GUIDELINE

DIAGNOSIS AND TREATMENT OF VENOUS MALFORMATIONS

Consensus Document of the International Union of Phlebology (IUP): Updated-2013

Lee BB, Baumgartner I, Berlien P, Bianchini G, Burrows P, Gloviczki P, Huang, Y, Laredo J, Loose DA, Markovic J, Mattassi R, Parsi K, Rabe E, Rosenblatt M, Shortell C, Stillo F, Vaghi M, Villavicencio L, Zamboni P

Corresponding Author:
Byung-Boong (B.B.) Lee, M.D., PhD, F.A.C.S.
Professor of Surgery & Director, Center for Vein, Lymphatics and Vascular Malformation, George Washington University School of Medicine, Washington, D.C., USA
Division of Vascular Surgery, Department of Surgery, George Washington University Medical Center, 22nd and I Street, NW, 6th Floor, Washington, DC 20037 USA

J. Lionel Villavicencio, MD
Distinguished Professor of Surgery, Department of Surgery, Uniformed Services University School of Medicine, and Director Emeritus Venous and Lymphatic Teaching Clinic, Walter Reed Army Medical Center, Bethesda, MD, USA

Huang, Ying, MD
Research Fellow, Division of Vascular and Endovascular Surgery, Mayo Clinic, Rochester, MN, USA

Paolo Zamboni, MD
Professor of Surgery, and Director, Vascular Diseases Center, University of Ferrara, Ferrara, Italy

Abstract

Venous malformations (VMs) are the most common vascular developmental anomalies (birth defects) . These defects are caused by developmental arrest of the venous system during various stages of embryogenesis. VMs remain a difficult diagnostic and therapeutic challenge due to the wide range of clinical presentations, unpredictable clinical course, erratic response to the treatment with high recurrence/persistence rates, high morbidity following non-specific conventional treatment, and confusing terminology.

The Consensus Panel reviewed the recent scientific literature up to the year 2013 to update a previous IUP Consensus (2009) on the same subject. ISSVA Classification with special merits for the differentiation between the congenital vascular malformation (CVM) and vascular tumors was reinforced with an additional review on syndrome-based classification. A “modified” Hamburg classification was adopted to emphasize the importance of extratruncular vs. truncular sub-types of VMs. This incorporated the embryological origin, morphological differences, unique characteristics, prognosis and recurrence rates of VMs based on this embryological classification. The definition and classification of VMs were strengthened with the addition of angiographic data that determines the hemodynamic characteristics, the anatomical pattern of draining veins and hence the risk of complication following sclerotherapy.

The hemolymphatic malformations, a combined condition incorporating LMs and other CVMs, were illustrated as a separate topic to differentiate from isolated VMs and to

rectify the existing confusion with name-based eponyms such as Klippel-Trenaunay syndrome. Contemporary concepts on VMs were updated with new data including genetic findings linked to the etiology of CVMs and chronic cerebrospinal venous insufficiency. Besides, newly established information on coagulopathy including the role of D-Dimer was thoroughly reviewed to provide guidelines on investigations and anticoagulation therapy in the management of VMs. Congenital vascular bone syndrome resulting in angio-osteo-hyper/hypotrophy and (lateral) marginal vein was separately reviewed. Background data on arterio-venous malformations was included to differentiate this anomaly from syndrome-based VMs.

For the treatment, a new section on laser therapy and also a practical guideline for follow up assessment were added to strengthen the management principle of the multidisciplinary approach. All other therapeutic modalities were thoroughly updated to accommodate a changing concept through the years.

Key words: Venous malformations, ISSVA Classification, Hamburg classification extratruncular and truncular types, angiographic classification, hemolymphatic malformation, congenital vascular bone syndrome, marginal vein, multidisciplinary approach

INTRODUCTION

The International Union of Phlebology (IUP), the largest international organization devoted to the investigation and management of venous disorders, established an expert Panel to formulate guidelines for physicians and health care professionals around the world on the evaluation and treatment of venous malformations (VMs). The aim of this Document is to provide recommendations for the diagnosis and treatment of VMs based on the best currently available scientific evidence. When scientific evidence was lacking or weak, a consensus of opinions among expert members of The Panel was reached to support the recommendations.

The guidelines in this Document are broad ranged and incorporate proven concepts, expert driven recommendations, and new discoveries. In the last decade, progress in both diagnostic techniques and minimally invasive technology has been significant in this difficult and challenging field. Imaging studies, radionuclide scans, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) technologies have largely been perfected. The endovenous therapy revolution has transformed the way clinicians treat patients with venous disorders including VMs.

Therefore, following the completion of the Consensus in 2009 [1], the expert Panel continued to review various issues, which were not included in the previous Consensus but were deferred to the next update. The Panel adopted a total of 20 new topics to update the Consensus, in addition to thoroughly reviewing the contents of the 2009 Consensus to accommodate rapidly changing concepts in the management of VMs.

It is the sincere hope of The Panel and the IUP, that these guidelines will serve its purpose: general guidelines based on scientific evidence to assist clinicians and patients in the diagnosis and treatment of VMs. The Panel recognizes that some guidelines may be impractical in certain parts of the world with limited access to advanced technology or special expertise. To this end, the Panel has incorporated the most important advances in this field to formulate the most up-to-date and sound guidelines based on the best available scientific evidence till year 2013 through the update of the last Consensus in 2009.

I. DEFINITIONS & CLASSIFICATION

General Overview

VMs are developmental anomalies (birth defects) of the venous system which range in clinical presentation from trivial to life-threatening. [2-5] They are the result of arrested development of the venous system during the various stages of embryogenesis. [6-9]

Together with arterial (AM), capillary (CM), and lymphatic (LM), as well as arterio-venous (AVM) malformations they are part of a large group of congenital vascular malformations (CVMs) which are developmental anomalies of the peripheral vascular system. [10-14]

VM is the most common form among various CVMs. Most VMs exist alone as an independent lesion, but some may occur in conjunction with other CVM lesions. Like other CVMs, VMs are grouped together with hemangiomas under the common umbrella of "Vascular Anomalies". But, hemangiomas are proliferative vascular tumors and not malformations. [15-18]

Hemangiomas, as vascular tumors have a distinctly different etiology, genetics, presentation, prognosis and treatment. [19-22] Infantile hemangiomas (IH) as hemangiomas of infancy are "self-limited" vascular tumors of childhood that involute in general, while CVMs are "self-perpetuating" embryologic tissue remnants that never involute spontaneously. Erroneously, VMs in particular may still be referred to as"hemangioma" especially in radiology or histology report. This is a historical misnomer and VM should be clearly differentiated from hemangiomas. A precise understanding of this critical fact and accurate diagnosis is essential for successful management of VMs. [23, 24]

CVM remains a difficult diagnostic and therapeutic challenge among many vascular disorders due to the wide range of clinical presentations, unpredictable clinical course, erratic response to the treatment with high recurrence/persistence rates, high morbidity following unspecific conventional treatment, and confusing terminology. [25-28]

CVM is therefore, considered a unique vascular disorder that carries a stigma of totally unpredictable behavior. "Recurrence and persistence" is the trademark of all the CVMs. High recurrence rates following treatment are generally due to the embryological characteristics of the CVMs which arise from embryonic tissue remnants derived from an earlier stage of embryogenesis. [29-32] These lesions are now classified as extratruncular lesions by the Hamburg Classification. [33-36]

Previous classification systems for the CVMs were established based purely on clinical findings. Most of them are name-based eponyms (e.g. Klippel Trenaunay Syndrome (KTS) and created before the modern technology was available for accurate diagnosis. These old classification systems failed to provide proper information concerning the etiology/embryology, anatomy, and pathophysiology involved in this vascular abnormality. [37-40]

Many VMs, as well, are still named after the clinician who first described the lesion. Besides, a lack of an accepted, universal classification system resulted in redundant

terminology (e.g. cavernous hemangioma, cavernous angioma, phlebangioma) only adding to the confusion.

Through the last two decades, two new classification systems have been established based on the experts consensus formulated through the workshop held in Hamburg, Germany in 1988 to fulfil the above criteria: Hamburg Classification [33-36] (Table 1) and ISSVA* Classification [1, 18, 21, 41] (Table 2).

*ISSVA: International Society of the Study for Vascular Anomalies

Table 1 (A & B)

1A. Hamburg Classification* of Congenital Vascular Malformations (CVMs) - Species

- Arterial malformation
- Venous malformation
- Arterio-Venous malformation
- Lymphatic malformation
- Capillary malformation
- Combined vascular malformation

* Original classification was based on the consensus on the CVM through the international workshop held in Hamburg, Germany, 1988, and subsequently modified based on the predominant lesion.

1B. Hamburg Classification of CVMs*: Forms - Embryological subtypes

1. Extratruncular forms
    - Infiltrating, diffuse
    - Limited, localized
2. Truncular forms
    - Obstruction or Stenosis
        - Aplasia; Hypoplasia; Hyperplasia
        - Stenosis; Membrane; Congenital spur
    - Dilatation
        - Localized (aneurysm)
        - Diffuse (ectasia)

* Represents the developmental arrest at the different stages of embryonic life: Earlier stage – Extratruncular form; Later stage – Truncular form.

*Both forms may exist together; may be combined with other various malformations (e.g. capillary, arterial, AV shunting, venous, hemolymphatic and/or lymphatic); and/or may exist with hemangioma).

<Table 2> ISSVA* 1996 Classification of Vascular Anomalies

Vascular Tumors

- Infantile hemangiomas
- Congenital hemangiomas
  - Rapidly involuting congenital hemangioma (RICH)
  - Noninvoluting congenital hemangioma (NICH)
- Tufted angioma (+/- Kasabach-Merritt syndrome)
- Kaposiform hemangioendothelioma
- (+/- Kasabach-Merritt syndrome)
- Spindle cell hemangioendothelioma
- Other, rare hemangioendotheliomas (e.g., epithelioid, composite, retiform, polymorphous, Dabska tumor, lymphangioendotheliomatosis)
- Dermatologic acquired vascular tumors (pyogenic granuloma, targetoid hemangioma, glomeruloid hemangioma, microvenular hemangioma, etc.)

Vascular Malformations

Slow-flow

- Capillary malformation (CM)
  - Port-wine stain
  - Telangiectasia
  - Angiokeratoma
- Venous malformation (VM)
  - Common sporadic VM
  - Bean syndrome
  - Familial cutaneous and mucosal venous malformation (VMCM)
  - Glomuvenous malformation (GVM)
  - Maffucci syndrome
- Lymphatic malformation (LM)

Fast-flow

- Arterial malformation (AM)
- Arteriovenous fistula (AVF)
- Arteriovenous malformation (AVM)

Complex-combined vascular malformations

CVM, CLM, LVM, CLVM, AVM-LM, CM-AVM

* ISSVA (International Society for the Study for Vascular Anomalies)

ISSVA Classification

This classification [1, 18, 21, 41] provides a comprehensive picture of vascular anomalies: vascular malformations and vascular tumors, with special merits to identify various vascular tumors in addition to flow-based classification of the CVMs.

It embraces all the pre-existing name-based classifications/syndromes which were strongly advocated to be abandoned by many experts to reduce unnecessary confusion (e.g. Hamburg Consensus Workshop of 1988). This remains a major controversy and possible weakness of this excellent classification.

In this classification, all venous anomalies are included in one group of venous dysplasias without distinguishing truncular and non-truncular lesions with different clinical course and therapeutic consequences.

Besides, a flow-based classification of the AVM to AV fistula (AVF) and AV malformation added substantial confusion despite both are same fistulous condition to allow AV shunting; it failed to distinguish the critical structural difference between (truncular) defects which allow direct connection between main vessels with no nidus in between to connect them, and (extratruncular) defects with dysplastic vessels/nidus to connect in the tissues level.

The complexity of the classification by accommodation of numerous name-based syndromes as a part of new CVM classification has made substantial limitation on its value for clinical implementation in the management of CVMs although its major credit remains in differentiating vascular tumors/hemangiomas from CVMs.

The ISSVA classification has been modified by many others to improve its clinical usage, for example, with further subclassification of VMs based on:

Anatomical location:

- Intra-dermal-forming superficial telangiectatic and/or venulectatic lesions
- Subcutaneous- presenting with nodules
- Intra-muscular, intra-articular or deep within other organs

Clinical manifestations:

- Localized: face, trunk, limbs, brain, spinal cord, lungs, etc.
- Generalized: Blue Rubber Bleb Syndrome (BRBNS), Glomovenous Malformations (GVMs), Genuine diffuse phlebectasisas (Bockenheimer)

ISSVA classification has been widely modified many times independently by different authors to compensate for its weakness (e.g. the extension of the confusion generated by many name-based eponyms adopted by ISSVA Classification).

In one of the last versions, a difference between extratruncular forms, named "malformations" and truncular one, named "malformations of major named vessels" was introduced. These changes made this classification similar to Hamburg Classification after all. [42]

Hamburg Classification

Hamburg Classification [1, 30, 33-36] limits its scope strictly to vascular malformations to clarify crucial morphological differences between the lesion involved to the main vessel trunks and the lesion, previously called "angioma", remaining peripherally as a separate defect with no direct involvement of the vessel trunk.

This morphological difference has been explained with an embryological mechanism as an outcome of the arrest or disturbance in the development of vascular system in various stages of angiogenesis. Extratuncular lesions are defects arising from the "earlier" stages of embryogenesis while the primitive vascular structures are still in the "undifferentiated capillary network to reticular/plexiform network stage" [8, 9, 34-37] Such angiomatous defects present as a cluster of amorphous vascular tissue. Truncular lesions are those arising from pre-existing vascular structures in maturation period) during the "later" stages of embryogenesis/angiogenesis. [8, 9, 34-37]

This new term extratruncular successfully replaced the often misleading old term "angioma" as an alternative, and stopped the confusion involved to the "angioma vs. hemangioma".

Extratruncular lesions have a general tendency to progress/worsen or to recur after treatment while truncular lesions do not. According to this embryologic concept, the worsening of the CVM lesions would depend on the type of the (endothelial) cells as the remnants of the primitive capillary network that maintains a tendency to grow and to cause often unpredictable biological behavior.

Hamburg Classification was further modified by the adoption of this new embryological interpretation providing appropriate information regarding lesion etiology, embryology, anatomy and pathophysiology of VMs. [43, 44] Therefore, based on a critical contribution of new embryological concept to manage the "recurrence" risk better, previous consensus-2009 group unanimously recommended Hamburg Classification as more clinician-friendly classification for the CVM management. [1]

We recommend the preferential use of the modified Hamburg classification of CVMs [Strength of recommendation:1 (strong), Quality of evidence:A (high) [45]*]*

Conclusion

Both classifications are mutually complimentary, one adding embryological while the other hemodynamic criteria for the CVMs, although there remains a substantial differences between two classifications.

Both classifications recognize that CVMs are frequently mixed, and VMs or AVMs may co-exist with LMs, or malformations of non-vascular tissue (bone, muscle, nerves, etc). These malformations are classified as mixed CVMs. If the CVM lesion has elements of the lymphatic system, the term hemolymphatic malformation (HLM) may be used. [46-48]

However, the current classification is far from the perfect and further modification will be necessary as our knowledge of the etiology, anatomy, embryology, histo-patho-physiology, hemodynamics, and possibly genetics of the CVMs continues to grow.

Embryological Interpretation of the Classification: *Extratruncular & Truncular lesions*

Clinical value of the differentiation between extratruncular vs. truncular lesions remains critical for treatment. Truncular VM lesions can be treated to improve the haemodynamic with no risk of provocation. By contrast, extra-truncular lesions are more complicated to manage due to their mesenchymal origin, keeping proliferative potential that can be stimulated by e.g. interventional procedures. These lesions create more clinical problems such as pain and progression. They have a much higher tendency to recur and

progress so that the treatment is often addressed not only to the dysplastic vessels but also to the organs which are infiltrated and compressed by the malformation.

Both groups are morphologically so different that the differentiation is straightforward: if you can`t name the originating vessel, you are dealing with an extratruncular VM.

Extratruncular VM lesions [30] are embryonic tissue remnants derived from an "early" undifferentiated to reticular/plexiform stage of vascular tissue development. Developmental arrest occurs before the main vascular/venous trunks are formed (pre-truncal embryonic lesions). These lesions maintain their unique embryonic characteristics of mesenchymal cells (angioblasts) and the ability to proliferate when stimulated by trauma, menarche, pregnancy, surgery, or female hormones. Therefore, these lesions naturally carry a high risk of recurrence if not treated radically on the contrary to the truncular lesions.

Extratruncular lesions are further subdivided into:
1. Diffuse, infiltrating
2. Localized, limited

Diffuse, infiltrating extratruncular lesions may cause symptoms due to compression of the surrounding structures (bones, muscles, nerves). They have a notorious reputation for causing pain due to embryological proximity of nerves and veins. They may also produce significant hemodynamic impact on the involved venous system that is dependent on lesion size and location. Growth is usually slow and proportionate to the person's growth and they persist throughout the rest of the person's life with a tendency to grow/progress. Distinctively, there is no spontaneous regression (cf. hemangioma).

Truncular VM lesions [30] are the result of developmental arrest that occurs in the "later" stages of venous trunk formation during maturation stage of angiogenesis. This arrest occurs long after the embryonic (reticular) stage of vascular development. These lesions are also known as "post-truncal fetal lesions" (cf. "pre-truncal embryonic lesion" for extratruncular lesion) with direct involvement of the vein trunk, and has nothing to do with the anatomical description of the body torso as a trunk (cf. head and neck as extratruncular part)**.**

Truncular lesions therefore, do not have the embryonic characteristics of mesenchymal cells (angioblasts) as observed in the extratruncular lesions and hence do not possess the critical evolutional ability to proliferate. The risk of recurrence after treatment is minimal to none. These lesions have hemodynamic consequences due to congenital valvular incompetence, obstruction (atresia, hypoplasia) or dilatation/ aneurysm formation with associated risk of thromboembolism (e.g. the marginal vein (MV)). [49-52]

Truncular lesions can present as aplasia or hypoplasia,[53, 54] obstruction, dilation or aneurysms. [55-58] (Table 1) Immature/ incomplete/ abnormal development of the main axial veins result in aplasia, hypoplasia, or hyperplasia of the vessel (e.g. agenesis/rudimentary femoral vein) or as a defective vessel: obstruction (e.g. vein web, spur, annulus, or septum) or dilatation (e.g. popliteal or iliac vein ectasia/ aneurysm).

