral or medial incisions are less visible and therefore preferred over dorsal scars. Extensive poorly delineated lesions in the hand and forearm may be better suited to treatment with cautious sclerotherapy.
Venous malformations (VM) are mostly sporadic, generally occurring as solitary lesions. Clinically, they present as soft compressible masses that often have a bluish appearance when superficial (Figure 5). VMs are present at birth and can sometimes go unnoticed initially but will grow commensurately with the child. Expansion of venous lesions typically occurs during the adolescent growth spurt. Painful episodes of thrombosis within VMs are common due to a low rate of blood flow, and can lead to the formation of characteristic phleboliths (Wassef et al., 2015). VMs can be extensive, even involving the axilla and chest wall and extend across the deep fascia into muscles. Despite significant involvement, affected musculature of the upper limb may still function well. Recurrent haemarthrosis can be a debilitating problem in VMs surrounding joints (Upton et al., 1999).

Glomuvenous malformations (GVMs) are distinct subsets of vascular malformation, characterised by the presence of a variable number of glomus cells (Boon et al., 2004). They are typically found on the extremities and account for approximately 5% of all VMs. GVMs are characterised by their superficial location, characteristic pink to purple-blue colour, and so-called cobblestone appearance. Unlike VMs, GVMs are typically firm, and pain is aggravated by compression garments (Boon et al., 2004). They are usually well-localized and respond well to surgical excision.

The basic surgical principles in VMs are very similar to those outlined for LMs. All possible measures to reduce bleeding must be considered. Pre-operative sclerotherapy is useful in some cases to reduce the risk of bleeding from surgery (James et al., 2011; Morgan et al., 2016) and pre-operative optimization of clotting factors and treatment
with low molecular weight heparin to raise low fibrinogen levels can be beneficial in some cases with localised intravascular coagulation (LIC) (Dompmartin et al., 2008; Mazoyer et al., 2002; Zhuo et al., 2017). Complete resection is often not possible, as VMs tend to extend beyond the deep fascia and involve muscles more commonly than LMs. Furthermore, it must be remembered that muscle function is often remarkably good despite extensive infiltration. Therefore, resection of involved muscles must be considered very carefully (Upton and Marler, 2005). Post-operative custom-made compression garments are very useful for tamponading surgical fields and dressing around difficult anatomical contours, for example the axilla and limbs.

Fibro-adipose vascular anomaly (FAVA) is a newly described fibro-fatty muscle-infiltrating complex vascular malformation with clinical, radiological and histopathological features distinct from intramuscular VMs (Alomari et al., 2014; Fernandez-Pineda et al., 2014). FAVA patients typically present with unusually high levels of pain and sometimes joint contractures, and usually show a poor response to treatments such as sclerotherapy. In the upper limb, FAVAs typically affect the forearm musculature. FAVAs are characterized by a more solid, heterogeneous diffuse appearance on MRI and ultrasound imaging unlike classical VMs, which are more fluid (Johnson and Navarro, 2017). Surgery for FAVAs within the upper limb is difficult, as extensive muscle involvement and neurovascular entrapment are common (Figure 6). In these cases, compartment decompression, partial resection, neurolysis, and tendon lengthening can be very effective. In addition, image-guided percutaneous
cryoablation is emerging as a safe and effective treatment for symptomatic FAVA (Fernandez-Pineda et al., 2014; Shaikh et al., 2016).

High flow vascular malformations

Owing to their locally aggressive nature, AVMs are the most formidable vascular malformation with potential to threaten limb and life. They are high-flow lesions, consisting of disorganized arteries and veins that directly communicate by bypassing the high-resistance capillary bed (Fevurly and Fishman, 2012). With increased shunting, a phenomenon of blood flow ‘steal’ can occur, which leads to problems of distal ischaemia including pain, ulceration, and tissue necrosis (Upton and Marler, 2005). The clinical progression of AVMs from quiescent to aggressive lesions with cardiac failure is reflected by the staging system described by Schobinger (Kohout et al., 1998; Lowe et al., 2012) (Table 2). However, AVMs, particularly those affecting the upper limb, do not necessarily progress consecutively through each stage (Upton and Marler, 2005).

Indications for operative treatment include uncontrollable progressive pain, digital ulceration, bleeding, compartment syndrome, cardiac failure or overall failure to thrive (Upton and Marler, 2005). Operative treatment is usually a combination of angiographic embolization and surgical resection. Pre-surgical embolization can improve outcomes and reduce morbidity (Morgan et al., 2016).

Combined vascular malformations
Combined vascular malformations (CVMs) contain at least two vascular malformations in one lesion; they can be simple malformations, malformations of major named vessels or a combination of both types. Multiple combinations exist; these lesions are often associated with skeletal and soft tissue overgrowth and abnormalities of the viscera and in rare cases undergrowth (Boyd et al., 1984). The principles of CVM management are similar to those outlined above for simple vascular malformations.