A unique group of truncular VMs are the persistent embryonic veins such as the MV of the thigh or the persistent embryonic sciatic vein. These vessels arise when fetal (truncal) vessels fail to undergo normal involution. [59-62]

Truncular lesions of obstructive nature (webs, hypoplasia) may have different hemodynamic impacts on their relevant venous systems depending on the location, extent/severity, and natural compensation through collaterals. Chronic venous insufficiency (CVI) develops in the territory drained by such truncular vein. Stenosing truncular lesions produce venous obstruction leading to a reduction in venous drainage. Membranous obstruction of the (suprahepatic) inferior vena cava (IVC) in primary Budd-Chiari syndrome is an example of a primary obstructive VM affecting a major vein. [63-66]

Truncular VMs may also occur in veins with the same embryologic origin or draining the same territory (e.g. stenosing lesions of the extracranial jugular veins, superior vena cava, and azygos vein system along the main outflow pathways of the cerebro-spinal venous system). [67-70]

Avalvulia/avalvulosis, or absence of valves is another form of hypoplasia that produces venous reflux. Together with atresia of the venous trunks and venous aneurysms, they are relatively common. The incidence of aneurysm has been reported to be 4% in nearly 490 cases of congenital anomalies of the venous system. [53, 71, 72]

Once hemodynamic physiology is discerned, localization and morphology of the lesion assist in refining procedural strategy and deriving a definitive treatment plan. Data from numerous studies showed that clinical course, prognosis, treatment outcomes as well as recurrence rates of the VMs are largely dependent upon mesenchymal origin of the lesions cells. [68, 69]

Based on data from morphologic studies by Belov et al, extratruncular malformations cells retain the evolutional potential to proliferate. [33-36] Consequently, extratruncular VMs grow and progress unpredictably responding to variety of triggering factors (such as injury, surgical interventions, hormones, infection etc.). Truncular VMs originate from the cells that do not retain proliferative evolutional potential and consequently they are associated with significantly better prognosis and outcomes than extratruncular VMs [33-36]

(please refer to the Consensus section "Genetic Interpretation of Embryological Classification of VM" for detailed discussion regarding embryology of extratruncular and truncular VMs).

There is a paucity of data available in the current body of literature to make a conclusive determination regarding the exact underlining genetic and molecular mechanisms responsible for differentiation between these two lesions, although data from recent genetic studies showed that regulatory genes of vasculogenesis and angiogenesis (TIE-2/PDGFB) play an important role in the development of extratruncular VMs. [73]

With currently available data, we can hypostatize that genes involved in stages of angiogenesis that follow the stage of mesenchymal cell maturation have an important role in the pathogenesis of truncular VMs. However, the exact pathophysiological and genetic mechanism responsible for the development of both subtypes of VMs still remains to be elucidated what provides a fertile research environment for genetic studies. Further research in this field is especially important for developing modern and future diagnostic and therapeutic frontiers given that we are entering the era of personalized medicine and that genetic therapeutic modalities are become increasingly utilized.

Integrated Classification System: New Consideration

Recent advancements in genetics combined with better understanding of the embryology and pathophysiology of VMs and development of novel imaging and treatment modalities allow the opportunity to fully integrate two different classification systems that have been traditionally utilized for the management of VMs. In addition, relatively recently introduced concept of the multidisciplinary team approach, characterized with full integration of expertise of different medical specialists, mandates unified classification systems as the basis for the contemporary management of VMs.

Modern imaging modalities (dynamic contrast enhanced MRI (dceMRI), Cartesian Acquisition with Projection-Reconstruction Like Sampling) are characterized by significantly higher specificity and sensitivity for the accurate assessment of hemodynamics of the lesion than imaging techniques used in the past allowing definitive differentiation between high flow (HFVM) and low flow vascular malformations (LFVM) in majority of patients.[80, 208, 209] Thus, implementation of accurate assessment of hemodynamic characteristics of the lesion in integrated classification system becomes important especially for the treatment planning.

We concerns multiple terms to describe identical hemodynamic characteristics since "low flow" and "slow flow" (as well as "high flow" and "fast flow") in the same lesion, which

are two mutually exclusive hemodynamic events determined by equal components of hemodynamics.

We therefore, recommend the use of the terms "low flow" and "high flow" rather than "slow flow" and "fast flow, respectively, when flow patterns of CVMs are described. . [Strength of recommendation:1 (strong), Quality of evidence:C (low) [45]*]*

We also recognize a prospective value of the utilization of integrated classification system (Table 3); as the basis for the diagnostic protocols and therapeutic algorithms, it affords the opportunity to streamline the evaluation process for CVM patients and to facilitate communication among practitioners. In addition, it affords the opportunity for the individualization of treatment strategies and for full integration of surgical, non-surgical, endovascular treatment options and multimodal treatment modalities.

Table 3. CVM Integrated Classification System

<table>
<tr><th colspan="6">Congenital Vascular Malformations(CVMs)</th></tr>
<tr><th colspan="3">Low Flow</th><th colspan="3">High Flow</th></tr>
<tr><td rowspan="4">Venous (VM)</td><td rowspan="2">Extratruncular</td><td>Diffuse/ Infiltrating</td><td rowspan="4">Arterial (AM)</td><td rowspan="2">Extratruncular</td><td>Diffuse/ Infiltrating</td></tr>
<tr><td>Localized</td><td>Localized</td></tr>
<tr><td rowspan="2">Truncular</td><td>Obstruction/ Narrowing</td><td rowspan="2">Truncular</td><td>Obstruction/ Narrowing</td></tr>
<tr><td>Dilatation</td><td>Dilatation</td></tr>
<tr><td rowspan="4">Lymphatic (LM)</td><td rowspan="2">Extratruncular</td><td>Diffuse/ Infiltrating</td><td rowspan="4">Arterio-venous (AVM)</td><td rowspan="2">Extratruncular</td><td>Diffuse/ Infiltrating</td></tr>
<tr><td>Localized</td><td>Localized</td></tr>
<tr><td rowspan="2">Truncular</td><td>Obstruction/ Narrowing</td><td rowspan="2">Truncular</td><td>Obstruction/ Narrowing</td></tr>
<tr><td>Dilatation</td><td>Dilatation</td></tr>
<tr><td colspan="3">Capillary (CM)</td></tr>
<tr><td colspan="6">Combined</td></tr>
<tr><td colspan="3">Syndrome Associated</td><td colspan="3">Syndrome Associated</td></tr>
</table>

Angiographic Classification of the VM Based on Communicating Venous Drainage Patterns:

Current classification systems have been validated as clinically applicable for making an accurate anatomical and hemodynamic diagnosis of the VMs, they serve as a basis for proper treatment selection, and significantly facilitate communication among different medical specialists. [74-76] However, they do not routinely incorporate data regarding relationship between VMs and the normal venous system. Consequently, deriving a definitive treatment plan remains challenging in a certain number of VM patients.

Phlebography not only determines hemodynamic characteristics of the lesion but it also allows the classification of the VM based on its anatomy in regards to the communication pattern with the draining venous system. Based on the appearance of the VMs and the draining venous system during phlebography all VMs can be classified into four distinct groups: Type I (isolated VMs without phlebographically appreciable venous drainage), Type II and Type III VMs (demonstrate normal-sized and enlarged venous drainage, respectively) and Type IV VMs (characterized by essentially ectatic dysplastic veins). [77-79]

Although above mentioned phlebographic classification does not provide information regarding the location of the VMs or the involvement of surrounding anatomical structures it provides useful data for treatment planning, especially when the sclerotherapy is considered as a treatment option. Puig et al [78, 79] demonstrated that sclerotherapy can be safely performed in low-risk patients with Type-I and Type-II lesions, while patients with type-III and type-IV VMs were at the increased risk of perioperative complications due to efflux of sclerosant from the VM during sclerotherapy and potentially lethal distal embolic events.[78]

Despite the fact that Type III and Type IV VMs are associated with higher rates of complications, they represent relative, rather than an absolute, contraindication for sclerotherapy. Thus, the initial determination of whether sclerotherapy can be performed safely must be made on clinical grounds for each patient and each lesion by an experienced practitioner with the knowledge of the VM extent, communicating pattern, hemodynamics, and the feasibility of other treatment modalities.

In properly selected patients sclerotherapy is technically feasible in Type III and Type IV VMs and the risk of severe side effects can be minimized by utilizing several techniques that limit venous outflow during the delivery of the sclerosant. A tourniquet or manual compression can be applied downstream of the venous outflow to minimize the risk of passage of the sclerosant into the systemic circulation, to help contain sclerosant within the VM and to assure maximal contact between sclerosing agent and the endothelial lining of the malformation. [80] Further, a focal compression with a surgical instrument, as simple as a clamp, could be utilized under fluoroscopy to occlude or reduce dominant venous outflow more effectively. [81]

Lastly, in the most challenging cases, where anatomy of the venous drainage is complex, multimodal (selective) treatment of the VM, including preoperative embolization of the draining vein followed by sclerotherapy of the VM, can be effectively utilized with minimum risk of major complications. [82] However, sclerosant specific minor complications should be anticipated (e.g. tissue necrosis, peripheral nerve palsy, blistering, skin pigmentation, fever and gastrointestinal irritation) and prepared for proper management although the majority of such complications are reported as self-limiting with spontaneous resolution. [82]

Therefore, a routine manual compression to be applied to treated areas and areas proximal to injection site, concurrent with sclerosant injections in all VM lesions, to decrease venous flow and to assure maximal contact between sclerosant and the endothelium of the VM. Type III and Type IV VMs should be carefully evaluated for communicating pattern with venous system such that an appropriate multimodal treatment strategy can be formulated in well selected patients to minimize the risk of severe and life-threatening complications.

In addition to phlebographic classification of the VM, phlebographic evaluation of patency and anatomic variations of the deep venous system deserves special consideration since estimated prevalence of at least one anomaly of the deep venous system in VM patients approximates 47% (e.g. aplastic or hypoplastic deep venous trunks: 8%). [53, 83] It has been also documented that prevalence of deep venous anomalies is even higher (18%) in patients with KTS. [83] In these patients venous blood flow from the affected extremity depends on superficial and/or abnormal vessels and treatment of the malformation carries the risk of the impairment of venous return from the affected extremity.

We recommend that during evaluation of CVMs the patency and anatomic variations of the entire venous system (deep and superficial, proximal and distal) is established before a definite treatment plan.
[Strength of recommendation:1 (strong), Quality of evidence:C (low) [45]*]*

VM combined with other CVMs: Hemolymphatic Malformation (HLM):

VMs may be found anywhere within the body in various numbers, shapes, extents and degrees, and exist either as one single type lesion or mixed condition with other CVMs: LM [84-87], AVM [88-91], and/or CM. [92-94] Combination of various CVMs, either VM and/or AVM with LM can be defined as HLM. [1, 30, 95-98]

Most HLMs are composed of one type of VM and one type of LM. But VM may be combined with LM in various combinations. In other words, VM and also LM may exist in the truncular form, defects of the main draining vessels, as well as extratruncular forms, areas of abnormal venous or lymphatic vessels embedded in the tissues shown as below.

Thus, possible combinations among four different subtypes are:

1) Truncular VM as defects of the main veins (aneurysms, hypoplasia or absence of main venous trunks) combined with truncular LM (aplasia, hypoplasia or dilatation of the main lymphatic ducts)
2) Truncular VM with extratruncular LM (areas of dysplastic lymphatics in the tissues)
3) Extratruncular VM (areas of dysplastic veins in the tissues) + truncular LM
4) Extratruncular VM + extratruncular LM

HLMs frequently include both the truncular and extratruncular form of LM or the truncular and extratruncular type of VM and sometimes it is possible to observe coexistence of all four components. [99, 100]

VMs may also exist with CM with a great variety from extensive cutaneous involvement to almost complete absence of the so-called “port wine stains”. Nevertheless, when VM co-exists with CM together with LM, it has been named as KTS to accommodate other defects involving the soft tissue and/or skeletal system. When this condition is further combined with an AVM, it has been named Parkes-Weber Syndrome (PWS).

Those different combinations have been defined by several authors in the past with various eponyms like “Klippel-Trenaunay”, Klippel-Trenaunay-Weber” and “Klippel-Trenaunay-Parkes-Weber syndrome”. However, those terms have been used mainly on a pure clinical evaluation basis, without any effort to establish the type of combination and the hemodynamic peculiarities involved in individual case properly based on necessary diagnostic procedures.

As such name-based eponyms have failed to meet the mandate to help the advanced management of these conditions, they have been replaced by the modern terminology of the modified Hamburg Classification. [1, 30, 33-36]

Diagnosis of HLM therefore, should be based on the recognition of all the different types of defect coexisting in each individual case. Various tests should be performed to identify each one of vascular malformation components, and following non-invasive tests are generally recommended as basic tests:

- Duplex ultrasound (DUS) [101-103]: to study venous and lymphatic dysplastic areas and main venous trunks morphology and hemodynamics
- T1 and T2 weighted MRI study [104-106]: to establish the precise involvement and extension of VM and LM, especially extratruncular lesions
- Radionuclide lymhposcintigraphy [107-109]: to study morphology and function of main lymphatic trunks

Whole-body blood pool scintigraphy (WBBPS) [110-112] is recommended as an optional test to identify/assess the VM lesions scattered throughout the body and also for the recognition of the LM by its negative blood pool findings.

Additional tests which are mostly invasive, if not less-invasive, may be helpful in specific cases, mainly when the basic tests have not given exhaustive results, especially to exclude the differential diagnosis of AVM:

- MR or CT venography or arteriography [113-115]
- Transarterial lung perfusion scintigraphy (TLPS) [116-118]
- Venography / phlebography (ascending, descending, segmental or local by direct puncture)
- Arteriography
- Direct puncture lymphangiography

If the basic test based on non-invasive technology has been done correctly, the diagnostic procedure can be completed in general without additional adjunctive tests of invasive nature [41, 119, 120] which are seldom needed for the diagnosis of HLM per se.

When a combination of VM and LM is demonstrated on the evaluation as the CVM components, the diagnosis of "HLM consisted of VM + LM" is now established. However, to better define the diagnosis, the type of each malformation - truncular or extratruncular - could be added.

Nevertheless, once the HLM is diagnosed, specific assessment on the possible involvement to other systems/organs like gastrointestinal [121], musculoskeletal, genito-urinary [122] or cardiopulmonary system, should be considered as HLM is known to be located in different organs as well. A simple whole body screening procedure with WBBPS is most practical for such condition.

The management of HLMs is quite complicated, owing to the combination of different malformations that makes the treatment of these patients more difficult.

The presence of both LM and VM generally exerts a negative impact on each other, particularly when the LM or the VM components have both the truncular and extratruncular form jointly.

Treatment strategy of HLM is based on the principle to treat the most severe component first. As the VM components are usually more significant, these VM lesions should be the first target of therapy. And the extratruncular forms of LMs in general are known to be less serious than the extratruncular forms of VMs, unless they are located in a critical region threatening a vital function.

In case of a combination of truncular and extratruncular VM, the extratruncular lesion is often more clinically significant and should be treated with priority except the MV, common truncular VM involved to the HLM due to the risk of venous thromboembolism (VTE) besides angio-osteopathy to cause vascular bone syndrome. [123]

Therefore, a careful and accurate assessment of the dominant component of HLM is essential before the therapeutic decisions can be made: the choice of the malformation to treat as first and the selection of the treatment modality.
Besides, every effort should be made to avoid the risk of an unwarranted deterioration of the untreated vascular malformation component (e.g. lymphatic leakage).

Syndrome-based Classification of VM

The term “syndrome” derive from the greek “sundromē” that means “concurrence of symptoms, concourse” and is referred in medicine to the association of several clinical signs, symptoms or phenomena that often occurs together. This definition indicates that “syndromes” in CVM could be referred only to “combined” defects and not to the malformations regarding a single type of anomaly.

Due to the great variability and combination of vascular malformations, several descriptions of syndromes (but not all) have been named with the physician credited with first reporting on the association. However, a lack of knowledge and of diagnostic tools in the past has often brought to confusing eponyms, like different names for similar diseases or same name for different diseases.

Besides, vascular anomalies are infrequently associated various underlying diseases or systemic non-vascular abnormalities especially among the CVM cases which often involved more than one type of the CVMs. Therefore, correct understanding on these name-based syndromes is often helpful for the safe management of the vascular malformation components in various syndromes together with their secondary outcome to the affected organs/systems (e.g. gastrointestinal bleeding). [124]

Exclusive use of eponyms (e.g. traditionaly KTS) to identify a vascular malformation could be often misleading, especially when is not used together with precise diagnosis based on modern laboratory tests. Nevertheless, their use can be accepted if they referred to particular anatomical sites (single or multiple), genetic defects, or treatment peculiarities, as happens in the most recent descriptions. [125, 126]

A precise description of the defect and a clear statement on active problems will help proper understanding of the syndrome/clinical case and add considerably to define a rational management strategy. Therefore, every syndrome has to be defined properly with:

- Description of vascular and non-vascular defects (anatomical understanding of the problem)
- Definition of active and passive clinical problems (reflection of the problem)
- Need for treatment, e.g. AVM, large MV, LM
- Combined HLM type, e.g. KTS, PWS, SMS and location (left/right; upper/lower limb)
- Truncular (e.g. MV) or extratruncular lesion (e.g. infiltrating intramuscular VM). Localized (e.g. venous aneurysm) or infiltrating lesion (e.g. intra-muscular, intra-articular)
- Combined LM (clinical/lymphoscintigraphy) with associated complications (e.g. recurrent erysipelas)
- Osteohypertrophy/osteohypotrophy (length difference (e.g. x cm))
- Thrombo-haemorrahgic complications including localized intra-vascular coagulopathy (LIC) and disseminated intravascular coagulopathy (DIC)
- VTE including superficial thrombophlebitis (STP), deep vein thrombosis (DVT), and pulmonary embolism (PE)
- Discrete CM (location)

Proper verification and assessment of the direct and/or indirect secondary effects of the primary pathology (HLM) to the various systems has to be included;

- Gastrointestinal system (e.g. GI bleeding, chyloascites, malabsorption syndrome)
- Cardiopulmonary system (e.g. pleural effusion, chylothorax)
- Musculoskeletal system (e.g. long bone length discrepancy, joint involvement, scoliosis, pelvis tilt)
- Genito-urinary system (e.g. lymph leak: chyluria, chylorrhagia)

The main known syndromes involved to the VM are following:

Klippel-Trenaunay Syndrome (KTS)

KTS is one of the oldest "syndromes" referred to predominant VMs described as the association of the "triad" of clinical signs of limb overgrowth, nevus and dilated abnormal superficial veins. [127-129] The eponym derives from the description of the French authors in 1900, even if similar cases were published earlier by Trelad et Monod in 1869. [130]

KTS is characterized, by the opinion of many authors, as a combined capillary-lymphatic-venous malformation as its vascular malformation components affecting the vascular system of an extremity. But KTS includes other congenital anomalous components affecting non vascular system (e.g. soft tissue and skeletal system); there is typically overgrowth of the affected limb.

However, this description opens many questions about what should be included in KTS and what should not.Main point should be to respect the principle of syndrome definition: a combination of different CVMs. Moreover, leading principle should not be the clinical picture (as it may be similar in different types of the CVM) but the morpho-functional defect, based on a precise laboratory diagnosis.

Another main point is that KTS is a combined CVM with (not without!) a main VM. Following conditions could be difficult to clear:

- ***Absence of one sign of the triad (naevus, limb overgrowth, dilated veins).***
  Klippel and Trenaunay described those cases as "incomplete". If the principle of combination of defects is the leading factor, this case could be included but only of two or more CVM coexistence. Moreover, the morpho-functional diagnosis, and not the clinical aspect, as indicated above, should be mandatory.
- ***Absence of LMs***.
  As several authors defined KTS as a combination of venous and lymphatic defects, there will be question whether the cases without LM combined should be included in the KTS syndrome. But, according to the definition of syndrome, if there is a combination of truncular and extratruncular VM, even in absence of LM, also those cases could be defined as KTS. However, these are usually diffuse VM, which have a different clinical picture than KTS, such as intraarticular VM and consumption coagulopathy. They behave clinically quite differently and require different treatment. For example, they are much more likely to have LIC and require anticoagulation. They rarely have deep vein hypoplasia or interruption and they do not have the typical marginal vein. Intra-articular VM is a feature of diffuse VM and not what considered to be the real KTS.
- ***Patients with a single type of VM*** (truncular defect, like MV or deep vein anomaly or extratruncular forms) alone.

As these cases do not meet the mandate of "syndrome" they should not be defined as KTS.

- ***Patients with a single type of VM and naevus without limb overgrowth.***
  This is a more difficult condition to define as KTS because a cutaneous CM is added to the main VM. As cutaneous capillary defects are very common and of little hemodynamic significance, those cases should not be considered KTS although two different conditions of the CVMs are involved.
- ***Patients with a single type of LM***, like lymphangioma as extratruncular LMs, ***and* with naevus** but no truncular or extratruncular VMs.
  These cases do not meet the mandatory condition of KTS (existence of VM) and could not be defined KTS.

Most cases are unilateral and affect the lower limb. Involvement of one lower extremity occurs 95% of the time, but in 5-10% of patients an upper limb is affected and it is possible to observe the involvement of pelvis, abdomen and thorax. KTS is sometimes bilateral and in about 15% of patients involvement of both a lower and a upper limb may occur and it is usually ipsilateral.

No racial or sex predilection is observed. The cutaneous lesions of CM are apparent at birth. The venous varicosities and limb hypertrophy may not be apparent initially.

The typical patient with KTS has the following clinical features:
1) a cutaneous lesion by CM, appearing as a flat blue or purplish lesion ("port-wine stain") that usually is confined to a relatively small area of the lateral surface of an extremity, but in about 20% of cases involves the entire limb and sometimes one side of the entire body; the stain may be distributed in a confluent geographic pattern or more randomly on the affected areas.
2) a complex (extratruncular) VM lesion can present as large clusters of abnormal veins throughout the entire extremity, which is infrequently associated with deep vein anomalies (e.g. occlusion by membrane, agenesis, atresia) as well as a large lateral venous collector known as the MV, which typically start along the foot and extend upwards, draining into the femoral or pelvic veins.
3) a LM is mostly involved as primary lymphedema which often accompanies lymphatic vesicles often on the surface of the CM lesions.
4) a limb hypertrophy or gigantism, manifested by an extremity that is longer and larger in circumference than the healthy extremity, often asymmetric and with involvement of the digits; it occurs in approximately 70% of patients and it is generally secondary phenomena by the VM and LM lesions as primary cause but also by non-vascular anomaly component of congenital origin to cause the hypertrophy of soft tissue and bone. But in some cases instead a hypertrophy a hypotrophy of the limb can develop possibly due to reduced microcirculation by a steal effect of the pelvic muscular lesion.

KTS can have additional intraabdominal and pelvic organ involvement by the CVM lesions especially to the genito-urinary tract and large intestine. This risk increases with the extension of the nevus to the abdominal and thoracic wall. Even many other secondary phenomena may be observed in patients with KTS as the results of complications to various primary vascular malformation lesions.For example, varicosities can produce venous stasis, which, in turn, can produce pain, bleeding, STP, DVT and PE. DVT and PE may occur in 10% of patients, particularly after surgery.Lymphedema induces susceptibility to infection and cellulitis.

Parkes Weber Syndrome (PWS)

PWS is the second old syndrome described by Frederik Parkes W.,1863-1962, in London in several papers up to 1907. Clinical aspects are similar to KTS with nevus, limb overgrowth and dilated superficial veins. However, the main morpho-functional aspect, which differentiates PWS from KTS is the AVM. The author described in his publication very precisely the clinical signs of AVFs. [131-133]

A combination of a cutaneous capillary-lymphatic-venous malformation with the AVMs define the syndrome.This syndrome is rare. Most cases are sporadic, although familial cases have been reported. Recent studies suggest that it may result from mutations in the RASA1 gene that provides instructions for making a protein known as p120-RasGAP. [134]

As PWS is an old, clinical finding based description as a syndrome like KTS, there are also some unclear points to be cleared in order to avoid confusion. Main leading concepts should the same as for KTS: a combination of defects, morpho-functional precise data and existence of an AVM as main defect.

Following conditions may be cleared:

- ***Absence of limb overgrowth***.
  It is generally known that AVM may not always stimulate the bone growth, especially if the malformation is not located near the epiphyseal plate/cartilage of the bone growth. However, if the case meets the mandate of syndrome (AVM + other CVM) it could be considered a PWS.
- ***Absence of nevus***.
  Like above, if limb overgrowth and other CVM coexist, these cases could be defined as PWS.
- ***Existence of AVM, limb overgrowth but not other CVM***.
  This is a condition that is often defined as PWS by some authors. However, this condition failed to meet the mandate of syndrome and should be defined simply as an “AVM”. But, if a coexistent VM or LM are recognized, the condition becomes PWS.

This syndrome is often confused with KTS because clinical features are similar: CM ("port-wine stain"), varicose veins and limb hypertrophy. However, if appropriate tests (e.g. arteriography) are performed in addition to simple clinical observation based diagnosis, the difference between the KTS and PWS should become clear.

Many papers in the literature use also the term "Klippel-Trenaunay-Weber syndrome", arguing that it should be defined in such way for the cases with the clinical triad plus AVM. But, as discussed before, this term is NOT appropriate because a clear difference exists between KTS and PWS and there is no reason to mix both expressions.

Therefore, we conclude that the diagnosis "Klippel-Trenaunay-Weber Syndrome" is wrong and misleading and should be avoided.

Servelle-Martorell Syndrome (SMS)

SMS is a rare condition; the diagnosis of which can be confused with KTS, PWS, and BRBNS. [133-137]

SMS is also known as phlebectatic osteohypoplastic angiodysplasia. It is characterized by VM lesions of the limbs, associated to soft tissue hypertrophy and skeletal hypoplasia. Typical aspect of SMS is the VM, mainly extratruncular, which involves the bones externally and also internally with a consequence of the bone hyportrophy.

VMs span a wide spectrum, varying from isolated subcutaneous ectasias to voluminous lesions infiltrating muscles and bones.Intra-osseous VM lesions lead to destruction of spongiosa and cortical bone, resulting in shortening and hypoplasia of the limb. It can further extend to the joint destruction with severe limitation of motion.

The ectasia and aneurysmal dilatation of the veins may result in a monstrous deformity of the extremity, especially when there is an extensive limb involvement.In some cases various anomalies of the deep venous system are observed: abnormal vein location, persistence of embryonic veins, partial or complete lack of valves, deep venous hypoplasia or aplasia.

Maffucci Syndrome

Maffucci's syndrome is a rare, congenital, nonhereditary mesodermal dysplasia, characterized by soft tissue VM and multiple enchondromas. [138-140]
The VMs are mostly located in the subcutaneous fat and appear as asymmetric blue or purple, soft, occasionally tender nodules. Lower and upper limbs are more frequently affected but oral or intra-abdominal VMs may also be found.

It is typically observed as a condition of skeletal growth disturbance with abnormal bone modelling, and in more than 50% of cases, the malignant transformation of enchondromas to chondrosarcomas is observed.Additionally there is also an increased incidence of other malignant tumors (breast, ovarian, pancreatic, parathyroid, and pituitary carcinomas or gliomas, spindle-cell hemangioendothelioma).

Proteus Syndrome

Proteus syndrome is a complex congenital hamartomatous disorder characterised by multiple cutaneous and visceral vascular anomalies, including LMs, VMs and AVMs, in association with cutaneous and skeletal diseases. [141-143]

Although the cause of Proteus syndrome is not definitely known, there is an evidence to suggest that it occurs after mutation of a somatic dominant gene that is typically lethal, except in the setting of mosaicism.

Soft-tissue abnormalities include lipomatosis, fatty hypertrophy, regional fatty atrophy, hyperpigmentation or cutaneous nevi, hyperkeratosis of the palms and soles.Skeletal abnormalities are frequent with striking findings: macrodactyly of the hands and feet, exostosis, bilateral genu valgum, kyphosis and scoliosis secondary to vertebral dysplasia.

Asymmetric overgrowth may manifest itself as progressive limb-length discrepancy, hemihypertrophy and partial gigantism, typically resulting in disfiguring deformities of the skull, hands, and feet.

CLOVES Syndrome: Congenital ***L***ipomatous ***O***vergrowth, ***V***ascular malformations, **E**pidermal nevi, and Skeletal Scoliosis [144]

This newly recognized phenotype comprises progressive, complex, and mixed truncal VMs, dysregulated adipose tissue, varying degrees of scoliosis, and enlarged bony structures without progressive bony overgrowth.

In contrast to the bony distortion so characteristic of Proteus syndrome, distortion in CLOVES occurs only following major or radical surgery.

Bockenheimer Syndrome [145]

It is a rare disorder of genuine diffuse phlebectasia characterized by a blue network of dilated veins. Phlebectasia involves more commonly upper, but also lower, extremities. The lesions are present at birth and are progressive. Usually they are localized in subcutaneous tissues without the involvement of muscles and bones.

Blue Rubber Bleb Naevus Syndrome [146, 147]

BRBNS is a rare familial disorder named after cutaneous VM lesions with bluish color and rubbery consistency. The syndrome is characterized by multiple distinctive cutaneous and gastrointestinal VMs. BRBNS usually is sporadic and generally presents at birth or in early childhood. Often it becomes characterized with a progressive development of the VMs that may increase in size and number with age. These lesions preferentially involve the trunk and upper extremities and can be very painful.

The cutaneous VMs that occur in this syndrome vary in depth and may or may not involve underlying muscle, bone, and joint spaces. VMs involving the extremities can be complicated by osseous bowing deformities, pathologic fractures, and overgrowth.

The most common site of bowel involvement in BRBNS is the small intestine. They can manifest as hematemesis, melena, or hematochezia.

Consumptive coagulopathy and iron deficiency anemia secondary to occult bleeding episodes are frequent complications. They may also cause intermittent small bowel obstruction due to intussusception or volvulus.

Gorham-Stout Syndrome [148, 149]

Gorham-Stout syndrome (disappearing bone disease, phantom bone disease, diffuse skeletal hemangiomatosis) is a very rare syndrome characterized by multiple intraosseous vascular malformations inducing massive osteolysis. Although VMs, LMs, and CMs are reported in this syndrome, the most common finding seems to be a predominantly LM.

The truncal bones and upper extremities are most commonly affected. The vascular malformation may be localized or diffuse, and the degree of bone resorption is variable. Patients with this disorder often present during childhood with an antecedent history of minor trauma resulting in a pathologic fracture. Recent studies suggest an increase of the osteoclast activity in this disease.

Controversy and Proposal:

Syndromes as diagnostic term of combined CVM has been controversial for the older one (mainly KTS and PWS), because of lack of knowledge. Confusing concepts has been transmitted till now regarding those clinical defects.

Even if these eponyms are still widely used, many wonders whether they should still remain as a specific entity but only to add the confusion despite they could easily be redefined in the “combined forms” of the vascular malformation.

However, KTS and PWS could be maintained in a new, modern option if a precise diagnosis is performed and the definition of the cases follows the main concept explained above.

A new proposal to improve its use with more precise description of each vascular defect belonging to KTS and PWS using CEAP classification as a model could be helpful for a better understanding, as following:

- Venous truncular defect: VT
- Venous extratruncular defect: VET
- Lymphatic truncular defect: LT
- Lymphatic extratruncular defect: LET

II. INCIDENCE & PREVALENCE AND ETIOLOGY & PATHOPHYSIOLOGY

Incidence & Prevalence

CVMs have a male-to-female ratio of 1:1. More than 70% of the CVMs are known to remain mixed in various extents, and these complex forms can include arterial, capillary, venous, or lymphatic elements as well. But, VMs are the most common type among various CVMs. However, when both extratruncular and truncular LMs are combined, its overall incidence is close to those of the VM if not higher. Besides, CMs might surpass the VM if all the birthmarks are correctly documented.

Nevertheless, extratruncular VMs are the most frequent malformations of all as an independent CVM lesion, and present in either diffuse or localized forms.

The estimated prevalence of deep venous anomalies in patients with predominantly VMs was 47% in one study. [53] Phlebectasia was the most frequent (36%), followed by aplasia or hypoplasia of the deep venous trunks (8%) and venous aneurysms (8%). [53]

Etiology- Genetic Background

Although the pathogenesis of VMs and the rest of various CVMs remains unclear, it has been speculated to involve developmental defects of the venous system secondary to genetic mutations. Genetic information on CVMs has greatly increased in recent years to explain on the etiologic background of CVMs. [150]

Although most CVMs are sporadic, autosomal dominant inheritance has also been reported to cause various CVMs. Lately, genetic study of families achieved the identification of mutated genes that have an important role in angiogenesis. [151-155] These mutated genes in some patients encode tyrosine kinase receptors and intracellular signaling molecules. [155] The endothelial-specific angiopoietin receptor TIE2/TEK, located on 9p21 was identified to cause familial mucocutaneous CVMs. [155] Most of GVMs, a variant of the VM were also confirmed to be inherited by the gene glomulin, a novel locus on the short arm of chromosome 1. [156]

Familial VM is characterized by autosomal dominant inheritance related to mutation of the 9P locus and is rarely seen clinically. [157] Further studies showed that somatic mutations in angiopoietin receptor gene TEK presented in various single or multiple VMs and led to loss of TIE2 receptor function [158], and upregulated expression of other vascular endothelial growth factors, such as βTGF and βFGF, which exacerbated the severity of the lesion. [159]

Nevertheless, vascular endothelial growth factor (VEGF) secreted by keratinocytes has been found to be responsible for inducing penetration of capillary vessels into the avascular epidermis. [160] A defective migratory response of endothelial cells to VEGF is the consequence of abnormal signaling of VEGF receptors. Hence, malformations develop if the differentiation is abnormal and there is an arrest in the development of normal vascular tissue. The persistence of the embryonic vascular system to cause additional abnormal development would result in CVMs.

Recently it has been identified within the HLA locus on chromosome 6p21.32 a high susceptibility loci associated with a development of truncular VM. Particularly, the number of copy numbers variations, due to deletion or duplication, was found to be significantly associated to an increased chance to develop truncular VMs. The region contains 211 known genes. By using pathways analysis focused on angiogenesis and venous development it has been highlighted several genes as possible susceptibility factors candidates involved in truncular VM. [161]

More in detail, since the phenotype was characterized by association of multiple sclerosis and VMs, it has been further applied a bioinformatics tool to select among the 211 genes those known to be involved in angiogenesis and vascular development rather than those linked to multiple sclerosis, immunity and neurodegeneration.

Focusing on specific functional pathways, as angiogenesis, obviously considering the VMs phenotype of the patients cohort, it has been obtained a more selective puzzle of interactions. For instance, GRB2 and HSPA1A and B genes directly act on angiogenesis and vascular development, TAF11 is known to be involved in artery passage and E2F1

transcription factor is known to be an angiogenesis positive inducer in hepatitis and cancer. Interesting HLA-DQA2 may also be implicated in angiogenesis by interacting with CD4. [162-165]

In addition, the expression of matrix metalloproteinase-9 was recently found to be increased in intramuscular VM lesions, suggesting that VMs have the capability for invasive growth and angiogenesis while expanding slowly due to the increase in hydrostatic pressure. [166] Besides, progesterone receptors identified in VMs is also suspected to cause the progress of lesions when hormonal levels change. [167]

Pathophysiology- Coagulopathy: Thrombosis and Fibrinolysis:

The coagulation disorders associated with VM are characterized by blood stagnation within the distorted and dilated low flow venous channels which leads to the activation of coagulation cascade with subsequent production of thrombin and the conversion of fibrinogen into fibrin. [168, 169] This is followed by fibrinolysis which is reflected by elevated levels of fibrin degradation products, including plasmin derived D-dimer epitopes. This simplified description of a complex hemo-pathologic pathway underlines pathogenesis of localized intravascular coagulopathy (LIC) and distinct coagulation profile that characterizes this unique coagulopathy associated with VM. [170, 171]

Newly-formed microthrombi in LIC bind to intravascular elementary calcium deposits and form pathognomonic stone-like structures called "phleboliths". [170, 172] Phleboliths can be detected during physical examination by palpation in patients with superficial VM. Phleboliths that are located in deep VM can be visualized on plain radiography, however they are most obviously detected on gradient-recalled echo sequences and T-2 weighted sequences. [173] The presence of phleboliths *may* represent indication for anticoagulation especially when the accompanying lesion is large and extensive.[174]

In the literature, LIC is often erroneously labeled as Kasabach-Merritt Syndrome, which is distinct clinical entity characterized by DIC and profound thrombocytopenia frequently associated with vascular tumors(168-170) By contrast, the platelet count in LIC is minimally diminished (in the 100-150 x 10^3/ml range). [174, 175]

LIC is of important clinical concern due to the potential for leading to more serious thrombo-embolic events, including STP, DVT, PE and the associated pulmonary hypertension, and thrombo-haemorrhagic DIC with life threatening hemorrhage which can occur during or following surgical resection or sclerotherapy. [176-180]

Conversion of LIC to DIC is marked by consumption of platelets and factors of coagulation. Increases in prothrombin time and decrease in coagulation factor V are the

earliest blood test findings. A number of events such as sclerotherapy, surgical resection, bone fracture, prolonged immobilization and pregnancy or menstruation are known to trigger conversion of the LIC to DIC, with haemorrhage related to consumption of coagulation factors and multiorgan failure related to disseminated microvascular thrombosis.