Vascular malformations associated with other anomalies

Klippel-Trenaunay-syndrome (KTS) represents a triad of capillary malformation, lympho-venous malformation and limb overgrowth. More recently, it has been shown that what was classically described as KTS is actually part of a spectrum of conditions that result from PIK3CA-related somatic mosaic mutations (Figure 1). KTS characteristically affects one lower extremity (88%) (Figure 7A), but bilateral cases and involvement of an upper extremity (29%) (Figure 7B), and extension into the trunk (23%) are not uncommon (Jacob et al., 1998; Lobo-Mueller et al., 2009).

CLOVES is an acronym (Congenital, Lipomatous, Overgrowth, Vascular malformations, Epidermal naevi and Spinal/Skeletal anomalies and/or Scoliosis, Seizures) for a syndrome with underlying somatic activating mutations in PIK3CA (Alomari, 2009; Kurek et al., 2012; Sapp et al., 2007). The clinical signs are usually present at birth and may be identified by prenatal imaging (Fevurly and Fishman, 2012). CLOVES is characterized by limb asymmetry with involvement of the upper limb in 50% of cases. The typical lipomatous masses on the trunk and/or limbs are accompanied by overlying CM and other associated low flow lesions (VM, LM) and
high-flow (AVM) vascular malformations. Other manifestations include epidermal nevi, bony anomalies including scoliosis, acral anomalies such as wide or triangular feet, syndactyly or macrodactyly and a widened gap between the first and the second toes (sandal gap).

Proteus syndrome (PS) is a rare condition that typically presents with segmental overgrowth, vascular anomalies including CM, VM, and LM, epidermal nevi, hyperplasia of multiple tissues, and a propensity to develop tumours (Figure 8). A mosaic somatic mutation of the AKT1 gene has been found in more than 90% of patients with PS (Johnson and Navarro, 2017). The striking phenotypic resemblance of Proteus to “PIK3CA-Related Overgrowth Spectrum” of disorders (PROS) might be because AKT1 is a downstream of PIK3CA and therefore activates similar downstream elements. In contrast to PROS disorders, the lesions in PS are not present at birth, but are characterized by progressive disproportionate overgrowth and may present with pathognomonic connective tissue naevi (Biesecker et al., 1999).

Parkes Weber syndrome (PWS) is distinguished from KTS by the presence of a high-flow arterio-venous malformation, in addition to a capillary one (CAVM) and limb hypertrophy (Weber, 1908; Weber, 1918; Young, 1988). PWS is caused by mutations in RASA1, an inhibitor of cellular growth, proliferation and differentiation. The lesions involve skin, muscle, and bone, and the overgrowth becomes increasingly prominent with growth, especially at puberty, after trauma to the limb, or during pregnancy. The lesions are present at birth and marked by a pink, warm, macular CM overlying the asymmetrically enlarged limb, often with an AVM heralded by an audible bruit and palpable thrill. Although PWS is more common in the lower
extremity, the upper limb is affected in about 23% of cases (Upton and Marler, 2005). The high-flow lesions can lead to symptoms as severe as heart failure.

Maffucci syndrome is a rare congenital condition that is characterized by simultaneous occurrence of multiple enchondromas and spindle cell haemangiomas that most commonly affect both hands resulting in deformities. Malignant transformation has been described, and over 30% of the enchondromas progress to chondrosarcomas. Patients with Maffucci syndrome also have an increased risk for other secondary malignancies, including gliomas. In 77% of these patients, somatic mutations in Isocitrate dehydrogenase (IDH) have been identified. Similar to Ollier’s disease (which does not include haemangiomas and is typically unilateral), monitoring with periodic physical and radiographic examination is required because of the risk of malignant transformation (Fatti and Mosher, 1986).

SUMMARY

The management of vascular anomalies remains demanding, but advances in interventional radiology, surgery and newer medical treatments have been promising. Systemic therapies, which could inhibit overgrowth and reduce vascular malformations by altering the PI3K-AKT-mTOR pathway in patients with PIK3CA mutations (Lackner et al., 2015) have the potential to revolutionize the management of vascular malformations (Keppler-Noreuil et al., 2015). Sirolimus, an inhibitor of the PI3K/mTOR pathway, is now being broadly applied in trials to a wide range of pathologies across the spectrum of vascular anomalies. Furthermore, newer generations of similar drugs are under development, including everolimus (Ricci,
2017; Trenor, 2016). Overall, these advances will aid the multi-disciplinary management of this wide ranging and often complex spectrum of conditions.
REFERENCES


Board PPTE. Childhood vascular tumors treatment (pdq(r)): Health professional version. Pdq cancer information summaries. Bethesda (MD), 2002.