We recommend utilization of consistent nomenclature to clearly distinct between Kasabach-Merritt Syndrome and localized intravascular coagulopathy (LIC) since these two terms are often erroneously interchangeably used in the literature. This is important because, in contrast to patients with Kasabach-Merritt Syndrome, LIC can be treated with heparin.[174, 176]
[Strength of recommendation:1 (strong), Quality of evidence:B (moderate) [45]*]*

Low fibrinogen level, most often occurring in extensive VM affecting an extremity, reflects high consumption due to clotting associated with high fibrinolysis and increased risk for bleeding and requires preventive management by low molecular weight heparin (LMWH). [42] A large skin surface and/or muscle involvement by the VM represent strong predictable criteria for coagulation disorders associated with VM showing strong positive statistical correlation. This is not only true for large VMs but also for multifocal VMs. These lesions also are characterized with significant elevation of D-dimer levels.

A hypercoagulable status is commonly associated with VMs and may present with chronic intermittent STP, DVT and PE. Therefore, we recommend that a thrombotic risk profile to evaluate a hypercoagulable state should be performed in all VM patients as a routine part of diagnostic evaluation. Prior to surgery or sclerotherapy, a detailed coagulation profile is critical in order to identify those patients at increased risk of hemorrhage due to an impaired primary hemostasis.

A chronic coagulopathy could also have a significant impact on patient's ability to respond to treatment. Severe deficiency of physiological levels of factors of coagulation or platelets may prevent a successful response to treatment. In such condition, cryoprecipitate, platelets, or fresh frozen plasma may be given to the patients with chronic coagulopathy (such as low platelets, low fibrinogen, or elevated D-dimers) to restore adequate coagulation environment, before performing a procedure (e.g. sclerotherapy or embolization). [181]

III. DIAGNOSTIC EVALUATION

Introduction

High prevalence of deep venous anomalies in VM patients is clinically relevant since exclusion (excision/obliteration) of VM can negatively affect venous blood return in patients with above mentioned pathology. In these patients venous blood flow from the affected extremity depends on superficial and/or abnormal vessels and treatment of the malformation carries the risk of the impairment of venous return from the affected extremity. Therefore, from a diagnostic standpoint, phlebographic evaluation of patency and anatomic variations of the deep venous system deserves special consideration in addition to phlebographic classification of the VM as recommended by The Panel as above.

Coagulation disorders occur at a high frequency in patients with VMs and are associated with potentially severe thrombo-embolic events and hemorrhagic complications. [1, 2] Currently there are no defined guidelines to how patients with VM should be screened and/or treated for coagulopathy and when to introduce anticoagulation. Thus, it is important to obtain accurate diagnostic algorithm for coagulopathies associated with VM to guide appropriate management of these potentially life threatening disorders.

Thrombo-embolic and hemorrhagic complications in VM patients have been reported following sclerotherapy, surgery, trauma, prolonged immobilization, hormonal changes including pregnancy and menstruation, and sepsis. [171, 176, 178, 181, 182]

Multivariate analysis of data from a prospective study determined that the main independent risk factor for LIC was the surface area of VM, with an odds ratio of 2.82 for LIC for VM with a surface area > 10 cm^2. [170] Palpable phleboliths were also independently associated with LIC, with an odds ratio of 3.16. [170]

In summary, extensive VM with large surface area, muscle involvement, and/or palpable phleboliths are strong predicting criteria for coagulation disorders associated with VM. [170]

We recommend a complete thrombophilia workup in patients with a history of thromboembolism or extensive venous malformations (VMs) (surface area > 10 cm, palpable phleboliths)"
[Strength of recommendation:1 (strong), Quality of evidence:C (low) [45]*]*

Clinical Evaluation

When these VM lesions present in superficial area along the skin and mucosa, they present as bluish or purple localized lesions giving a sufficient clue of the VM. But when

present in deep anatomic location, it is difficult to detect the lesion through clinical examination alone.

But the majority may present with "swelling and pain" as most common clinical findings to give a clue for further examination, and especially phleboliths detected on the plain soft tissue X-ray are excellent clue for the VM with the intraluminal venous stasis and subsequent thrombosis. Occasionally direct puncture needle aspiration of the lesion confirm the VM with the venous blood or rule out with clear fluid/lymph aspiration.

Therefore, the diagnosis of VMs in general is not always easy and infrequently mimic other CVMs and even to some malignant tumors as well. [42, 183]

Proper clinical evaluation of patients with VMs is essential. A thorough history, including a detailed birth and family history must be taken. The physical examination should include careful assessment (inspection, palpation, auscultation) of both the arterial and venous systems including a detailed pulse exam, making note of any edema, skin changes, varicosities, induration, pigmentation, thrombophlebitis, or ulcerations to suggest CVI. An enlarged or longer extremity, digital anomalies and asymmetric growths of any part of the body must be recorded.

A specific description of VM lesions as a "localized" or "diffuse" lesions are very helpful, based on the criteria, whether there is no skin or mucosal involvement and are confined to one tissue plane, and the lesions margins are either well defined or ill-defined.

Localized lesions generally have well-defined or circumscribed margins and have a sharp abrupt transition from the surrounding tissue. These lesions remain confined to tissue and fascial planes. By contrast, diffuse lesions often cross the tissue and fascial planes and hence have an ill-defined margin with an irregular interface with the surrounding tissues.

Traditionally pain associated with VMs was considered as an inevitable consequence of the pathogenesis and progression of VM. However, recently the pain in the VM has been found to have a close relationship with underlying coagulopathy to cause LIC in many VM patients. Although LIC was believed to be latent and asymptomatic recent data shows that LIC results in painful local thrombosis in up to 92% of affected patients. [170]

The significant reduction of D-dimer levels was positively correlated with significant pain relief. Therefore, diagnostic algorithms which involves combined clinicians' assessments of pain severity reported by patient and measurement of D-dimer blood levels have been increasingly utilized in stratifying patients into those who do and do not require LMWH anticoagulation not only for prevention of potentially fatal thrombo-

embolic events but also for pain reduction and subsequent increase of quality of life (QoL).

Many VM cases are associated with other CVM lesions especially with LM/primary lymphedema. Therefore, special attention to cellulitis and lymphangitis is mandated on the examination. The VM with pelvic or genital involvement may exhibit hematuria and rectal bleeding. The appropriate combination of non-invasive to minimally-invasive tests should follow in order to confirm or exclude the clinical impression. [184-187]

Non- to Less- Invasive Diagnostic Tests: Essential

Duplex Ultrasonography (DUS)

DUS is the first test of choice for non-invasive evaluation of patients with VMs. [101-103]

- B-mode to differentiate tumors vs. malformations
- Doppler mode to assess flow characteristics

B-mode reveals the ultrasonographic features of the mass, the borders and the size. Additional information are added by the study of the flow pattern and contrast media (e.g. hepatic "hemangiomas).

On B-mode ultrasound, VMs typically present as compressible vascular spaces. Lesions may be found in the subcutaneous or intra-muscular tissues presenting as hypo- or anechoic vascular spaces. Spectral and Power Doppler would demonstrate flow on augmentation. Thrombosed or previously sclerosed lesions would appear partially- or non-compressible. These features allow for differentiation of VMs from LMs that appear as non-compressible cystic spaces or AVMs that demonstrate high flow.

A dedicated vascular laboratory with expertise in the diagnosis of vascular anomalies should be performing these studies. Sonographers should be trained specifically in this field and should appreciate the complexity and the range of conditions they may encounter. Ultrasound assessment should be correlated with MRI findings. In case of deep intra-muscular lesions, MRI may need to be obtained first to aid in locating the lesion on ultrasound.

DUS is also useful in the assessment of the extracranial cerebral venous outflow [188-190] in addition to evaluation of aneurysms, stenoses, intraluminal obstacles and valve malformations of the jugular veins at cervical level. [191-195]

We recommend duplex ultrasound (DUS) as the first diagnostic test for all patients with VMs, This test is safe, non-invasive, cost-effective and reliable to determine flow characteristics."
[Strength of recommendation:1 (strong), Quality of evidence:A (high) [45]*]*

It should be noted, however, that DUS is limited in its ability to assess involvement of associated structures such as nerves and bone, and is less helpful in defining the extent of lesions not located in the extremities. Assessment of the feeding and draining vessels is best obtained by phlebographygraphy and/or varicography. Nerves can be precisely identified concerning involvement and course by neurosonography.

Other non-invasive studies, such as plethysmography, segmental pressure measurement, and pulse volume recordings should be used selectively and clinical correlations with abnormal findings (e.g. outflow obstruction) need to be established. Airplethysmography in the study of outflow obstruction and reflux has been well validated.

Standard plain X-ray is still useful to identify abnormal findings in the soft tissue (e.g. phlebolith) and other malformation-related abnormalities along the skeletal system.

<Table 4. Duplex Ultrasound Assessment of Vascular Anomalies (VA) >
An ultrasound study of VA should provide the following information:

General Principles

- All ultrasound findings should be interpreted in the context of the clinical presentation and in particular time of onset, family history and rate of progression.In all patients, the opposite side should be investigated together to assess for possible occult malformation lesions and compare the morphology or the flow characteristics.
- In case of unilateral lesions, comparison with the opposite side to identify normal size and structures is mandated.
- The ultrasound examination of the limbs should be made in the upright and lying position and the difference of in size of the vessels should be recorded.

B-Mode-

- Gross ultrasonic morphology of the lesion and whether it is primarily composed of a soft tissue solid mass (tumor) or vascular channels with little soft tissue (vascular malformation).
- The lesion measurements in length and cross-sectional diameter. [99]
- Location with respect to known landmarks.

- Location and depth of the lesion in the tissue (sub-cutaneous, intra-muscular, inter-muscular, peri-articular, intra-articular, etc.).
- Compressibilty of vascular channels and presence/absence of thrombus within the channels.
- Evidence of previous treatments (hyperechoic walls/segments), sclero-thrombus, and surgical scarring should be identified and commented on.
- Presence of other vessels in the vicinity and their contribution to the lesion. Normal anatomy should be identified and excluded. In case of arterial vessels, comparison with the contralateral side should be performed to identify normal anatomy.
- In case of macrocystic LMs, the size and number of cysts observed.

Flow Characteristics

- Spectral, Color and Power Doppler examinations should confirm the flow characteristics.
- Flow characteristics (no flow, low flow, or high flow) should be determined; assessment of flow direction under different postural and respiratory conditions should be included in the evaluation [97, 98, 120-122]
- In case of VM involving the lower limbs, a separate venous incompetence study needs to be done to map the incompetent pathways. This is especially relevant when investigating truncular VMs or complex malformations such as KTS.

Other Observations:

Comments should be made regarding:

- Whether the lesion is unilateral or bilateral.
- If the underlying tissue shows hypertrophy, or atrophy.

Bone Scanogram

Scanograms are long bone radiographs that provide accurate measurement of the long bone length of the upper and lower limbs. Scanograms are needed to assess any bone length discrepancy between the limbs. This Document would become an objective criteria for the further management.

Computed tomography with intravenous contrast [196-198]

CT venography has a unique value for evaluation of obstructed, anomalous, atretic, or absent veins and other truncular anomalies of large veins in the chest, abdomen or pelvis. CT accurately identifies the underlying pathology, confirms venous obstruction or extrinsic compression, delineates anatomic variations and extent of venous thrombosis.

Magnetic resonance imaging and MR venography/phlebography. [199-202]

MRI and MR venography(MRV) is excellent for evaluation of VMs. The test is reliable, it confirms the extent and type of the VM, delineates feeding and draining vessels, distinguishes between different soft tissues (muscle, fat) and the vascular structures. MRI and MRV is therefore, essential imaging modality to provide highly accurate diagnosis before performing interventions on VMs .
The use of MRI in infants and children, who would need anesthesia for the test should be selective and carefully planned.

Magnetic resonance (MR) or computed tomographic (CT) venography is recommended for evaluation and treatment planning for VMs, as they are informative with regard to the extent of the lesion, involvement of surrounding anatomic structures and relationship between lesion and normal circulation.
[Strength of recommendation:1 (strong), Quality of evidence:B (moderate) [45]*]*

Non- to Less/Minimally-Invasive Diagnostic Tests: Optional

- WBBPS: transvenous angioscan utilizing radioisotope-tagged red blood cells. [110-112]

WBBPS is an optional test to screen for multiple VM lesions scattered throughout the body. It allows qualitative and quantitative evaluation of the VM lesion especially during the course of multisession sclerotherapy as a cost-effective measure. It is an excellent tool for routine follow up and to assess the progress of treatment and the natural course of the VM lesion. It can exclude the LM where the absence of an abnormal blood pool over the lymphatic lesion is the typical finding.

- TLPS: transarterial angioscan utilizing radioisotope-tagged microsphere albumin [116-118]

TLPS is not indicated for evaluation of the VM lesion but its major function is to rule out the presence of a combined AVM lesions. TLPS can detect a micro-shunting condition of AVM lesion which can be often be missed even with conventional arteriography.

- Radionuclide Lymphoscintigraphy (LSG) [107-109]

LSG is essential to rule out lymphatic dysfunction especially due to the presence of a truncular LM known as primary lymphedema, which often exists with the VM lesion (e.g. KTS).

- Microscopic fluorescent lymphangiography [203, 204]
- MR lymphangiography [205, 206]
- Ultrasound lymphangiography
- Endoscopy/colonoscopy for lesions involving the GI tract
- Cystoscopy for the involevement of urinary tract

- Echocardiography to assess the pulmonary pressure which may be elevated following repeated asymptomatic PEs

Invasive Diagnostic Tests

- Ascending, descending, and/or segmental venography/phlebography
- Standard and/or selective arteriography
- Percutaneous direct puncture angiography: arteriography, phlebography,
- varicography, lymphography

"Invasive" tests are seldom needed to establish the diagnosis of the VM and can be deferred until intervention is required. It is required for treatment planning either surgical or endovascular. However, invasive tests may be required for diagnosis when non- to minimally invasive tests (e.g. CT and/or MRI) fail to confirm the diagnosis or to delineate important diagnostic details.

For example, an obstructive truncular VM lesion along the iliac vein often needs more precise anatomic information. Ascending phlebography combined with intravascular ultrasound (IVUS) studies is essential for proper management. Descending phlebography is an indispensable tool to assess deep venous reflux along the pelvic veins and/or sciatic veins. These studies are required before treatment with embolotherapy.

Direct puncture phlebography is also very useful to identify a large efferent vein of extratruncular lesions. These veins can be treated in advance to allow more effective therapy with reduced risk of recurrence, with subsequent embolotherapy or sclerotherapy.

New Advanced Diagnostic Test

Dynamic Contrast Enhanced Magnetic Resonance Imaging (dceMRI):
A critical component in the process of diagnostic investigation of VMs is the determination that the lesion is truly low flow, and that there is no high flow or arterial component, as the treatment of low flow (VM/LM) lesions and high flow (arterial lesions) is completely different. Failure to identify the presence of arterial flow can have serious negative implications in the patients outcome.

Historically, a significant number of patients have required catheter based angiography to determine this, as conventional MRA and CTA are frequently inconclusive. The newly described technique of dceMRI is very useful in this regard, with approximately 85% accuracy.

Standard contrasted MRV leads to a relatively high false positive rate, in some instances due to the inexperience of those interpreting the test. In many cases, this may be due to microfistular shunting being overemphasized by contrast MRA. This can be reduced by the use of dceMRI and by the application of the test by an experienced practitioner.

dceMRI yields more information, including flow characteristics, soft tissue involvement, and the relationship to normal anatomy as a new generation of radiographic technologies.[207, 208]

dceMRI is not only capable to diagnose vascular malformations but more importantly to differentiate high flow from low flow has been provided. [80, 208] If the lesion is not apparent on the dynamic gadolinium enhanced images until the capillary phase or more typically the venous phase as determined by comparison with visualization of normal vessels, the lesion is considered to be a low flow abnormality.

dceMRI provides the most critical information, especially regarding a lesion that will be treated surgically. dceMRI not only determines hemodynamic quality, but also demonstrates the true extent of the lesion as well as soft tissue compartments involved, all of which becomes important in planning the surgical approach.

The hemodynamic and anatomical characteristics determined by dceMRI allow for implementation of either catheter-based embolization for high flow lesions, or transcutaneous sclerotherapy for low flow lesions, with or without surgical resection, depending on the extent of the lesion, cystic quality, and involvement of vital structures.

As with the majority of sophisticated imaging techniques, dceMRI requires the use of sedation or general anesthesia in the pediatric population due to the length of time required to perform the study, the need to hold still, and the noise of the magnet.

CAPRTtime Resolved Imaging

Cartesian Acquisition with Projection-Reconstruction like sampling (CAPR time resolved imaging) has been reported as an advanced imaging technique to be able to provide high temporo-spatial resolution imaging that allows for highly accurate characterization of the CVMs and treatment planning.

In a small series of patients with VMs authors demonstrated excellent correlation between CAPR time resolved technique imaging results and conventional angiography (which was performed at the time of treatment). Data of this study also suggested that delayed imaging should be utilized to capture complete filling of very slow VMs. Although initial results associated with CAPR time resolved imagining are promising

larger clinical trials are needed before this imaging modality can be accurately evaluated in the management of VMs. [209]

Blood Tests: Coagulation Profile Assessment - D-dimer

Plasma D-dimer represents a direct measurement of endogenous fibrinolysis. D-dimer (a degradation product of cross-linked fibrin) measured with rapid enzyme linked fluorescent immunoassay is being increasingly utilized in the assessment of VM patients and is considered to be the biochemical gold standard for ruling out an episode of thrombo-embolic events. Assessment of the coagulation profile and D-dimer levels is indicated in patients with extensive VMs. Extensive VMs are often associated with LIC, a chronic form of DIC and/or secondary hypofibrinogenemia (von-Willebrand-Juergens-syndrome) due to spontaneous hemorrhage.

D-dimer has been demonstrated to be increased in a significant number of patients affected by extratruncular VMs. This is due to LIC, especially in large or extensive extratruncular VMs containing phleboliths. LIC as characterized by elevated D-dimer levels has been observed in approximately 40% of patients with VMs. [210]

Elevated D-dimer is highly specific for VMs and may assist in the diagnosis of occult VMs and help differentiate GVMs and LMs (normal D-dimer levels) from other multifocal venous lesions. [210]

Patients with severe LIC would present with highly elevated D-dimer levels associated with low fibrinogen levels. Lesions commonly affect an extremity and have a high risk of hemorrhage. Anticoagulation with LMWH can be used to treat the pain caused by LIC and to prevent decompensation of severe LIC to DIC. [170]

In such cases, the consumption of platelets and fibrinogen would present a serious risk of bleeding resulting in a thrombo-haemorrhagic state. Measurement of hemoglobin and platelet counts is especially recommended to exclude chronic blood loss from VMs involving the GI tract. Furthermore, concurrent thrombophilia and in particular severe thrombophilias such as protein C and S deficiency and circulating lupus anticoagulants would increase the risk of concurrent thrombosis.

We recommend measurement of baseline D-dimer and fibrinogen levels as part of the initial laboratory evaluation for all patients with extensive extratruncular VMs . [Strength of recommendation:1 (strong), Quality of evidence:C (low) [45]*]*

Although D-dimer is non-specific for VTE, elevated D-dimer levels in VM patients should be considered to have a high positive predictive value for LIC. [210] D-dimer has a limited role in post-operative detection of VTE (see Section IX: Follow-up Assessment). Thrombophilia screening and prophylactic anticoagulation is especially recommended for high risk lesions (e.g. lesions involving the orbit). [211]

In summary, patients with *extensive* VMs or *high risk* lesions in particular should undergo the following laboratory tests:

- Full blood count including hemoglobin levels and platelet count.
- D-dimer- quantitative assay
- Fibrinogen
- PT, APTT
- Thrombophilia screening

Histopathology

The evaluation of the majority of VMs can be achieved with the non- to minimally invasive tests alone. But, occasionally, a biopsy of the lesion may be required to provide a histological diagnosis. This is especially relevant when the differential diagnosis includes a non-involuting vascular tumor such as a non-involuting hemangioma (NICH). [212-215] These lesions have high flow on Doppler and persist indefinitely and may be confused with an AVM. Furthermore, biopsy may be required to differentiate between lesions of GVM vs. BRBNS. GVM is lined by cuboidal cells that are positive for smooth muscle actin and myosin.

Histologist should be informed that the clinical impression/diagnosis is VM in order to avoid generic diagnosis of “angioma” or “hemangioma”.

Immunohistochemistry:

Histopathologic evaluation, with the use of hemotoxylin and eosin (H&E) and Elastic-van-Gieson-stained techniques, provides more definitive and detailed information regarding structural changes of the venous structures that arise by embryologic dysmorphogenesis, helps in the differential diagnosis between infantile hemangiomas and vascular malformations and has been incorporated in the classification system and diagnostic algorithm for the CVMs.

VMs are characterized by dilated sinusoidal vascular channels and spaces with variably thickened walls lined by flattened, mature endothelial cells with the lack of pericyte-

endothelial interaction and the absence of increased endothelial mitotic activity with subsequent lack of increased endothelial proliferation. [18, 216]

They have normal surrounding reticulum, but frequently there is absence of distinct internal elastic lamina. These histological characteristics serve as the foundation for the proper classification, investigation, and management of VMs and represent the basis for the landmark classification system initially proposed by Mulliken and Glowacki in 1982. [216]

Relatively recent advances in immunohistochemical techniques allowed more detailed investigation of structural abnormalities and greater tissue diagnostic accuracy especially in complex VMs with unpredictable clinical course and ambiguous histology on conventional microscopy. Immunohistochemical detection of GLUT-1 antigen allows unequivocal differentiation between infantile hemangiomas and CVMs. [217]

North et al demonstrated that all infantile hemangiomas stained positive for GLUT-1 antigen. [218] Other studies showed that all types of CVMs stain negatively for immunohistochemical markers specific for infantile hemangiomas such as GLUT-1 as well Lewis Y antigen. [219]

Immunohistochemical analysis for Willms tumor-1 (WT-1) protein that included 117 vascular neoplasms and 50 CVMs (VMs=16) showed positive expression of WT-1 in all vascular tumors and negative WT-1 expression in all VMs, save that WT-1expressoin was observed to be positive in AVMs. [220, 221]

More recently, in a study of 130 clinically symptomatic CVMs, S-100 immunostain antibody was utilized to identify the presence of neural tissue within CVMs. Although non-specific for the VMs (the presence of neural tissue was detected in AVMs, as well) the value of the immunohisotchemical modality that utilizes S-100 immunostain antibody is in the fact that the absence of nerve tissue in hemangiomas could allow differentiation between clinically and radiographically similar appearing VMs and hemangiomas and helps in a better understanding of the pathophysiology of CVMs on a molecular level. [222] α-smooth muscle antibody stain is used to detect either the absence of smooth muscle or irregular smooth muscle clumps within venous wall, which is likely responsible for ongoing dilatation and “pari passu” pattern of growth of the VMs. [223] A more recently developed monoclonal antibody (D2-40), to onco-fetal antigen M2A, is highly specific for lymphatic endothelium and is negative for normal or malformed venous, arterial, or capillary endothelium which is especially diagnostically applicable for making an accurate distinction between VMs and LMs. [224]

In addition to immunostain D2-40, vascular immunostains PROX1, and vascular endothelial growth factor receptor 3 (EGFR-3), have been proposed to distinguish LMs from AVMs and/or VMs. [225] The use of antisera anti-desmin/actin can delineate truncular defect of smooth muscle cell characteristic of primary venous aneurysm and other truncular VM. [55]

In 2013, Rosler et al performed immunohistochemical analysis for cluster of differentiation-31 (CD-31), D2-40, GLUT-1 and Ki67 in order to differentiate nine IH, seven VM and five LM. [226] In addition, utilizing quantitative real-time PCR (qPCR) authors analyzed the expression levels of β1, β2, and β3 adrenoreceptor mRNAs. Data from this study showed that all VMs as well as LMs showed CD-31 positive immunostaining of endothelial cells and negative GLUT-1 staining. [226]

Immunostaining for Ki67 was positive in proliferative hemangioma endothelial cells, confirming the growth potential, and negative in VMs. qPCR analysis showed that the expression levels of β adrenoreceptors were significantly increased in IHs independent of the proliferative or regressive phase. [226]

VMs showed very low expression levels of all three subtypes of β-adrenocreceptor mRNAs. This was the first study to provide the evidence of distinctions between IH and VMs based on the β-adrenoreceptor subtype mRNA levels. [226] Data from this study can potentially reveal the mechanism by which β-blocker medications are reasonable treatment option for certain types of hemangiomas but not for VMs.

IV. DIAGNOSIS- SPECIAL ISSUES

Differential Diagnosis With the AVM:

In a diagnostic algorithm for CVMs, a very important step, which follows initial differential diagnosis between CVMs and true vascular neoplasms (most commonly IHs), is the differentiation between VMs and AVMs.

Despite distinct embryologic, histologic, clinical, hemodynamic and radiologic findings AVM are often confused with VMs and many physicians still do not understand the difference between these two vastly different lesions due to confusing and frequently contradictory nomenclature which historically characterized majority of the literature discussing CVMs. [227-229]

Moreover, the complexity of many AVMs contributes to the diagnostic challenge and consequently, many patients have been discouraged by the lack of correct diagnosis and proper treatment despite numerous visits to different clinics (from primary care physicians to subspecialists). Since the morbidity, treatment modalities and long-term

prognosis significantly differ between AVMs and VMs, accurate classification and proper diagnosis is critical for the successful management of these lesions. [230, 231]

Proper utilization of a diagnostic protocol and terminology outlined in this Consensus will permit more effective communication between different medical specialists and will improve the management of CVM patients.

Etiology and Pathophysiology

The AVMs are the least common CVMs representing approximately 10–15% of all clinically significant lesions. [3] In contrast, the VMs are the most common type of CVM and they comprise approximately 2/3 of all CVM. [75, 232] The estimated incidence of predominantly VMs is approximately 0.8% to 1% in general population. [233]

CVMs arise by embryologic dysmorphogenesis without increased endothelial proliferation that leads to structural and functional anomalies of the vascular system. [152, 234] The (extratruncular) AVMs preserve its embryonic form originating from the "reticular" stage of embryogenesis that occurs prior to the primordial blood vessels maturation. [235]

This anatomical environment provides a direct communication between the developing artery and the vein, passing through an area of dysplastic capillaries (termed as nidus) and allows blood flow shunting through the nidus. The increased blood shunting into the nidus causes local and systemic symptoms that are related to the hemodynamic alterations to both arterial and venous blood flow, as well as vascular hypertrophy that can induce compression, erosion, infiltration and/or destruction of surrounding normal anatomic structures. [236, 237]

Pathohistologicaly the AVMs demonstrate heterogeneity that reveals arterial endothelium hypertrophy and thickening and/or dystrophic calcification localized within fibrous or fibro-myxomatous extracellular matrix. [18, 238]

Based on their embryonic stage of developmental arrest, there are two sub-types of AVMs: extratruncular and truncular, which are outcomes of developmental arrest in the early and late stages of embryogenesis, respectively. [33, 239] Extratruncular AVMs are associated with a higher rate of recurrence following both surgical and non-surgical treatment modalities and resistance to therapy, presumably because they possess mesenchymal characteristics of independent growth potential. [12]

Clinical Presentation

Differential diagnosis between AVM and VMs can be made by clinical assessment in the significant number of cases. Thus, a meticulous medical history and a detailed physical examination are essential initial steps in the management of CVM.

Like other subtypes of CVMs, AVMs are present at birth. It is estimated that approximately 40% of AVMs are detectable during the perinatal period. [240, 241] Other AVMs are clinically not apparent until later in life and their rapid growth and appearance may be stimulated by trauma (e.g. blunt trauma, fracture), the effects of hormones (during puberty, pregnancy or menstruation), infection or they may occur in the absence of any identified triggering factors. [41, 89]

Clinically, AVM are characterized by more "aggressive" progression and expansion of the lesion, unpredictable clinical course, wide range of presenting symptoms and significantly higher morbidity than VMs. AVM patients can present with pain, functional impairment, concerns about cosmetics, cutaneous and/or muscular ischemia, infection, and even ulceration(s) due to "steal phenomena" and subsequent diminished distal arterial blood flow. If extensive, AVMs can lead to severe episodes of life-threatening hemorrhage, limb-threatening ischemia and high output cardiac failure due to large volume arterio-venous shunting. [89]

In contrast to VM, AVMs may produce a profound hemodynamic impact that affects the entire vascular system regardless of its location, resulting in much more severe local and systemic disorders. [41] Data from a recent study demonstrated that AVM patients have increased exercise intolerance and disproportionate increase of cardiac output secondary to significant arterio-venous shunting. [242]

On inspection and palpation AVMs demonstrate skin discoloration and/or swelling and elevated cutaneous temperature and/or thrill, respectively. Frequently, a bruit secondary to aberrant anatomy and consequently altered hemodynamics can be appreciated over the affected area. This is opposite to the VMs which appear as bluish, soft and easily compressible, non-pulsatile masses that usually enlarge with activity, Valsalva maneuver (e.g. crying in children) or dependent posture, and empty with elevation. [31, 243] There is no increase in local skin temperature or thrill when the VM is palpated, and there is no bruit present on auscultation.

Although the majority of AVMs are solitary and occur in the skin and subcutaneous tissues, they can also occur with other types of CVMs as multiple, infiltrating lesions that can involve multiple soft tissue planes including muscles, abdominal viscera and the central nervous system. These mixed AVMs can be associated with osteo-muscular hypertrophy (e.g. PWS) and their treatment can be very complex and challenging and it

frequently exceeds the level of expertise of any single medical specialty.[132, 244, 245] In these patients multidisciplinary approach is particularly important.

Imaging Modalities

Clinical evaluation often underestimates the involvement of deep structures such as muscles, bones, joints or abdominal viscera and frequently is not sufficient to differentiate AVMs from VMs in some of the more complex-combined cases. Therefore, evaluation by modern imaging modalities (DUS, MRI and angiography/arteriography and venography) is of paramount importance to the correct diagnosis and treatment plan for AVMs.[246]

The absence of arterial blood flow through the lesions is the characteristic used to differentiate VM from AVM and some authors use the term fast-flow or high-flow vascular malformation to describe AVM based on hemodynamic characteristics determined during imaging.

Unlike the VMs, which on Doppler ultrasonography demonstrate monophasic, biphasic and no detectable flow in 78%, 6% and 16% of cases respectively,[247] ultrasonography of AVMs is characterized by multidirectional (high-flow Doppler signal with low-resistance arterial waveforms) blood flow, rapid arterio-venous shunting and high amplitude arterial waveform with spectral broadening.[248, 249]

In contrast to AVMs, on grey scale ultrasound VM appear as hypoechoic or heterogeneous lesions with anechoic structures visible in <50% of cases.[74] In some cases flow in VMs is only detectable with compression and release of the malformation.[103] DUS is useful to confirm the diagnosis, as it is rapid, easy and shows the low-flow velocity and vascularization, but it is frequently inadequate to demonstrate the extent of the lesion. Thus, MRI and/or CT is the imaging modality to be needed in the evaluation of the AVMs.

AVMs have a significantly different appearance on MRI than their low-flow counterparts (VMs).[250, 251] AVMs typically demonstrate low signal regions known as flow voids that can be observed on T1- and T2-weighted images, distinguishing them from VMs which demonstrate high T2-weighted signal.[207, 252-254] High-flow hemodynamics leads to a infiltrative or focal webs of flow voids that can be seen on both T1- and T2-weighted spin-echo sequences.[255, 256] In contrast to VMs, MRI frequently demonstrates a characteristic absence of mass effect in AVMs.[199, 257] The presence of feeding arteries dilatation and draining veins with a paucity of venous lakes are also indicative of AVMs, rather than VMs.

However, utilization of MRI in distinguishing between AVMs and VMs can be challenging in some cases since numerous particulars can mitigate above mentioned observations. For example, a blood vessel that passes within an imaging plane may give an intraluminal signal despite high-flow, which can be a falsely positive finding for a low-flow lesion (VMs). In these cases time-resolved imaging of contrast kinetics (TRICKS) and time-resolved echo-shared angiographic technique (TREAT), where images are acquired sequentially every few seconds are utilized to accurately determine flow hemodynamics within the CVM. [80, 201] These techniques have an additional advantage of being able to delineate dominant or multiple feeding vessels which can be useful for treatment planning. [80]

In inconclusive cases, when MRI is not definitive in assessing flow characteristics and when suspicion of arterial flow cannot be excluded based on MRI findings, an appropriate diagnostic workup includes an arteriogram.[80] Arteriogram allows precise evaluation of feeding arteries and draining veins and is used to evaluate the extent of lesion and to plan the treatment. In some patients arteriography can be utilized to provide an opportunity to intervene. This approach avoids unnecessary diagnostic arteriograms.

The most important aspect of diagnostic evaluation of VMs is to differentiate these lesions from high flow AVM lesions since the treatment is quite different, and failure to identify the presence of an AVM component may result in treatment failure and recurrence. Treamtment of the venous outflow without attacking the nidus of an AVM also can have serious conequemces as considerable venous hypertension can develop.

Differential Diagnosis With the Hemangioma

VMs may be confused with a more common vascular anomaly, the infantile or neonatal hemangioma. Although both VMs and hemangiomas are vascular anomalies, these conditions are fundamentally different not only in their anatomic, histologic, and pathophysiologic findings but also in their clinical course. [18-20]

A VM is a birth defect that develops within the peripheral vascular system and manifests as a malformed vessel, whereas a hemangioma is a vascular tumor that originates from endothelial cells.

Differentiating VM from hemangioma should be the first step in the diagnosis of VMs. Most cases do not require imaging, because a correct diagnosis can be based on the history and clinical picture. Ultrasonography and MRI can be of use when clinical features are atypical.

Natural History

In most cases the differential diagnosis can be made on the basis of the natural history, because the unique growth pattern of the mass lesion often allows to distinguish a VM from a hemangioma. [258]

Infantile Hemangiomas usually are not present at birth and not initially noticed by parents and caregivers. They appear suddenly during the early neonatal period as rapidly growing tumors but usually self-limited. They have a distinctive course characterized by a two-stage process of growth and regression. During the neonatal period, they start with a proliferation phase of rapid growth that may last several months. After a stationary period, they undergo an involutional phase of slow gradual regression, which is usually complete before age 12 years.

In contrast, VMs are always present at birth as inborn errors, even they might not be apparent, and they grow steadily commensurate with the child's systemic growth. VMs never disappear or regress and remain present throughout the patient's life.

Clinical Picture

Physical examination is very important because the clinical characteristics of the mass are often useful to make the distinction between hemangioma and VM. [259, 260] However, deeper lesions are impossible to assess fully on clinical criteria alone.
Hemangiomas during the proliferative phase are high-flow lesions that often appear as strawberry-like, pulsatile masses with increased cutaneous warmth. However, these clinical signs may be absent or difficult to detect in subcutaneous lesions.

VMs have different characteristic clinical features: the colour of the mass is bluish, it's not detected any pulsatility and there is no local increase in skin temperature. Furthermore they are soft and easily compressible with a typical increase in size on Valsalva maneuver.

Ultrasonography

Ultrasonography is a non-invasive imaging technique very useful for differentiating hemangiomas and VMs as the first-line imaging study for the children. [77, 247] Clinically , if the mass is deep-seated, located in the subcutaneous tissue or in the muscle layer, a hemangioma may mimic a VM. In these cases the clinical diagnosis may be impossible and instrumental investigations are necessary to confirm the differentiation between the two entities.

Hemangioma typically appears in the proliferative phase as a well-circumscribed, solid mass consisting of a parenchymal tissue which is intensely hypervascular. Most hemangiomas are hypoechoic, although up to 18% have been reported to be hyperechoic. They show a high-flow Doppler signal with low-resistance arterial waveforms.

The spectral analysis of arterial and venous flow and the measurement of flow velocities is extremely helpful to identify the Doppler flow characteristics of hemangiomas based on high vessel density and high peak arterial Doppler shift: vessel density in excess of five per square centimetre, and peak arterial Doppler shift greater than 2 kHz, taken together are highly specific and give a positive predictive value of 97% for the diagnosis of proliferative haemangioma.