Lowe LH, Marchant TC, Rivard DC, Scherbel AJ. Vascular malformations: classification and terminology the radiologist needs to know. Semin Roentgenol. 2012, 47: 106-117.

Luks VL, Kamitaki N, Vivero MP et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. J Pediatr. 2015, 166: 1048-54 e1-5.


Figure legends

Figure 1: PI3K-AKT Pathway and associated clinical overgrowth disorders
(reproduced with permission from Keppler-Noreuil et al., 2014 (John Wiley and Sons))

Figure 2: Infantile haemangioma
A patient with an infantile haemangioma on forearm and wrist. Note areas of involution with settling of discolouration.

Figure 3: Kaposiform haemangioendothelioma (KHE)
A patient with KHE affecting the right arm. This patient was successfully treated with sirolimus.

Figure 4: Lymphatic malformation
A patient with an extensive lymphatic malformation affecting the length of the arm. Note the lesion predominantly affects the tissues above the deep fascia.
Figure 5: Venous malformation

A patient with a venous malformation affecting the thumb pulp. Note the lesion engulfs the neurovascular structures within the thumb and involves the entire pulp tissue.

Figure 6: Fibro-adipose vascular anomaly (FAVA) of the forearm.

A patient who had extensive involvement of the flexor compartment of the forearm. Intra-operative pictures of a forearm compartment decompression and neurolysis of the median and ulna nerves. Note a central area of focal thrombosis has been excised from the flexor digitorum superficialis (FDS) musculature.

Figure 7: Patient with PIK3CA overgrowth spectrum

(A) Involvement of the leg with a low flow malformation, limb overgrowth, and a capillary malformation.

(B) Same patient with macrodactylous overgrowth of the ring finger.

Figure 8: Proteus syndrome

Hand manifestations of a patient with Proteus syndrome.
Figure 1

PI3K-AKT Signaling Pathway

**PIK3CA-Related Overgrowth Spectrum (PROS)**
- Macrodactyly
- Hemihyperplasia
- Multiple Lipomatosis (HHML)
- Fibroadipose overgrowth (FAO)
- Muscle Hemi hypertrophy
- Facial Infiltrating Lipomatosis
- CLOVES
- Megalencephaly
  - Capillary Malformation (MCAP)
- Skin disorders:
  - Epidermal nevi,
  - Seborrheic keratoses,
  - Benign lichenoid keratoses

Cell cycle/apoptosis regulation, metabolism, angiogenesis

- Proteus Syndrome (AKT1)
- Lipodystrophy syndrome - Hypoglycemia (AKT2)
- Hemimegalencephaly and Me ga lencephaly-poly microsyr i a-
  polydactyly-hy drocephalus (MPPP) (AKT3)

Bannayan - Riley - Ru valca ba
  and Cowden and Type II
  Segmental Cowden syndrome
  Lhermitte-Duclos disease

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<td>Servelle-Martorell syndrome</td>
</tr>
<tr>
<td>Composite haemangioendothelioma</td>
<td></td>
<td>Sturge-Weber syndrome</td>
</tr>
<tr>
<td>Dabska tumour</td>
<td></td>
<td>Limb CM + limb hypertrophy</td>
</tr>
<tr>
<td>Kaposi sacroma</td>
<td></td>
<td>Maffucci syndrome</td>
</tr>
<tr>
<td>others</td>
<td></td>
<td>Macrocephaly-CM</td>
</tr>
<tr>
<td>Malignant vascular tumours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiosarcoma of the soft tissue</td>
<td></td>
<td>Microcephaly-CM</td>
</tr>
<tr>
<td>Epitheloid haemangioendothelioma</td>
<td></td>
<td>CLOVES syndrome</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>Proteus syndrome (PS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Banayan-Riley-Ruvalcaba syndrome</td>
</tr>
</tbody>
</table>
Table 2. Schobinger clinical staging system for AVM. From (Kohout et al., 1998).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Quiescent</td>
<td>Pink-bluish stain, increased warmth, arteriovenous shunting detectable with continuous Doppler scanning or 20 MHz colour Doppler scanning</td>
</tr>
<tr>
<td>II Expansion</td>
<td>Stage I + Enlargement, pulsations, thrill and bruits and tortuous/tense veins</td>
</tr>
<tr>
<td>III Destruction</td>
<td>Stage II + either dystrophic skin changes, ulceration, bleeding, persistent pain or tissue necrosis</td>
</tr>
<tr>
<td>IV Decompensation</td>
<td>Stage III + Cardiac failure</td>
</tr>
</tbody>
</table>