Ultrasonography of VM typically shows in grey-scale a well-defined sponge-like collection of enlarged vessels spaces presenting as hypoechoic structures. Blood can be seen flowing into the cavities, especially after applying and releasing manual compression. Colour flow imaging shows a low-flow Doppler pattern. Other important features include phlebectasia, and the presence of phleboliths.

Magnetic Resonance

MRI is the second non-invasive test for differential diagnosis of hemangioma and VM although it is NOT as critical as ultrasonography. MRI may be indicated for diagnostic confirmation when the ultrasound findings are not clear. This investigation allows to better define the anatomy and the vascularisation of the lesion, so distinguishing hemangiomas and VMs. In many cases, MRI and ultrasound with colour flow imaging are complementary. [106, 256, 261]

MR imaging of proliferating hemangiomas often shows a lobulated, solid mass that is hyperintense to muscle on T2-weighted images and isointense to muscle on T1-weighted images. Typically, prominent draining veins will be identified along both central and peripheral and some smaller arterial high-flow vessels are seen as flow-voids. There is intense, uniform, diffuse enhancement following intravenous administration of gadolinium contrast.

In the involuting phase, appearances are more varied and heterogeneous, as the lesions contain varying amounts of fibrous tissue, fat and rarely calcifications among cutaneous infantile hemangioma. Contrast enhancement decreases and becomes inhomogeneous.

MRI findings of the VMs including the typical appearance of VMs as a collection of serpentine structures and its relationships with adjacent tissue/structures were thoroughly described in diagnostic section of the VM.

Computed Tomography

CT with intravenous contrast enhancement has been used for the differential diagnosis of hemangiomas and VMs. [114] Yet CT involves significant exposure to ionising radiation making it less useful although CT gives superior resolution for osseous lesions.

Histology
Tissue biopsy is sometimes required for the differential diagnosis when the lesion shows progressive enlargement and atypical clinical or imaging features. Hemangiomas are distinguishing in the proliferating phase by endothelial hyperplasia with the formation of syncytial masses and a typical multilaminated basement membrane. In VMs specimens are not hypercellular, showing multiple vascular channels with a flat endothelium overlying a single-layered basement membrane and GLUT-1 positivity.

Chronic Cerebrospinal Venous Insufficiency by Truncular VM:

Truncular VMs are the result of the developmental defects of vascular trunk formation during the later stage of embryogenesis, Truncular VMs are subdivided into obstruction (intraluminal defects, segmental aplasia or hypoplasia), and dilation (aneurysms). [1, 30, 31] Obstructive lesions can be respectively subdivided in intraluminal obstacles (septa. webs, membranes, fixed and rudimental valves) and in wall stenosis (hypoplasia, agenesis). [1, 30, 31]

Truncular VMs may have different hemodynamic impacts on their relevant drained apparatus/organ. Independently from the area where they occur, the impact is chronic and progressive in the clinical course, depending upon their location, extent/severity, and natural compensation through collaterals.

For instance, CVI of the lower extremities develops in territory drained by truncular veins. Stenosing truncular lesions (e.g. primary intraluminal obstruction of iliac vein) determine a reduction in venous drainage leading over time to CVI of different severity stages. [262, 263]

Membranous obstruction of the IVC in primary Budd-Chiari syndrome is a further example of congenital lesion as a truncular VM determining a focal segmental occlusion of the suprahepatic IVC. This disorder can lead to profound portal hypertension due to hepatic venous outlet obstruction with severe consequences consisting in chronic hepatic failure and liver sclerosis. [63-65, 264]

Chronic cerebrospinal venous insufficiency (CCSVI) is a syndrome characterized by restricted venous outflow from the brain, in consequence of respectively intraluminal defects, wall stenosis, or also external compression, striking the internal jugular (IJV) and/or azygos veins. Intraluminal obstacles and hypoplasia\agenesis, documented with a combination of techniques (intra and extravascular ultrasounds, catheter and MR venography) are morphologically quite similar to those above described for truncular VMs. [67, 265-267]

The reported prevalence of CCSVI is highly heterogeneous in literature. However, a meta-analysis reveals that CCSVI was found mainly in multiple sclerosis patients, but also possibly associated to other neurodegenerative diseases and even to healthy controls. [268]

In CCSVI usually more than one segment of the major extra-cranial and extravertebral cerebral veins is affected. Consequently, disturbed flow and formation of collateral venous channels have been described. [269-271] The IJV flow objectively measured by means of 2D MR drains approximately 75% of the cerebral arterial inflow, whereas it falls to respectively 64% and 52% if one or two stenosis are documented. [272]

The extensive flow diversion through collaterals channels, permits to avoid intra-cranial hypertension. Venous hypertension in cerebral veins was never assessed. However, a slight but significant gradient across the stenosis has been measured. [273] The two main consequences of CCSVI on brain pathophysiology have been recently highlighted by the means of objective non conventional MRI measures:

1) Impaired brain perfusion. Venous outflow obstruction determines diffuse hypoperfusion of the brain parenchyma(e.g. multiple sclerosis patients). [274]
2) Impaired cerebro-spinal fluid (CSF) dynamics. CSF is ultra-filtered at the level of the lateral ventricles, circulates in the CSF spaces and finally is re-absorbed into the venous system, at the level of the superior sagittal sinus.

In CCSVI, impaired cerebral venous outflow is linearly related to the impaired venous hemodynamics. [275, 276] Finally, Color Doppler sonography and plethysmography both clearly measure an impaired postural control of cerebral venous return. Passing from supine to up-right posture the cervical venous outflow is significantly faster in controls respect to CCSVI. [70, 277-279]

Summary
Truncular VM as cause of CCSVI is supported by gross anatomy and imaging techniques evidences of intraluminal defects and segmentary hypoplasia, typically seen in truncular VMs. [1, 267, 280] In addition, embryology [280] compared with morphologic characteristic of some CCSVI lesions, further suggests truncular VMs. [67, 68, 273]

Finally, focal alterations in collagen component, [281] and specific genetic and environmental factors [282] further suggests truncular VMs to explain the origin of CCSVI stenosing lesions.

Nowadays, there are increasingly thriving studies leading to a CCSVI diagnosis through multimodal techniques, in which the different methods are used in combination in order

to increase diagnostic accuracy. [269, 283] An ideal screening device is cervical plethysmography. [279, 284] It tells us how much the venous return is affected but needs to be corroborated by Doppler sonography [67, 267-269, 283], MRV [266, 269, 272, 283] , and CT venography [269] to define exactly both morphology and location of venous obstruction. Invasive catheter venography/phlebography and intravascular sonography should be used only when treatment is planned. [269]

V. TREATMENT: OVERVIEW

Multidisciplinary Team Approach

Surgical excision alone based on limited knowledge of the natural history and biology of the VM through earlier decades frequently resulted in poor outcomes. [285-288] These poor outcomes contributed to the confusion associated with the management of CVMs leading to mistaken prejudice and the concept that such lesions cannot be treated. [289-292]

But lately new endovascular therapies utilizing various forms of embolo/sclerotherapy were developed in order to improve the clinical outcome of extratruncular VM lesions. For truncular VM lesions, endovascular balloon dilatation and stenting techniques were also found to be beneficial in correcting the stenosing condition, and thermal ablation may be useful in the elimination of long axial refluxing segments of certain VMs such as MV/KTS.

Endovascular and/or percutaneous therapy (e.g. ethanol sclerotherapy) is now a universally accepted independent therapy of VMs in the poor surgical candidate with extensive lesions extending beyond the deep fascia with involvement of muscle, tendon and bone as seen in diffuse infiltrating extratruncular lesions. [293-296]

A new concept of the multidisciplinary team approach emerged aimed at the prevention and control of "recurrence/persistence" with minimal possible complications and morbidity based on full integration of surgical, non-surgical and endovascular treatment options. This team concept is extended not only useful for diagnosis but is also essential for "combined" treatment using two or more different techniques.

Embolization is typically combined with surgical resection. Furthermore, surgical resection may often require a vascular surgeon, a hand and/or plastic surgeon, or other specialists altogether. [239, 297, 298]

The multi-disciplinary team often includes medical and allied health teams: Vascular Surgery, Pediatric Surgery, Plastic & Reconstructive Surgery, Orthopedic Surgery,

Neurosurgery, Anesthesiology, Pathology, Physical Medicine & Rehabilitation, Oral-Maxillofacial Surgery, Head & Neck Surgery, Cardiovascular Medicine, Psychiatry, Dermatology, Interventional Radiology, Diagnostic Radiology, Nuclear Medicine, General Medicine, Neurology, Hematology, Genetics, General pediatrics, Occupational therapy, and many other health care practitioners. [1, 239]

Multidisciplinary team approach is also mandatory for proper selection/combination of the treatment modalities. All the decision related to the management should be based on the consensus among this multidisciplinary team approach as well as life-time follow up on the natural course and treatment outcomes.

General Principle

Not every VM lesion is amenable to treatment. Furthermore, not every VM lesion should be treated. Its mere presence often makes the practitioner feel obligated to treat. The only lesion assessed by the multidisciplinary team with justified indications such as severe symptoms or complications of the lesion should be considered for treatment. Although extratruncular VM lesions are more serious than truncular lesions with much poorer long term outcome, an overzealous approach sometimes does more harm than good. [1, 11, 123]

Observation sometimes remains the best approach yet until figuring out the exact nature of the lesion; “Not to intervene” is sometimes a wiser choice than to casually intervene without a full understanding of the biology and natural history of the VM lesion. Another important approach is to refer complicated case to an experienced center where the patient can be treated effectively by well organized team in early childhood and not having to wait until after reaching adolescence. [1, 3, 22, 123]

A “controlled” aggressive approach is favored where every effort is made to minimize collateral damage during treatment. In limb and life threatening situations, sacrificing limb over life may be necessary. The decision to initiate treatment should be based on the accepted indications. [81, 299-301]

When the benefit of treatment outweighs the risk of complications and morbidity, less risky treatment options (e.g. foam/liquid sclerotherapy) should be first line therapy. “No treatment is the best option if feasible”. In contrast to the treatment of AVMs, all VM lesions can be treated using a less aggressive approach. [291, 302-305]

The traditional conservative approach to the young pediatric patient with a VM is still valid, especially for the common VMs as far as there is NO evidence of bony involvement (e.g. leg length discrepancy). It is usually safe to delay treatment until the

child reaches to the age of two or more years before beginning diagnostic procedures and treatment. [184, 306-308]

However, for the VM lesion at a life or limb threatening anatomic location an earlier treatment approach is preferred over a more conservative one; for the lesion complicated with a life or limb-threatening condition (e.g. hemorrhage) treatment should be started expeditiously despite the risk of the associated morbidity.

General Measures

1. Explain the diagnosis- an accurate diagnosis should be documented and communicated with the patient, parents or guardians of the pediatric patient and the referring doctor. Care should be taken to explain the difference between a tumor, such as a hemangioma, and a vascular malformation. This forms an integral part of educating the public and other medical specialties. Care should be taken to avoid confusing and redundant terminology such as "port wine stain" or "hemangioma".
2. Treat associated or secondary complications. Examples include associated anemia from bleeding. Manage any associated pain and/or superficial recurrent thrombophlebitis.
3. Graduated compression stockings and garments. This is especially important for lesions involving the lower limbs. Compression garments are also useful in the treatment of upper extremity VM lesions. Compression therapy can help with symptoms, which include edema and help prevent other complications such as superficial thrombophlebitis.
4. Support and Education. Refer the patient to support groups and recommend websites or print material to further educate the patient. Provide a referral for counseling or psychiatric assessment if required.
5. Refer to and consult other specialists. In case of leg length discrepancy, it is essential that children are referred early on to pediatric orthopedic surgeons, if vascular surgery alone or a combined treatment did not succeed in compensation of the length discrepancy. [309-312] VM lesions involving the central nervous system require assessment by neurosurgeons and interventional neuroradiologists. Coagulation issues may require consultation with a hematologist. Other specialists should be consulted as required. Allied health practitioners such as physiotherapists should also be involved and should form an integral part of the multi-disciplinary team approach.
6. Family members screening and genetic counseling. In cases of inherited malformations such as GVMs or BRBNS, family member screening and genetic counseling may be indicated.

General Indications

Indications for intervention may include the following conditions or complications of VMs and its associated conditions (e.g. LM) [100, 313-320]

- Bleeding in various conditions/extents, from the skin or mucosa lesion to intramuscular or retroperitoneal hematoma, hematuria, rectal bleeding, hematemesis, hemoptysis, or intracerebral or intraspinal bleeding
- Signs and symptoms of CVI (painful varicosity, edema, skin changes, indolent ulcers, recurrent STP)
- Lesions located at a life threatening region involving or close to vital structures (e.g. proximity to the airway), or located in an area threatening vital functions (e.g. sight, eating, hearing, or breathing)
- Disabling pain
- Functional impairment (e.g. genital region)
- Cosmetically severe deformity
- Lesions located at regions with high risk of complications (e.g. hemarthrosis, thromboembolism)
- Lesions combined producing the vascular-bone syndrome (length discrepancy of the lower extremities, affecting the bone itself) or the destructive angiodysplastic arthritis (Hauert disease)
- Lesions obstructing the outflow and drainage of vital organ (e.g. liver, brain)
- Lesions generating a low perfusion and|or other relevant hemodynamic effects in the drained territory.
- Recurrent thrombosis of the affected area in extratruncular forms
- PE from venous aneurysm or other venous dysplastic areas
- Consumptive coagulopathy with clinically equivalent lesions
- Persistent lymph leak due to a combined LM with/without infection
- Recurrent sepsis, local and/or general, due to a combined LM

We recommend that before treatment of any VMs the embryologic subtype of the VMs (extratruncular vs. truncular) be identified. The risks of thromboembolism, bleeding, injury to the surrounding structures (nerves, skin, bone, etc.) and likelihood of functional improvement and improved QoL after potential treatment should be fully assessed. The presence of any other associated vascular malformations (arteriovenous shunting, LMs) should also be determined. Careful assessment of the extent and severity of the VM lesion and identification of draining deep vein system is mandatory.
[Strength of recommendation:1 (strong), Quality of evidence:B (moderate) [45]]

Anticoagulation Therapy to the VM-Extratruncular and Truncular

We do not consider administration of antiplatelet agents, such as aspirin or ticlopidine, and other non-steroidal anti-inflammatory drugs and analgesics is indicated since they

have been shown to be of little or no clinical benefit in patients with VM-associated coagulopathy and/or pain releif. [174, 179, 182]

A retrospective case series, however, reported the efficacy of LMWH to treat the pain caused by LIC, to normalize coagulation profile, and to prevent progression of severe LIC to DIC (especially in patients with low fibrinogen level). [170]

Extensive, multifocal, infiltrating, painful VMs should be treated with weight adjusted dose (100 U/kg/d) of LMWH. In addition, elevated D-dimer in painful VM that interfere with daily functional capacity and QoL represents indication for the initiation of LMWH treatment. Based on available data LMWH treatment should be continued for 20 days. [170]

Since not all VMs can be cured and some patients might not initially respond to LMWH anticoagulation pain relief treatment the goals of therapy should be determined by both the patient and physician at the time of initial evaluation, prior to starting the treatment, to minimize patients frustration and to increase compliance with the treatment plan.

It is worth emphasizing that VM patients can become severely coagulopathic even during minimally invasive procedures (e.g. endovenous laser ablation, ultrasound guided foam sclerotherapy) as well as diagnostic procedures (e.g. MRI, angiography). [174] Patients with KTS and extensive VM, including children, are known to be at significantly increased risk of DVT and subsequent PE. [321-323]

We recommend anticoagulation with prophylactic dose of LMWH <u>prior to</u> invasive or minimally invasive interventions in patients with with extensive VM, evidence of LIC, in KTS patients and in those with thrombophilia.
[Strength of recommendation:1 (strong), Quality of evidence:C (low) [45]*]*

Superficial and small VM represent relative indication for peri-procedural LMWH anticoagulation. In this subgroup of patients peri-procedural anticoagulation should be initiated based on the evidence of abnormal coagulation profile, past medical history positive for hypercoagulability and/or evidence of the involvement of deep venous system.

We also recommend full anticoagulation with weight adjusted LMWH in patients with VM and thrombophilia, in patients with KTS and a history of thromboembolism, unless there is contraindication to anticoagulation.
[Strength of recommendation:1 (strong), Quality of evidence:C (low) [45]*]*

Prophylactic anticoagulation should be initiated based on hypercoagulability assessment and the presence of coexisting malformations, following the previously described anticoagulation protocols.

It is worth emphasizing that anticoagulation and close monitoring should be initiated in patients with coexisting aplastic deep venous system since despite the absence of deep veins in this subgroup of patients thrombus formation in the MVs that are entirely superficial can be considered as "pseudo DVT" since these abnormal veins serve as substitute channels for the aplastic deep veins and the venous blood return from the affected lower extremity depends on their patency. [80]

The introduction and duration of anticoagulation therapy should be based on clinical and hematological grounds and to be re-evaluated regularly for each patient and each VM. It has been proposed to initiate prophylactic therapy with weight adjusted (100 U/kg/d) subcutaneous LMWH 10 days before and to continue 10 to 20 days after any surgical procedure (including above mentioned minimally invasive procedures). [174]

To ensure adequate compliance with the LMWH anticoagulation therapy, to increase comfort with therapy and to decrease the needle phobia the insertion of temporary indwelling subcutaneous catheters should be considered in pediatric patients. Patients with extensive VM require a regular long-term, regular coagulation profile assessment and monitoring.

Further prospective studies are needed to provide Level 1 data that will serve as basis for establishing accurate treatment protocols in regards to dose of anticoagulants and duration of prophylactic and therapeutic anticoagulation in VM patients.

VI. TREATMENT: NON-SURGICAL

Observation and Conservative Management

Conservative approach also includes proper skin care, local wound- bleeding or ulcer care, compression dressings, and compression therapy with elastic garment and/or bandage. Life style modification and appropriate physical therapy including special orthopedic footwear would improve daily life and limb function. The need for psychological support especially for a visible deformity should not be underestimated. Drug therapy of complications like superficial thrombophlebitis is also required and recurrent (DVT) would need life-long anticoagulation.

We recommend conservative, most frequently compression treatment to most asymptomatic patients with VMs. We also recommend that any treatment other than for very small, localized VMs be performed by vascular specialists, usually with multidisciplinary consultations."
[Strength of recommendation:1 (strong), Quality of evidence:B (moderate) [45]*]*

Drug/Medical Therapy

There is no specific drug to improve/control the VM lesions in contrast to the infantile/neonatal hemangioma. Anticoagulation is often required to treat thrombotic complications and resultant morbidity associated with VM lesions.
Nevertheless, pain therapy remains a major issue for medical management of the VM since nerve infiltration or compression precipitates severe pain. Even antiepilectic drugs like gabapentin are seldom indicated in order to relieve the symptomatology.
Diosmine and oxerutine may improve edema and symptoms in patients suffering from small anomalies.

Sclerotherapy in general

Sclerotherapy remains the major therapeutic tool for the treatment of VMs. Various liquid sclerosants introduced to destroy the endothelial cell layer of the malformation lesions. Each liquid agent has own unique property and side effects so that careful selection of the sclerosing agent is mandated especially for superficially located VM lesions(e.g. hand/palm, feet/sole, mucosas) and also the lesion located in anatomical regions with the risk to develop a compartimental syndrome secondary to the oedema caused by the therapy(e.g. forarm, orbit, anterior tibial department, psoas msucle)

Ethanol Sclerotherapy

Ethanol has been the gold standard embolic agent in the treatment of AVMs by which all other agents are compared. But, ethanol is a potent irritant sclerosant causing trans-mural destruction of the vessel wall. Therefore, ethanol sclerotherapy requires special training and experience in order to minimize the risk of complication and subsequent morbidity. Although this agent still has a special role in the management of AVMs, it should be used only discriminately in the treatment of VM and LM. [324-326]

Ethanol sclerotherapy has a high rate of complications and morbidity if the VM is located close to large nerves or skin, in the lip, tongue, gum/oral mucosa, the genital region, or in the hand at fingers, or in the foot at the toe, or palm, sole with or without transdermal extension. VM lesions with transdermal extension or in close proximity to the skin or mucosa are known to carry a high risk of skin or mucosa necrosis.

Therefore, the "indiscriminate" use of the ethanol to treat all VM lesions has been called into question because the majority of VM lesions are seldom life or limb threatening.

Lately, ethanol gel has been introduced in Europe for the treatment of slow malformation lesions. The presence of ethylcellulose allows more effective local effects with fewer systemic side effects in lower dose of ethanol. [327]

Sclerotherapy With Other Liquid Sclerosants

Before the era of the ethanol, various liquid sclerotherapy agents were used in the treatment of VM lesions over the past several decades often resulting in high recurrence rates and poor long term results. [-328-329]

Ethibloc and polidocanol (POL) are the two most popular liquid agents that have been widely used in Europe for several decades. Ethibloc is an emulsion made of viscous ethanol and corn protein but its mechanism of action is mechanical occlusion followed by intravascular fibrosis. It carries a high risk of non-target vascular occlusion due to its viscosity.

In the U.S. sodium tetradecyl sulfate (STS) and ethanolamine oleate have been used with limited success in the treatment of VM lesions. Because of the high morbidity associated with ethanol, STS remains the major sclerosant in the treatment of VM lesions.

Bleomycin is useful in treating VMs in sensitive locations such as the orbit and airway, because it does not cause thrombosis and therefore produces minimal postprocedural swelling. The dose per session and lifetime dose must be carefully controlled to minimize the risk of pulmonary fibrosis.

Ultrasound-Guided Sclerotherapy With Foam Sclerosants

Due to the high morbidity associated with the use of ethanol in the treatment of CVMs, interest in the development and utilization of detergent based sclerosants (e.g. STS, -POL) for the treatment of VMs has resulted in a new treatment approach based on ultrasound guided foam sclerotherapy (foam UGS). This procedure using STS or POL can deliver satisfactory results with minimal morbidity. [330-333] The superiority of foam versus liquid sclerotherapy could be shown in a prospective comparative randomized study by Yamaki et al. [331]

This treatment is especially useful in the treatment of localized subcutaneous or intra-muscular lesions and in the treatment of patients with KTS. An approach similar to that used in the management of lower limb venous incompetence would be highly effective in

the management of these patients. Furthermore, intradermal VMs and GVMs can be successfully treated with direct vision sclerotherapy using foam or liquid agents. [334]

Foam UGS is a safe alternative in the treatment of a selected group of "diffuse infiltrating" VMs which would otherwise be treated with ethanol. The associated risk of collateral damage seen with ethanol sclerotherapy (e.g. nerve injury, muscle contraction), can largely be avoided with foam sclerotherapy. Foam sclerotherapy can deliver good relief of symptoms and clinical improvement with minimal risk of complications, in this extended group of infiltrating VM lesions. [332]

Higher recurrence when treating large lesions remains the major disadvantage of foam sclerotherapy compared with ethanol sclerotherapy. But foam sclerotherapy produces excellent short to mid-term control of small VM lesions. Long term assessment of foam sclerotherapy outcomes is required in order determine if these results apply to all types of VM lesions.

Foam sclerotherapy of vascular malformations requires adequate training and experience. This procedure in the treatment of varicose veins has been associated with a number of rare but significant complications. [335] Rare cases of stroke and transient ischemic attacks (TIA) have been reported following foam sclerotherapy for varicose veins. [336] Patients with a known patent foramen ovale (PFO) or other right-to-left shunts are at a higher risk of neurological complications of foam sclerotherapy.

Indiscriminate infusion of foam sclerosants results in a drop in the active concentration, activation of platelets and the coagulation system resulting in a procoagulant state within the target vessels and a higher recurrence rate. [337] If foam sclerotherapy is performed the European guidelines of foam sclerotherapy should be considered. [338]

Given the interaction of detergent sclerosants with plasma proteins, coagulation, antithrombotic, fibrinolytic and other physiological systems, the unknown fluid mechanics and undefined rheology of foams in large low flow embryonic vascular spaces, and given the possibility of drainage into the central venous system, and the potential for systemic complications and cerebrovascular events, special caution against the use of large volumes (> 15-20 mL) of sclerosants foams is warranted. The recommended maximum safe volume of foam, based on local and international standards, should not be exceeded.

Fluoroscopic & Ultrasound Guided Sclerotherapy (FUGS)

Combining sonographic and fluoroscopic guidance to deliver sclerosants has a particular relevance to the treatment of VM lesions. [339, 340]

Ultrasound guidance is used to identify and localize the target vessel(s), contrast medium is then injected allowing visualization of the target lesion and the draining veins on fluoroscopy. STS or POL foam is then introduced slowly into the lesion which appears radiolucent on fluoroscopy displacing most of the radio-opaque contrast agent. The injection is stopped when the draining veins to take up the foam sclerosant. Compression is applied and maintained for seven days postoperatively.

Fluoroscopy allows a more comprehensive visualization of the target lesion and draining veins which is otherwise not possible with ultrasound imaging alone. FUGS is particularly useful in treatment of intra-muscular VM lesions.

Embolotherapy

Embolotherapy with currently available embolization agents: coils, glue, and/or particles embolization [1, 22, 41] are not ideal for VM lesions since these lesions are generally low flow and high volume lesions with large diameter vascular channels. Micro particles and coils are usually not large enough to occlude such lesions effectively and are often washed out.

Embolization agents are unable to produce complete destruction of the vessel endothelium. Incomplete endothelial cell destruction carries a significant risk of lesion recurrence. Furthermore, these agents only produce mechanical compression of the lesion and cessation of flow that results in thrombosis.

The role of endovascular therapy is therefore, relatively limited with the exception of N-butyl-cyanoacrylate embolotherapy (NBCA). NBCA is ideal as an adjunctive agent used to fill up the VM lesion preoperatively to facilitate surgical excision and reduce the risk of bleeding. NBCA improves the safety and effectiveness of surgical excision and reduces the risk of bleeding.

Endovenous Thermal Ablations Therapy

Endoluminal thermal ablation may have a complementary role in the management of larger truncular VMs (e.g. the MVs). These new techniques have demonstrated efficacy in the treatment of venous incompetence and are currently being assessed in treatment of VMs in general. The findings so far are encouraging but more detailed studies are needed to further assess the efficacy of these new modalities to the VM as well. [340, 341]

Laser Treatment [342-345]

Principles of Laser Treatment

VM presents in a wide spectrum, from localized venous lesions in which the venous lacunae are connected to the venous circulation by capillaries through to localized venous anomalies connected by veins to the venous circulation, and diffuse venous ectasias. Furthermore, multiple venous lesions tend to coexist with venous ectasias and deep vein anomalies.

In principle the techniques of laser applications in congenital vascular tumors (hemangiomas) and in vascular malformations are similar, but the aim is different. In tumors the goal of treatment is to induce regression or fibrosis, in vascular malformations the aim is to destroy the pathologic vascular structure, because there is no spontaneous regression. This means that the parameters for treatment of vascular malformations must be more aggressive than for those vascular tumors.

Truncular VM

Laser coagulation is, in contrast to sclerotherapy, a local and not a regional procedure. This means that no systemic or distant side effects can happen, but it also means that an effect can occur only where the laser hits the tissue. Furthermore blood is a perfect absorber so the laser radiation will not hit the vessel wall but cooks/boils the blood. To prevent this effect one has to remove all blood completely by rinsing of the fiber. This explains why in simply varicose veins, which can be treated easily with the foam or radiofrequency, the intraluminal laser therapy is not favored over these techniques. But in VM laser is an ideal tool for diseases that cannot be treated by easier techniques.

Large truncular VM lesions, such as enlarged persistent marginal veins, are a better indication for surgery or sclerotherapy. However, in a difficult anatomical situation such as after previous surgery or in incomplete MVs, an intraluminal procedure is indicated. Comparable to the macrocystic LM under color-coded duplex sonography (CCDS) control the vessel is punctured and a saline rinse is installed to clean up the fiber tip. With a maximum power of 10 W under CCDS the coagulation is performed, while any direct contact of the fiber end with the vessel wall has to be avoided. This would immediately cause a perforation with bleeding.

Another option is diffuse irradiating interstitial applicators which are in use in the therapy of interstitial malignancies, such as liver tumors. The advantage is that vessel wall coagulation is more homogeneous; the disadvantage is that the puncture is larger and more difficult to handle. A string maneuver in kinked vessels is nearly impossible.

Laser fibers with wavelengths of 1310 to 1470 nm are now in use for endovenous ablation. Theoretically, these lasers target the water in the vein wall rather than hemoglobin, minimizing the risk of perforation and bruising.

In large conducting veins such as those seen in KTS, endovenous laser ablation alone is often inadequate to achieve complete, permanent occlusion. It can be combined with embolization of venous outflow and post laser sclerosant injection.

Extratruncular VM

Similar to the extratruncular LM, all tissues can be affected by extratruncular VMs and so all the laser techniques are in use.

Soft Tissue Phlebectasias

Because the vessel wall opposed to the blood is the target, if possible the ectatic vessel will not be punctured, but irradiated paravasally, as with the perforator vein laser coagulation. In cases where a paravasal application is not possible, but only an intraluminal application similar to the truncular procedure, the fiber tip has to be rinsed with saline solution to prevent carbonization followed by perforation. If there is no direct drainage over larger veins an additional sclerotherapy can be performed. Postoperatively a compression bandage is obligatory for 24 hours. LIC is not a contraindication for this technique because a thrombus formation can be avoided with this procedure.

Glomuvenous Malformation ("Glomangioma")

An effective therapy for multiple glomangiomas (glomangiomatosis) is the treatment with Nd:YAG laser with continuous surface cooling. In solitary lesions the interstitial puncture technique is used like as for microcystic lymphangioma.

Capillary-Lymphatic Malformation

Capillary-lymphatic malformations may be discriminated from the classical PWS by light staining, and can be bluish-red to black in color. Due to the lower erythrocyte concentration, the basic absorption for the Flash Lamp Pumped Dye Laser (FDL) is reduced so the results of dye laser therapy are generally worse than for PWS. However, the ectatic venules in the epidermis are a good indication for the potassium-titanyl-phosphate (KTP), pulsed Nd:YAG or chopped CW Nd:YAG with fluid cooling cuvette. However, in these lesions the birthmark is only the tip of the iceberg. In nearly all cases there is a mixed venous-lymphatic malformation in the underlying organs. Capillary-lymphatic malformations are observed either in association with KTS or alone. So the general anesthesia needed for the laser therapy in childhood may also be used for clinical examinations if necessary.

“Port-Wine Stains” with Associated Vascular Malformations (Neurocutaneous Syndromes or Phakomatoses)

Capillary or dermal vascular malformations are occasionally associated with deeper vascular anomalies. The key point is that these cutaneous signs permit early diagnosis, thus helping in further recognition of more complex syndromes. Sturge-Weber Syndrome is the most well-known vascular malformation complex associated with “port-wine staining”.

The same malformation affects the soft tissue of the face with the risk of subsequent hypertrophy. This can be detected early by CCDS and especially by thermography with hyperthermy. If this is shown despite the FDL-therapy, the growing tissue will be treated in cases of dermal hypertrophy with a double pulse pulsed Nd:YAG/pulsed dye laser or in cases of more subcutaneous or soft tissue hypertrophy with the transcutaneous ice cube-cooled Nd:YAG laser, just as for infantile hemangioma but with a higher power of 60W.

The large PWS of the extremities in KTS sometimes need the same combination of pulsed dye laser, transcutaneous ice cube-cooled Nd:YAG laser or in cases with hyperkeratinization, CO_2 laser. In Proteus syndrome with patchy PWS of the hands or feet the effectiveness of pulsed dye laser therapy is limited, just as it is for other mixed capillary lymphatic malformations. However, even here the treatment of ectatic vessels with pulsed Nd:YAG or KTP laser is possible.

So from the standpoint of the lesions in general one can say that the more smaller vessels like capillaries are present the shorter the wavelength and the pulse duration, and the larger the diameter of the vessels the longer the wavelength and the longer the exposure time. Due to these biophysical rules one can say the more extratruncular malformation the more a laser indication, the more truncular malformations, the more surgical or intraluminal techniques.

Endoscopic Laser Treatment

This laser application is possible in the treatment of airway, intestinal and genito-urinary tract VM lesions. The treatment is performed with Nd:YAG laser. Use of the Nd:YAG laser for laryngeal VMs helps to avoid tracheotomy and open surgical resection. [346]

VII. TREATMENT: SURGICAL

General Overview

Among the various surgical procedures available for the treatment of VM lesions, the vascular procedures to correct hemodynamic derangements (venous hypertension) should have a priority. Examples include reconstructive surgery (e.g. venous bypass, tangential resection of venous aneurysm) and ablative surgery (e.g. removal of the MV; excision/removal of vascular defects).

Non-vascular (non-hemodynamic) operations aiming to correct the secondary consequences of VM should be deferred until appropriate primary vascular procedures are performed. Examples of non-vascular operations include orthopedic surgery (e.g. Achilles tendon lengthening) and plastic and reconstructive surgery to correct cosmetic deformities. [1, 22, 307-309] Sometimes it is feasible to perform vascular and non-vascular operations in one session. [292, 297, 299, 306]

A "combined" surgical approach is also preferred in situations where other surgical specialists are needed such as neurosurgeon, urologist, plastic surgeon, etc.

Reconstructive Surgical Therapy

Reconstructive (open) management of the VM is mainly indicated for various truncular lesions with direct involvements of all the named veins (e.g. the iliac vein, IVC). From a simple excision of the intravenous web/membrane to segmental resection of the involved vein combined with various reconstruction techniques can provide excellent long term results. [296, 347-349]

For example, venous aneurysms of main veins as one form of truncular VM (e.g. aneurysm of the popliteal vein, the superficial femoral vein and others), can be treated successfully either with a total resection and bypass/transposition with new vein segment, or partial tangential resection and suture aneurysmorraphy if the aneurysm is eccentric type.

Valve function restoration is also technically feasible with vein valve transplant or transposition of the superficial femoral vein with normal valves into deep femoral vein as an antireflux measurement for the deep vein dysplasia of the lower limb with extensive reflux. [350-352] However, the experiences are all anecdotal and its long term efficacy remained to be assessed.

Combination of muscular venous entrapment with intra-jugular lumen defect can be successfully managed by removal the luminal obstacle together with a patch angioplasty, which is complemented with omohyoid muscle surgical transection.[353]

Endovenous Reconstructive Therapy- Angioplasty and Stenting

Angioplasty and stenting has been shown to be efficacious in the treatment of obstructive iliac vein and vena caval lesions as a new treatment modality of endovenous reconstruction to restore the venous flow. This endovascular approach is also useful for treating stenosing truncular VM lesions: webs, septum, and stenosis of the iliac vein, IVC, jugular vein, and azygous vein, and to relieve chronic venous hypertension. [66, 123, 263, 264, 315] However, when truncular VM lesions should fail to respond to the endovascular therapy, excisional surgical therapy with/without bypass reconstruction is the treatment of choice.

Resective Surgical Therapy

Open surgical excision combined with the endovascular therapy (embolo/ sclerotherapy), is the most effective means to control extratruncular VM lesions.

Even in the condition of deep veins hypoplasia, a "limited" resection of dilated superficial dysplastic veins of the lower limbs to control the bleeding can be tolerated. It has been demonstrated that such limited resection stimulates compensatory dilatation of hypoplastic deep veins. [25, 299] But for the aplasia/agenesis of deep vein system, such excision is contraindicated with high risk of venous gangrene due to the lack of collateral venous outflow tract. Therefore, it is absolutely mandatory to distinguish anhypoplasia with residual lumen from aplasia before any attempt of surgical excision.

Intramuscular VM lesions in general should be considered percutaneous alcohol therapy as the first choice even if the lesion is a limited type and surgical resection should remain an alternative only for small and easy accessible lesions. Excluded are extended lesions with complications like chronic thrombophlebitis, severe pain syndrome and/or talipes equinus. [184, 292, 299, 354-356]

Extensively infiltrating intramuscular VM lesion is not an indication for resective surgery due to the high risk of complication (e.g. hemorrhage) and subsequent morbidity. However, occasionally surgical intervention is required with the transfixing suture of large dysplastic veins under the tangential clamping of the lesion to reduce the hemodynamic impact of the unresectable lesions. [349, 357, 358]

For treatment of VMs, including the MV, we recommend sclerotherapy, laser therapy, heat-ablation with laser or radiofrequency, or surgical removal., depending on the expertise that is available, *if evaluation confirmed suitable anatomy and assured satisfactory residual venous drainage.*
[Strength of recommendation:1 (strong), Quality of evidence:C(low) [45]*]*

VIII. SPECIAL ISSUES AMONG VMs

Congenital Vascular Bone Syndrome (Angio-osteodystrophy)

General Overview

Congenital vascular bone syndrome (CVBS) is defined an alteration in bone growth due to CVMs in childhood. Abnormal circulation around and/or inside the bone may induce lengthening or shortening of it. The result is an angio-osteo-hypertrophy or angio-osteo hypotrophy. [307, 308]

The phenomenon of limb lengthening is well known from several publications of the past, including those of Trelad et Monod, Klippel and Trenaunay, and Parkes-Weber. [47, 130, 359, 360] After introduction of angiography and very later of DUS, it was possible to demonstrate that there were cases with AVF and cases without. However, both had limb lengthening, which was poorly understood.

After different experimental studies, it is today mainly accepted that limb overgrowth is always due to hypervascularization, by macroshunts in some cases and by microshunts, less recognizable, in others. [309, 360] Beside hemodynamics, several tissue and bone growth factors may be involved in the phenomenon, but they still need to be further investigated. [361]

Bone shortening may be induced by local bone compression of abnormal vascular masses which press the bone because of endovascular hypertension due to AVFs or venous stasis. Other rare cause of hypotrophy of the limb could be a global reduction of blood inflow because of a congenital local hypotrophy of arteries.

In some cases of angio-osteodystrophy, mainly in the condition of hypertrophy, the MV coexists, which can sometimes be the only recognizable VM. Among the VM groups, incidence of long bone lengthening by CVBS was found in 19% and shortening in 7%. In AVMs incidence was, respectively, 49% elongation and 4% shortening. [307]

Diagnosis and Management

Diagnosis is based first on clinical recognition of the CVM, mostly by the VM together with a limb length difference. First laboratory examination with plain X-rays would demonstrate bone changes and allows a precise measurement with bone scanogram. DUS is next crucial test which should be performed by an expert in vascular malformations in order to investigate/assess specific condition of the CVM lesions involved, like the site of abnormal vascular masses, signs of AVFs, existence of fistulas

in the periostium or inside of the bone. [362] Intraosseous localization of CVM can be seen by MR or CT examinations. [363]

Development of the CVBS with resultant long bone length discrepancy or the destructive angiodysplastic arthritis (Hauert disease) with resultant immobility [364] is a unique situation where an earlier treatment approach is preferred over a more conservative one (e.g. the MV resection). [10, 11, 123]

The treatment strategy should be set with special consideration on unique condition of the bone affected by vascular malformations among young age patients, which will continue to grow till the end of growth period. During childhood, removing the CVM lesion may stop the growing effect on the bone making it possible to get a spontaneous correction of limb length discrepancy. It means the treatment should be done *early* in order to give a sufficient time available for the natural compensation/correction.

Therefore, earlier assessment of the VM lesion to cause the abnormal long bone growth, either longer or shorter, should be carried on expeditiously and start an aggressive control of the lesion(s) itself whenever feasible regardless of age before the epiphyseal plate is closed to complete bone growth in average till age 16 to 18.

The sclerotherapy or surgical removal of the malformation lesion in relation with the bone growth is all effective. [312] In case of existence of the MV, its resection should be considered with priority. [365]

Adjunctive procedure in case of a significant length difference can be added (e.g. the application of staples) even during the bone growth period. But, the orthopedic procedures to the healthy side "non-affected" limb to correct a leg length discrepancy should be discouraged in this bone-growing age in particular. [307-312]

Only when this approach to control the primary cause of angio-osteo-hypertrophy/hypo-trophy should fail or not feasible, the manipulation of the "affected" bone itself should be considered preferably *after* the bone growth is completed since the outcome of the epiphyseal stapling is totally unpredictable, often giving more harm than good.

In adults, only by the orthopedic methods the leg length difference can be corrected. Limb/long bone elongation technique according to Ilizarov or osteotomy is available as an option. [366, 367] In cases of limb shortening and significant bone alteration, the elongation techniques may be not possible because of the extensive weakening of the bone. Removal of vascular defects before the orthopedic surgery may be necessary to avoid extensive bleeding which may be very difficult to stop.

Marginal Vein- Increasing Clinical Significance

The MV is an abnormal superficial draining vein of the lower limb which is sited on the lateral edge of the extremity. [59] MV is a remnant of an embryonic vessel that normally regresses spontaneously before birth. It is classified as a truncular VM according to Hamburg classification. [35, 36]

It has to be emphasized that there is inconsistent terminology that characterizes majority of the literature discussing the lateral MV including terms "superficial", "embryonic" etc. From the anatomical stand point the term "superficial" is a misnomer since despite the fact that the lateral MV originates from the superficial compartment of the lower extremity it frequently penetrates the deep fascia and involves muscles of the deep compartment.
Thus, the utilization of the proper and unified nomenclature is desirable to accurately reflect the anatomic location of the entire vein and to emphasize the high risk of potentially fatal thromboembolic events associated with the MV thrombosis.

Main venous system development in the embryo passes from a first phase in which a posterior/lateral (peroneal/fibular vein) drains into the cardinal vein, to a second phase in which a sciatic vein becomes a main vessel while medial draining vessel develop and a third phase in which the early lateral veins regresses. [69, 368] Failure of regression of the early peroneal vein will result in the existence at birth of the MV.

The MV persistence may be the result of a failure in the development of the definitive deep venous system (absence or hypoplasia of femoral or popliteal vein), in which case it remains as the main draining vein of the limb or it may exist together with normal deep veins. Extension may be variable, from only a limited calf vein to an extension to the thigh and even to the lateral and posterior gluteus. Several perforants, sometimes huge in caliber and fragile in consistence, connect the vein to the deep venous system.
Mild/micro AVFs has been described in cases of extensive aplasia of deep veins.[54, 355, 356]

MV is typically valveless and to cause venous stasis resulting in discomfort and, sometimes, extensive swelling and even pain. Combination with nevus and limb length discrepancy (limb lengthening or shortening) often presents as vascular malformation components of KTS. In case of coexistent lymphatic extratruncular dysplasia, clinical picture may appear more complex and of difficult comprehension.

From a therapeutic standpoint, evaluation for the presence of the MV deserves a special consideration since the hemodynamic alterations associated with blood stasis in these frequently valveless, truncal VM, that are result of embryologically developed errors of

late stages of vascular morphogenesis, carries a high risk for thrombo-embolic events: DVT and PE.

Correct assessment of MV together with the deep venous system is crucial for the treatment planning. Clinical examination is often easy to demonstrate the MV. However, collaterals or even the MV itself may not be easy to remain visible by increased subcutaneous fat or combined with extratruncular LM in which thickening of subcutis by lymphatic abnormal tissue may hide the vein. [31]

DUS examination is mandatory for the mapping of the MV course, extension of reflux, and site and size of perforants. Precise study of main deep veins should be performed systematically. CT or MR phlebography may be helpful to complete diagnosis. Classical phlebography is rarely performed; however, in difficult cases, it can be helpful to understand hemodynamic.

Proper technique should be known and performed correctly because standard phlebography in a large MV may show only the vein itself with poor demonstration of the deep venous system even if this is normal, bringing to a wrong conclusion of aplasia of deep veins. Therefore, phlebography should be combined with DUS, phlebography alone should be avoided. [60, 66, 369]

In patients with normal to mild hypoplastic deep veins, surgical treatment of the MV is quite worthy to try since it will eliminate altered hemodynamics as the possible source of thrombosis without compromising lower extremity blood return. In this subgroup of patients perioperative anticoagulation with LMWH should be considered.

Prophylactic anticoagulation should be initiated based on hypercoagulability assessment and the presence of coexisting malformations, following the previously described anticoagulation protocols.

In the rare case of aplasia of the deep veins, the MV is the main draining system and cannot be removed. [307] When the MV resection is considered to correct the limb length discrepancy in childhood, vein removal should be performed as early as possible to enable to give a sufficient time for spontaneous length correction. [66, 312]

Surgical removal of the vein may be performed in one or more steps depending upon the capacity/tolerance of the deep vein system to accommodate the diverted blood flow from MV following the excision. Treatment can be sometimes difficult because of extreme fragility of the vein with defective vessel wall with lack of media, huge and fragile perforants (bleeding danger) or infiltration of the vein by dense lymphatic dysplastic tissue to dissect. Stripping is not recommended because of bleeding risk from large

perforators or collaterals. Semi-closed surgical removal is considered the most save technique with liberal use of the tourniquet technique.

Treatment by foam sclerotherapy is less effective and risky for DVT in case of large perforators. Endovascular ablation by laser or radiofrequency is generally unsuitable for the MV under thin skin because of high risk of skin damage. Nevertheless, the results of surgical excision are good; recurrence has not been reported. [311]

IX. FOLLOW UP ASSESSMENT

Evaluation Methods of the Therapy Results:

Post-treatment follow-up assessment is recommended with periodic clinical examinations, laboratory tests and instrumental investigations (DUS, MRI, WBBPS, phlebography). The effect of the treatment can be described based on the objective criteria: complete disappearance (100%), near complete disappearance (shrinkage more than 85%), shrinkage of more than 50%, and shrinkage less than 50%.

The area and volume of the lesions can be also calculated based on the formula: Area = π x 1/2 x long diameter (a) x 1/2 x short diameter (b); and volume (V, as an ellipsoid) = (4/3) x π x 1/8 x a x b x (a + b).

These evaluations are requested after each session of treatment and have to be made by a multidisciplinary clinic team, to confirm or modify the initial treatment strategy until the planned therapy is completed. [370]

Clinical assessment may be based on the improvement of the QoL. Each symptom and sign (pain, discomfort, limitation of motion) has to be documented before starting the treatment through medical history and photographs. After the treatment it is necessary to assess the subjective improvement of symptoms and simultaneously the objective evidence of the improved clinical signs (reduction of the size of lesion, improved range of motion).

Ultrasonography is useful to demonstrate the occlusion of VM after sclerotherapy, showing non-compressibilty, endovascular fibrosis or intraluminal thrombosis and the absence of blood flow, especially after applying and releasing manual compression. Comparisons with the initial images should be performed and lesion number, size and flow should be documented.

DUS and venous mapping should be performed after treatment of truncular VMs to demonstrate the complete ablation of embryonic trunks or the regression of venous reflux.

MRI is an excellent tool for assessment of treatment results and establishment of the long-term management strategy. A delay of six months is necessary to evaluate by MRI the therapeutic response to sclerotherapy, allowing time for the resolution of the post-operative inflammatory response.

MRI shows the absence of enhancement in the central portion of the treated lesion with intense peripheral hyperenhancement secondary to reactive hyperemia. When treatment is effective a post-operative scar appears dark on T1-weighted images and progressive shrinkage of the lesion is often observed. In cases of extensive malformations, gadolinium-enhanced imaging can demonstrate residual perfusion of the malformation for directing additional treatment.

MRI is also useful to detect post-operative muscle fibrosis in intramuscular VMs.

WBBPS may be periodically added to the DUS and MRI for the interim assessment of the residual VM lesions during the multisession treatments. WBBPS allows to obtain a quantitative measurement of the reduction percentage of radioisotope count over the region of interest after the treatment to compare with pre-treatment value.

Direct puncture phlebography allows the angiographic monitoring of sclerotherapy, confirming the immediate success of the treatment. In multistaged treatments it's also useful for monitoring session by session the progresses of therapy.

D-dimer is of limited value in diagnosis of post-operative thrombo-embolic complications. D-dimer is a non-specific test and has a high negative (rather than positive) predictive value and is best used to exclude rather than diagnose VTE. Extensive VMs have an elevated baseline level of D-dimer and unless a baseline is available, any post-operative measurement is of little value. Furthermore, sclerotherapy treatment itself can result in elevation of D-dimer levels. [371]

Lung perfusion scan is not a routine examination. It is only necessary when treatment is complicated by acute PE. Echocardiography is also useful to assess the right heart and the pulmonary pressures. [372]

Postoperative Evaluation Protocol:

The patient or patient's parents/guardian should be informed of the post operative requirements. All possible symptoms which may be of concern post treatment should be described and the patient or parents/guardian is instructed to contact the treating

practitioner urgently if they arise. Practitioner follow-up of the parent's or guardian's concerns should be appropriate addressed in a timely manner. Contact details of the treating phlebologist should be provided.

The Panel recommends the follow-up processes should include:
An assessment of the treatment should be made by examining the patient on the following occasions:

- Preferably on the first day after treatment if feasible as the baseline assessment to evaluate the response.
- One week- DUS follow up for DVT especially for high risk patients.
- Six-12 weeks after the completion of the course of treatments, a DUS should be organized to assess the effectiveness of the procedure and look for persistence/early recurrence.
- Six-12 months after the completion of the course of treatments, a repeat DUS +/- a follow-up MRI should be arranged to assess the effectiveness of the treatment and look for persistence/late recurrence.

Indicators include: At each assessment the findings should be recorded and discussed with the patient or parents/guardian and include:

- Success of treatment including resolution of symptoms
- Degree of sclerosis and any recanalization
- Any complications
- Patient satisfaction

Reviewing processes to include:

- Where clinically indicated, further appropriate treatment is offered, or referral made.
- Treatment and assessment records are complete and include:
  - Location of the lesion treated.
  - Treatment parameters used including sclerosant form, concentration and volume and laser fluence, power and energy density.
  - Diameter of the lesion(s) treated.
  - Type and size of compression garment applied and recommended time of application.
  - Post treatment assessment of resolution of symptoms.
  - After post treatment assessments, what further treatment is indicated/offered (e.g. UGS or direct vision sclerotherapy) (if any), any referral made, and whether the treatment plan has been completed.
- Any adverse effects or interventions and their resolutions

Complications

- STP, DVT and PE

- Involving vital or critical structures
  - Airways
  - Eyes and extension into brain
  - Perineum, genitals
  - Intra-articular (Hauert disease)

- Thrombosis and calcification. DIC

- Chronic venous hypertension, lipodermatosclerosis and ulceration

- Limb hypertrophy, scoliosis and other orthopaedic abnormalities.

- Nerve damage. Peri-operative electroneurography may be useful to detect nerve injury, particularly in VMs of the facial region and of the upper or lower limbs.

X. CONCLUSIONS

Multidisciplinary approach with full integration of open surgical and endovascular therapy has become the mainstay of treatment in the contemporary management of VMs.

A team approach using new treatment strategies can improve the long-term treatment outcomes and reduce the morbidity and recurrence/persistence rates compared with conventional approaches.

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Appendix A. Lists of Abbrevated Terminology (in alphabetical order)

N.	**Abbreviation**	***Terminology***
1	AM	*Arterial Malformation*
2	APTT	*Activated Partial Thromboplastin Time*
3	AVF	*Arterio-Venous Fistula*
4	AVM	*Arterio-Venous Malformation*
5	BRBNS	*Blue Rubber Bleb Nevus Syndrome*
6	CAPR	*Cartesian Acquisition with Projection-Reconstruction Like Sampling*
7	CCDS	*Color-Coded Duplex Sonography*
8	CCSVI	*Chronic Cerebrospinal Venous Insufficiency*
9	CLOVES	*Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Skeletal Scoliosis*
10	CM	*Capillary Malformation*
11	CSF	*Cerebro-Spinal Fluid*
12	CT	*Computed Tomography*
13	CVBS	*Congenital Vascular Bone Syndrome*
14	CVI	*Chronic Venous Insufficiency*
15	CVM	*Congenital Vascular Malformation*
16	dceMRI	*Dynamic Contrast Enhanced Magnetic Resonance Imaging*
17	DIC	*Disseminated Intravascular Coagulopathy*

18	DUS	*Duplex Ultrasonography*
19	DVT	*Deep Vein Thrombosis*
20	FDL	*Flash Lamp Pumped Dye Laser*
21	FUGS	*Fluoroscopic & Ultrasound Guided Sclerotherapy*
22	GLUT-1	*Glucose Transporter-1*
23	GVM	*Glomuvenous Malformation*
24	H&E	*Hemotoxylin and Eosin*
25	HFVM	*High Flow Vascular Malformation*
26	HLM	*Hemo-Lymphatic Malformation*
27	IH	*Infantile Hemangioma*
28	IJV	*Internal Jugular Vein*
29	ISSVA	*The International Society for the Study of Vascular Anomalies*
30	IUP	*International Union of Phlebology*
31	IVC	*Inferior Vena Cava*
32	IVUS	*Intravascular Ultrasound*
33	KTS	*Klippel-Trenaunay Syndrome*
34	LET	*Lymphatic Extratruncular*
35	LFVM	*Low Flow Vascular Malformation*
36	LIC	*Localized intravascular Coagulopathy*
37	LM	*Lymphatic Malformation*
38	LMWH	*Low Molecular Weight Heparin*
39	LO	*Limb Overgrowth*
40	LSG	*Radionuclide Lymphoscintigraphy*
41	LT	*Lymphatic Truncular*
42	MRI	*Magnetic Resonance Imaging*
43	MRV	*Magnetic Resonance Venography*
44	MV	*Marginal Vein*
45	NBCA	*N-Butyl-Cyanoacrylate*
46	NICH	*Noninvoluting Congenital Hemangioma*
47	PE	*Pulmonary Embolism*
48	PFO	*Patent Foramen Ovale*
49	POL	*Polidocanol*
50	PT	*Prothrombin Time*
51	PTP	*Potassium-Titanyl-Phosphate*
52	PWS	*Parkes-Weber Syndrome*
53	QoL	*Quality of Life*
54	qPCR	*Quantitative Real-Time PCR*
55	RICH	*Rapidly Involuting Congenital Hemangioma*
56	SMS	*Servelle-Martorell Syndrome*
57	STP	*Superficial Thrombophlebitis*
58	STS	*Sodium Tetradecyl Sulfate*
59	TIA	*Transient Ischemic Attack*
60	TLPS	*Transarterial Lung Perfusion Scintigraphy*
61	TREAT	*Time-Resolved Echo-shared Angiographic Technique*
62	TRICK	*Time-Resolved Imaging of Contrast Kinetics*
63	UGS	*Ultrasound Guided Sclerotherapy*
64	VA	*Vascular Anomalies*

65	VEGF	*Vascular Endothelial Growth Factor*
66	VET	*Venous Extratruncular*
67	VM	*Venous Malformation*
68	VMCM	*Familial Cutaneous and Mucosal Venous Malformation*
69	VT	*Venous Truncular*
70	VTE	*Venous Thromboembolism*
71	WBBPS	*Whole Body Blood Pool Scintigraphy*
72	WT-1	*Willms Tumor-1*

Appendix B. Ratings of the quality of evidence and grading recommendation system used in the Consensus

Table 1. Grading Recommendations According to Evidence[1] (Chest, 2006;129:174-181.)

Grade of Recommendation/Description	Benefit vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational	Weak recommendation, best

		studies	action may differ depending on circumstances or patients' or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable