

ISVI-IUA Consensus Document

Diagnostic Guidelines of Vascular Anomalies: Vascular Malformations and Hemangiomas

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The diagnostic approach to vascular anomalies should include the distinction between vascular tumors (i.e. hemangiomas) and congenital vascular malformations (CVMs). This step is based more on history and clinical examination rather than on instrumental evaluation. In children Duplex ultrasound and histology can be helpful to separate hypervascularized tumors from CVMs. Appropriate record of objective measures as size or flow volume is required in order to evaluate the progress of the pathology and/or to assess the results of adopted therapeutic interventions. The anatomic, pathological and hemodynamic characteristics, the secondary effects on the surrounding tissues and the systemic manifestations should be defined. Basic diagnostic tools are Duplex sonography followed by MRI or CT scanning. The definition of the vascular anomaly should be according to the Hamburg classification and should separate vascular tumors from vascular malformations followed by separation of high flow from low flow CVMs. Diagnostic investigations are best undertaken at centers where subsequent therapeutic interventions will be performed.

[Int Angiol 2015;34:1-2]

Key words: **Vascular neoplasms - Vascular malformations - Hemangiomas - Lymphatic abnormalities - Angiography - Genetic testing.**

Prologue

Abnormal development of the vasculature during embryogenesis leads to more or less clinically apparent symptoms, which in some cases may be associated with anatomic deformities, severe life-threatening conditions, a significant decrease in daily functional capacity and quality of life and can negatively affect patient's emotional and social well-being. The management of these lesions is often complex and can be frustrating for patients, their families as well as for most vascular specialists. The relatively low incidence of vascular anomalies among general population combined with the fact that their management often falls within the purview of several different medical and surgical special-

ties has traditionally resulted in insufficient expertise in the management of these conditions. Nevertheless, in recent years we observed an increased interest to improve the treatment of these patients with a truly multidisciplinary approach to this health problem. At this time, it is necessary to acknowledge the outstanding activity of the group of experts who have gathered with the aim to share their experiences and to provide guidelines for the diagnosis of vascular anomalies.

One of the leading experts in this process is Professor B.B. Lee, the main author and coordinator of the Consensus. Professor B.B. Lee began his career as a founding member of the transplant and vascular surgery program at Georgetown University in Washington, DC and has made very important achievements in the development of transplant surgery in the USA and Korea. Simultaneously he has also made a tremendous contribution to the field of lymphedema and vascular malformations. His list of publications includes more than 600 items most of them dedicated to the topic of vascular malformations and lymphedema. In recognition of his contributions, in the USA he obtained the title Distinguished Fellow of the Society for Vascular Surgery.

I would also like to emphasize the contribution of Professor P.L. Antignani, a co-chair of the Consensus faculty. His professional career has been associated with a permanent interest in the non-invasive investigation of vascular diseases, which is reflected by his presidency of the Italian Society of Vascular Investigation.

There are multiple reasons why guidelines or consensual documents are created - to transfer new knowledge, to improve the quality of standard management, to reduce the possibility of inadequate care, and to reduce the costs of treatment. The impact of these documents may sometimes be limited if they are followed with insufficient adherence. However, I am convinced that this will not be the case with these newly prepared recommendations. Thanks to their scientific standard and usefulness in daily clinical practice, the recommendations provided in this Consensus will be welcomed and fully applicable.

KAREL ROZTOCIL

President of International Union of Angiology

Introduction

Vascular malformations and hemangiomas altogether as vascular anomalies remain one of the enigmas in modern medicine. Given the paucity of knowledge in this field, employing an appropriate diagnostic approach to vascular anomalies is a major challenge for most physicians. Furthermore, achieving a precise diagnosis of a vascular anomaly is a complex task requiring in-depth knowledge of embryology, pathophysiology and appropriate acknowledgement of the clinical, hemodynamic and morphologic features.

As a joint initiative, the International Union of Angiology (IUA) and the Italian Society for Vascular Investigation (ISVI) established an expert Panel under the auspices of the International Union of Phlebology (IUP) to formulate guidelines for physicians and vascular technicians/sonographers on the evaluation of vascular anomalies. The aim of these guidelines is to provide recommendations for the diagnosis of vascular anomalies based on the best currently available scientific evidence. When scientific evidence was lacking or weak, a consensus of opinions amongst 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 technologies in this difficult and challenging field has been significant. Imaging studies, radionuclide scans, duplex ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) technologies have largely improved.

Recommendations in this document are graded according to the available scientific evidence. The Panel adopted the system used by Guyatt *et al.*^{1, 2, 3} and the document has two grades of recommendations: Grade 1 (strong) recommendation, which is reserved for those investigations, where the benefits clearly outweigh the associated risks and Grade 2 (weak) recommendations, reserved for those diagnostic investigations where the benefits do not significantly outweigh the associated risks. The quality of evidence can be high (A), moderate (B), low or very low (C) (Appendix A).

It is the sincere hope of the Panel that these guidelines will serve their purpose: general guidelines based on scientific evidence to assist clinicians in the diagnosis of vascular anomalies. 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 state-of-the-art and the best-practice guidelines based on the scientific evidence available in year 2014.

Definitions and Classification

Attempts at the diagnosis and classification of vascular anomalies have a long history starting with the indiscriminate use of eponyms and descriptive terms such as “port-wine stain”, “strawberry hemangioma”, “cherry angioma” and others.

With the rapid proliferation of descriptive terms and eponyms, the need to develop a meaningful classification of vascular anomalies became evident. Subsequently, two comprehensive classifications were introduced in the last 30 years. The first attempt was a milestone approach that differentiated vascular anomalies into vascular tumors and vascular malformations. This classification was introduced by John Mulliken *et al.* in 1982⁴ and formed the basis of the subsequent International Society for the Study of Vascular Anomalies (ISSVA) Classification.⁵⁻⁷

The second milestone was the development of the Hamburg classification in 1988 proposed by Dr. Stefan Belov who classified the vascular malformations based on the morphology of the lesions/vessels involved. This classification was soon modified to incorporate the newly discovered embryological findings.⁸⁻¹⁰

In the Hamburg classification, vascular malformations were further subclassified to “extratruncular” and “truncular” forms based on the embryological stage of the emergence of the pathology. The term “extratruncular” was initially re-introduced to replace the popular misnomer “angioma”. The use of the term “angioma” when referring to vascular malformations created significant confusion as it implied a neoplas-

tic pathology and lead itself to confusion with "hemangioma" which represents a true vascular tumor with an entirely different nature.¹¹⁻¹³

Clinically, extratruncular lesions are masses of abnormal small/mid-sized vessels infiltrating various tissues. These lesions result from the defective development during the earlier stages of embryogenesis while the vascular structure is still in the status of plexiform primordial network.¹⁴⁻¹⁶ By contrast, truncular lesions originate from fetal vessel trunks and develop during the later stages of vascular trunk formation. Clinically, truncular malformations present as defects of fully formed and often named vessels (Table I).¹⁷⁻¹⁹ Truncular lesions are predominantly hemodynamic disorders while extratruncular lesions are predominantly organic diseases with a great tendency to progress/recur due to their unique embryological characteristics originated from the mesenchymal cells/angioblasts.²⁰⁻²²

This classification was in part adopted by ISSVA in 1996 in Rome with the maintenance of the subgroups according to the vessels involved. In the ISSVA classification system of vascular anomalies, hemangiomas are considered to be separate from the vascular malformations as true vascular tumors with an often benign nature and the additional differentiation into high

flow and low flow malformations based on the hemodynamic flow characteristics. In this classification, some of the eponymic syndromes were maintained (Table II).

The ongoing use of eponyms in this field is controversial. Undoubtedly descriptive terms can be misleading and not helpful in conveying the correct anatomico-pathological nature of vascular anomalies. Nevertheless, certain eponyms may be useful to highlight non-vascular complications of some conditions, for example, seizure in Sturge-Weber syndrome and kidney tumors in Von Hippel-Lindau and Maffucci syndromes.²³⁻²⁵

TABLE II.—ISSVA classification of CVM and vascular tumors.

VASCULAR MALFORMATIONS:

- Fast-flow
- Arterial malformation (AM)
- Arteriovenous malformation (AVM)
- Arteriovenous fistula (AVF)
- Slow-flow lesions:
- Capillary malformation CM (port wine stain, telangiectasia, angiokeratoma)
- Venous malformation (VM)
- Lymphatic malformation (LM)
- Combined vascular malformation (CVM, CLM, CLVM, CAVM, CLAVM)

VASCULAR TUMORS:

- Infantile hemangioma
- Congenital hemangioma
- Other

TABLE I.—Modified Hamburg Classification of Congenital Vascular Malformation (CVM).

Main classification based on its predominant vascular malformation component:

- Arterial malformation
- Venous malformation
- Arterio-venous malformation
- Lymphatic malformation
- Capillary/ microvascular 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.

Subclassification based on its embryological stage of the defect:

- Extratruncular forms
 - Infiltrating, diffuse
 - Limited, localized
- 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).

The future of the knowledge in this field will be based on new genetic and proteomic findings.²⁶⁻²⁸ Genetic defects have been identified in hereditary hemorrhagic teleangiectasia (HHT), glomovenous malformations (GVM), cerebral cavernous malformations, some primary lymphedemas, some cutaneo-mucosal venous malformations (VMs), capillary malformations (CMs), arteriovenous malformations (AVMs) and PTEN (phosphatase and tensin homologue) related syndrome.²⁹⁻³¹

Based on the previous consensus publications of the IUA on arterio-venous malformations and the IUP on venous malformations^{6, 7, 20} the Panel decided to adopt the modified Hamburg Classification as basis for the diagnostic work up of vascular anomalies. This was based on the anatomical and embryological foundation of this classification and the firm belief that the differentiation of malformations into truncular and extratruncular provides the useful practical tool in the diagnosis and management of these conditions.³¹⁻³³

An updated ISSVA classification which incorporates new genetic and histologic information, new diagnoses and syndromes, and takes into account truncular vs. non-truncular forms, was recently approved by the ISSVA and will be available for citation from the ISSVA website <http://www.issva.org>.³⁴

Clinical Evaluation

Patients with vascular anomalies usually seek help because of pain, disfiguration and/or functional impairment. Patients of any age may be referred for evaluation and hence the physician and vascular technologist must be comfortable dealing with a diverse group of patients that may include the pediatric as well as the neonatal age groups. Age is considered a determinant factor in the clinical evaluation of vascular anomalies since the fetus, newborn, infant, child and adult can present with different signs and symptoms closely related to their lifetime period.

The diagnostic algorithm used in the evaluation of vascular anomalies should be based on an accurate clinical assessment, which includes a thorough history and a detailed physical examination. The most important aspect of his-

tory is whether the lesion was present at birth (vascular malformations) and the rate of growth (proportionate or disproportionate to the child's growth). An exception to this is the subtype of hemangiomas termed RICH (rapidly involuting congenital hemangioma) and NICH (non-involuting congenital hemangioma), both of which proliferate in utero. RICH may be highly vascular, occasionally causing pre-and peri-natal high output states, and/or transient postnatal self-resolved thrombocytopenia.³⁶⁻³⁸

The physical examination should include careful assessment (inspection, palpation, auscultation) of the lesion(s) as well as the arterial, venous and the lymphatic systems. It should also include assessment of blood pressure and peripheral pulses on the affected side and the contralateral limb, making note of visible dilated vessels/varicosities, thrombophlebitis, skin temperature, edema, skin changes including pigmentation, induration or ulcerations and other changes attributed to chronic venous insufficiency (CVI).

Clinical examination of the involved limb should include assessment of the limb size, volume, symmetry, co-existing soft tissue or bony hypertrophy or atrophy.^{6, 7, 39-41} Clinical progress should be documented by serial photography.

Hemangiomas vs. congenital vascular malformations

The differentiation between hemangiomas and congenital vascular malformations (CVMs) is critical especially when dealing with pediatric cases. The two entities represent entirely different pathologies although grouped together under the common umbrella of *Vascular Anomalies*.^{6, 42-44} CVMs are errors of morphogenesis and structural abnormalities while hemangiomas are vascular tumors. A precise understanding of this critical fact is essential in reaching an accurate diagnosis.

Clinical history can differentiate between most cases of tumors and CVMs although adequate or clear history is not always available.⁴⁵⁻⁴⁷ In particular, the unique growth pattern of the mass lesion often allows the differentiation. Fundamental differences between hemangiomas and vascular malformations include the timing of their clinical appearance, their growth patterns,

the biologic behavior or growth characteristics of their endothelial lining in the cell culture, the stromal cellular and extracellular matrix compositions and the response of the lesions to pharmacotherapeutic agents.

Hemangioma of infancy (HOI)

Hemangiomas of Infancy (HOI) are the most common forms of pediatric vascular tumors that have a distinct etiology, genetics, presentation, prognosis and treatment.^{42, 43, 48} These lesions are proliferative vascular tumors that are typically NOT present at birth and appear later during infancy.^{44, 49, 50} These tumors take on a distinctive course of self-limited growth characterized by a two-stage process of proliferation and regression. HOI grow rapidly and disproportionate to the child's growth, then undergo a plateau phase and finally undergo involution. The majority of HOI have undergone atrophy by the age of 10. HOI possibly stem from placental tissue. Histologically, these lesions stain positive for glucose transporter-1 (GLUT-1) during all stages of growth and involution.^{36-38, 51} HOI during the proliferative phase may be high-flow lesions that may appear as pulsatile masses with increased cutaneous warmth. These clinical signs may be absent or difficult to detect in subcutaneous lesions.

Hemangiomas of infancy (HOI) vs. congenital hemangiomas

HOI should be differentiated from congenital hemangiomas, which form a small group of pediatric vascular tumors. Congenital hemangiomas are fully grown *in utero* and are present at birth and hence do not undergo post-natal proliferation like HOI. Histologically, congenital hemangiomas do not stain with GLUT-1.

Two sub-types of congenital hemangiomas are commonly encountered: Rapidly Involuting Congenital Hemangioma (RICH) and Non-involuting Congenital Hemangioma (NICH). RICH undergo spontaneous involution during the first year of life while NICH persist lifelong.³⁶⁻³⁸

Other (vascular) tumors

Infrequently, other tumors such as a Kaposiform Hemangioendothelioma (KHE), angiosar-

coma or other tumors may need to be differentiated from a CVM.⁵²⁻⁵⁴

Congenital vascular malformations (CVM)

CVMs are structural abnormalities of the vascular system and NOT tumors. These lesions result from arrested development during various stages of embryogenesis. While HOI are not present at birth, CVMs are always present at birth.

By contrast to HOI, CVMs are always present at birth as inborn errors, even though they may not be apparent. These anomalies grow steadily commensurate with the child's systemic growth. HOI, by contrast, grow disproportionate to the child's growth. CVMs never regress spontaneously and remain present throughout the patient's life as embryologic tissue remnants with 'self-perpetuating' growth.

CVMs may involve any vessel type and can be broadly classified into:

- Arterio-venous Malformation (AVM)
- Venous Malformations (VM)
- Lymphatic Malformations (LM)
- Capillary Malformations (CM)

Arterio-venous malformations (AVM)

AVMs are high flow structural anomalies that form anomalous interfacial communications between arterial and venous systems. A fully mature AVM may manifest as a warm, enlarged pulsating mass. The enlarged size is due to the increased size of the anomalous vessels as well as an associated soft tissue hypertrophy.⁵⁵⁻⁵⁷ AVMs may be quite subtle in young children and the initial presenting sign may be pallor of the overlying skin due to a cutaneous "steal". Lesions in deeper tissues may not always be clinically recognizable. Hemorrhage can be a presenting sign of an occult AVM. AVMs in neonates may appear as a faint pink stain and may not be readily differentiated from a CM.⁵⁸⁻⁶⁰

The associated soft tissue and/or bony hypertrophy may result in the enlargement (in length and circumference) of the affected side. AVMs involving the limbs may present with bony and soft tissue hypertrophy of the affected limb (Parkes-Weber syndrome). The soft tissue hypertrophy involves the subcutaneous fat with a

significant number of patients developing severe lymphedema. The muscle is usually hypertrophied, as opposed to VM or Klippel-Trenaunay Syndrome (KTS).^{61,62} High-output cardiac failure may be caused by large AVMs involving the shoulders, chest, abdomen, liver, kidneys, pelvis or buttocks.^{7, 57-60}

Venous Malformations (VM)

VMs are structural abnormalities of veins and venules. VMs are the most common developmental anomalies of the venous system. These defects are caused by developmental arrest of the venous system during various stages of embryogenesis.⁶³⁻⁶⁵

VMs can be classified into:

1. Extratruncular VM- lesions may be found in most tissues and may present as clumps of dilated veins or venous lesions.
2. Truncular VM- lesions can present as aplasia, hypoplasia, obstruction, dilation, duplication or aneurysms. A unique group of truncular VMs are the persistent embryonic veins such as the marginal vein of the thigh or the persistent embryonic sciatic vein. These vessels arise when fetal (truncal) vessels fail to undergo normal involution.

Lymphatic malformations (LM)

Nomenclature of the LMs is still confusing and old terms such as lymphangiomatosis, lymphangiectasia or lymphatic dysplasia are widely used to describe various related entities. Currently, LMs are classified into two groups based on their clinical presentation and morphology:

1. Extratruncular LM- These lesions form cystic masses and typically infiltrate other tissues in a localized or generalized distribution. Such lesions may be macrocystic or microcystic or present as a combination of both forms.
2. Truncular LM- These involve structural abnormalities of the lymphatic trunks and present with lymphedema and thoracic duct disturbances.

When LM involve the skin and subcutaneous tissue only, the prognosis is uniformly good. When the lesions involve the upper airways, viscera or bone, the prognosis is generally poor with a significant mortality rate.⁶⁶⁻⁶⁸

*Capillary Malformations (CM)*⁶⁹⁻⁷¹

CMs are the most common type of CVMs. Descriptive historical terminology referring to CMs has included "port-wine stain" and 'nevus flammeus'.

As the congenital malformation of the superficial dermal blood vessels, CMs are present at birth and grow in size commensurate with the child. They remain present for life and have no tendency of involution. The clinical progression of CMs is variable and depends on the anatomical location of the lesion.

CMs may be found in association with other CVMs including VMs, AVMs and LMs. A significant number of dysmorphic syndromes have been associated with CMs.

The Panel recommends adequate Clinical History to be obtained and a thorough Physical Examination to be conducted prior to instrumental investigations. Clinical examination should guide the request for further studies. (GRADE 1B)

The genetic basis of an increasing number of vascular anomalies has been identified in recent times⁷² (Appendix C and D). Here, we briefly review some of the key syndromic vascular anomalies.

Syndromic hemangiomas⁷³⁻⁷⁷ (Appendix C)

Approximately 30% of patients with facial segmental hemangiomas may have PHACES Syndrome (OMIM 606519) [Posterior fossa or other structural CNS lesions, Segmental Hemangioma, Arterial anomalies, Cardiac anomalies, Eye anomalies, and Sternal or other midline deformities].^{73, 74}

Evaluation includes: MRI +/- contrast of the brain, and MRA of the brain, neck and upper chest, ophthalmologic, cardiac and sternal anatomy assessment, and thyroid function tests. Symptomatic airway hemangiomas are seen in increased incidence in patients with "beard" distribution cutaneous hemangiomas (Segment 3).⁷⁵

Segmental hemangiomas on the lower midline back may be associated with congenital renal, sacral, lower spine, or genitourinary anomalies, and should be evaluated radiologically.⁷⁶

LUMBAR Syndrome (Lower body hemangioma and other cutaneous defects, Urogenital anomalies, Ulceration, Myelopathy, Bony deformities, Anorectal malformations, Arterial

anomalies, and **Renal** anomalies) and **PELVIS** syndrome (**Perineal** hemangioma, **External** genitalia malformations, **Lipomyelomeningocele**, **Vesicorenal** abnormalities, **Imperforate** anus, and **Skin tag**) designate a spectrum of clinical features which may be in patients with segmental perineal hemangiomas.⁷⁷

Syndromic vascular malformations^{28-31, 78-83} (Appendix C)

Syndromic Vascular Malformations include Klippel-Trenaunay (capillary-lymphatic-venous malformation with limb hypertrophy), Parkes-Weber Syndrome (similar to Klippel-Trenaunay with arteriovenous shunting), Sturge-Weber Syndrome (facial capillary malformation in trigeminal distribution, leptomeningeal angiomas, glaucoma, and seizures), Blue-Rubber-Bleb-Nevus Syndrome (BRBNS) (generalized small venous malformations), Proteus Syndrome (vascular malformations, truncal lipohypoplasia, scoliosis, cerebriform plantar surfaces, nevi, partial gigantism, and digital anomalies), Ollier Disease/Maffucci Syndrome (hemangioendothelioma, enchondromatosis), HHT (multifocal AVMs), Gorham's Syndrome (lymphangiomatosis with osteolysis), and several lymphatic anomaly/lymphedema syndromes.

PTEN-related vascular anomaly syndromes include Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome and have distinctive clinical and radiologic features. Patients with PTEN syndromes are at increased risk of malignancy (e.g. thyroid, breast, colon, brain, genitourinary), which can present earlier than typically seen in the general population.

Genetic mutations have been identified for many vascular malformation syndromes: familial mucosal VMs: (Tie2 mutation), AVMs with multifocal CMs (CM-AVM; RASA-1 gene), GVM (glomulin), HHT (endoglin, activin A receptor type II-like 1 gene - ACVRL1, SMAD4, one morphogenetic protein 9 BMP9), and Proteus Syndrome (AKT1), CLOVE Syndrome (congenital lipomatous overgrowth, vascular malformation, epidermal nevus, scoliosis), and multiple mutations associated with lymphedema syndromes (including VEGFR3/FLT4, FOXC2, SOX18).⁷⁸⁻⁸⁰

Mutations are either germline (in the case of familial vascular malformations, with variable

penetrance in some cases) or somatic (e.g. postzygotic mutations such as mosaic AKT-1 mutations in Proteus Syndrome, PIK3CA in CLOVES and GNAQ in Sturge-Weber Syndrome).⁸¹⁻⁸³

Non-invasive Diagnostic Evaluation

Difficulties in the diagnosis are due to the need to have both excellent spatial and temporal resolution in the imaging of the anomalies. This should be tailored to the hemodynamic characteristics of the malformation which may range from the ultra high flow of truncular AVMs to the extreme stagnant flow in venous anomalies or absence of detectable flow in LMs.

Appropriate images of the anomalies should be obtained first with generally available imaging tools like ultrasound, CT scan and MRI.⁸⁴⁻⁸⁶ Diagnostic algorithm for vascular anomalies should start with an ultrasound investigation first, followed by non-invasive MR or CT scans and finally invasive investigations like angiographies when indicated.⁸⁷⁻⁸⁹ Additional investigations include nuclear medicine imaging such as radionuclide lymphoscintigraphy, whole body blood pool scintigraphy (WBBPS) and transarterial lung perfusion scintigraphy (TLPS).⁹⁰⁻⁹²

The Panel recommends the primary diagnostic approach to be based on non-invasive investigations. The basic investigation should include duplex ultrasound integrated with MR examination. (GRADE 1C)

Duplex Ultrasonography (DUS)

Ultrasound is the most essential instrumental examination for vascular anomalies. Ultrasound is widely available and its low cost and lack of radiation exposure makes this modality the primary tool for the study of vascular anomalies.⁹³⁻⁹⁵

However, ultrasound examination is a procedure that is operator dependent and hence adherence to standard protocols to achieve consistent outcomes is of crucial importance. 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 is limited in defining the extent of lesions not located in the extremities and hence ultrasound assessment should be correlated with MRI findings. In case of deep intra-muscular lesions, MRI may help in locating the lesion on ultrasound.

Ultrasound investigations are also limited in presence of air (e.g. lungs) or when anomalies are located within bones. Bony anomalies may be studied using other imaging modalities such as CT or when located within the cranium using transcranial equipment.

Limitations in the hemodynamic evaluation of occlusive venous status by ultrasound can be compensated with intravascular pressure measurement and/or intravascular ultrasound (IVUS). However, IVUS or invasive pressure measurements are not commonly indicated and seldom recommended in routine cases.

In childhood the missing collaboration of patients can be a problem.

Duplex ultrasound examination procedure

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 contralateral side should be investigated together to assess for possible occult malformations and to compare the morphology, to identify normal size and flow characteristics. In case of unilateral lesions, comparison with the contralateral side to identify normal size and structures should always be performed.

The ultrasound examination of the limbs should be made in the erect and supine positions and the difference in size of the vessels should be recorded.

CW-Doppler localization

Initial assessment with CW-Doppler is recommended to localize the lesion, determine the basic flow characteristics and to guide the duplex examination.

Patient position

Most vascular anomalies should be investigated in both the supine and the erect/dependent position. Certain CVMs such as VMs and LMs may fill up in one and drain and clinically disappear in the other position. In the evaluation of the limbs, both limbs should be examined in supine/dependent and standing/elevation.

Probe selection

A high frequency linear transducer is in general suitable to assess most superficial lesions, however the probe can be selected depending on the location and depth of the target lesion. Probe frequency in case of broadband transducers should be optimized to obtain the best image. When assessing facial lesions or anomalies in neonates and small children, a 'hockey-stick' probe may be selected. In case of superficial lesions, minimum pressure should be applied on the probe using a thick layer of ultrasound gel to prevent excessive compression on the lesion.

Key procedure outcomes

The ultrasound examination should aim to achieve the following four key procedural outcomes:⁹⁶⁻⁹⁸

1. Define the Lesion: diagnosis, classification and measurements
2. Localization and relationship with regional structures
3. Pre-operative mapping
4. Post-operative follow-up studies

1. Define the lesion: diagnosis, classification and measurements

Aims

To recognize the presence of a vascular anomaly and to differentiate between vascular tumor and malformation. In case of CVMs, the lesion should be classified as a high flow (AVM), low flow (VM) or no flow (LM) lesions. In case of vascular tumors and hemangiomas, the lesion should be classified as *proliferative* demonstrating high flow vs. *involved*. The dimensions of the lesion and flow characteristics should be ac-

curately documented. This information will be helpful to monitor the progression of the lesion and in the follow-up of the patients.

B-mode

A thorough B-mode examination should be completed prior to Doppler examination. B-mode can provide a valuable initial description that can narrow down the diagnosis and is essential in differentiating between CVMs and HOI. While CVMs present as a collection of anomalous vessels or cystic spaces (LMs), HOI present as a soft tissue mass. Compressibility on B-mode can further differentiate VM (compressible) from thrombosed or sclerosed VM (non-compressible), LM (non-compressible cystic spaces) and AVMs (partially-compressible). B-mode will help in the evaluation of axial trunks and will determine patency, duplication, presence of valves in venous vessels and aplasia or hypoplasia of the whole vessel length or segments of the affected vessels. Additional information on the structure of the lesion may be echogenicity and separation from surrounding tissue which may be regular or irregular.^{99, 100} B-mode examination will also help identify important adjacent structures such as nerve trunks.

Doppler mode

Doppler assessment should determine whether there is flow within the lesion (active tumors, AVMs, VMs) or no flow (LMs, involuted tumors, thrombosed/sclerosed VMs). If there is flow within the lesion, whether it needs to be induced (VMs) or is spontaneous (active tumors and AVMs). If flow is spontaneous, whether it is a high velocity, low resistance pulsatile flow (AVMs).

Doppler examination should include both Color Doppler and Spectral analysis. For examination in the color mode, the pulse repetition frequency (PRF) should be adjusted to the flow velocity of the investigated vessel. In other words, PRF should be increased for arterial flow and reduced for low flow in VMs. Depending on the ultrasound system used, when assessing high flow malformations, the setting of the color Doppler may have to be set on real time (no delay and overwriting by the software). Power Doppler is more sensitive than Color Doppler and can be

used when detecting flow with low amplitude.

Spectral analysis should include both spontaneous and augmented blood flow and the derived data including the peak velocity and the Resistive Index (RI) in arterial vessels ($[\text{peak systolic velocity} - \text{end diastolic velocity}] / \text{peak systolic velocity}$) should be documented.

Reflux time in venous vessels should be incorporated in a complete venous incompetence mapping of the lower limb veins.

Diagnosis and classification

At the conclusion of the B-mode and Doppler study the following information should be obtained:

— The lesion should be classified into a vascular tumor or a CVM or other (e.g. lipoma, hematoma, lymph node, etc.).

— If vascular tumor, the flow characteristics should be used to define whether the lesion is active or involuted.

— If a CVM, then the lesion should be subclassified into an AVM vs. VM vs. LM.

Measurements

Dimensions of the lesion should be documented and adequate number of B-mode images demonstrating the basic morphology of the lesion should be obtained. Numerical data regarding size, flow and the hemodynamic characteristics of the lesion should be recorded to monitor the progression, the natural evolution and the success or failure of the interventions.^{101, 102} In the evaluation of LMs, the size and number of lymphatic cysts should be documented. Adequate number of images should be obtained and stored for future reference.

2. Localization and relationship with regional structures

Aims

To accurately document the relationship of the lesion with the regional blood vessels and the surrounding normal anatomical structures and landmarks. Normal blood vessels should be identified and the affected side should be compared

with the contralateral side. Information obtained should be sufficient enough to guide further imaging strategies such as MR or CT.

Localization

Anatomical localization should be obtained relative to regional landmarks recognizable by clinical or ultrasound examination (e.g. intramuscular infiltration).

Relationship with regional structures

Regional vascular structures including arterial, venous and lymphatic trunks should be identified and the relationship with the anomaly assessed. All 'normal' regional vascular structures should be clearly identified and delineated from the anomaly. This can be achieved by comparing the affected side with the contralateral side looking for differences in size and flow patterns. The architecture in connection with in- and out- flow vessels should be studied and afferent arterial 'feeders', efferent 'draining' veins and presence of a nidus should be documented.^{103, 104}

Flow characteristics in the involved vessels in relationship with major regional vascular trunks should be assessed. The flow pattern in presumably 'normal' vessels should be assessed and any findings to suggest AV shunting should be looked for, localized and documented. In case of mixed truncular and extra-truncular lesions (such as those seen in certain VMs), involvement of presumably 'normal' vessels should be assessed. In case of VMs involving the lower limbs, a complete venous incompetence study of lower limb venous system and mapping of the pathway of reflux should be obtained. In this phase, persistent embryological vessels such as a persistent sciatic artery/vein or a persistent marginal vein should be looked for.

Other regional structures should be clearly identified and labeled in images obtained. In particular, in case of intra-muscular CVMs, the muscles involved should be identified and adequate images obtained. Regional nerves, fascia and tendons should be identified. For lesions involving the sole of the feet, the relationship to plantar fascia and tendons should be defined.

Based on ultrasound findings, further investigations such as MRI should be arranged to com-

plete the diagnostic evaluation and to prepare an appropriate management strategy and therapeutic intervention.

3. Pre-operative mapping

Aims

To define the anatomical location of the lesion in relation to surrounding structures, defining communications with the normal vascular system including any feeding arteries or draining veins and proximity to important nearby structures such as nerves, normal vessels and vital organs in order to guide a surgical or percutaneous approach to the malformation.

Assessment

This investigation is best performed directly prior to the intervention. Prior ultrasound findings, MRI images, other investigations and clinical photographs should be reviewed and ideally displayed at the time of the procedure. Any changes (e.g. a new thrombus or occlusion) compared with the prior assessments should be identified and noted.

All target lesion(s) should be identified. It may be useful to add CW-Doppler examination to localize deep seated lesions or Type IIIa AVMs⁷ prior to percutaneous sclerotherapy or embolization. Some practitioners utilize color Doppler with intraoperative hockey-stick head for the same indication. Sonographic assessment should be complemented by skin markings to guide punctures and to plan the optimal approach. Significant near-by structures should be identified and marked on skin. Nerve trunks should be visualized prior to intervention as nerve damage is one of the most serious complications of endovascular or surgical procedures employed to treat CVMs. Nerve damage may be caused by compression secondary to edema/compartiment syndrome or direct toxic effect of sclerosing or embolic agents (in particular ethanol).

4. Post-operative follow-up studies

Appropriate follow-up ultrasound examination is essential in monitoring complications,

success or failure of intervention. Post-operative follow-up studies need to be targeted and timed appropriately depending on the aim of the examination.

Post-operative ultrasound examinations to look for complications such as deep vein thrombosis (DVT) should be done within 7 days of the procedure; otherwise an important silent DVT with potential for embolism may be missed.

Post-operative studies to assess the success of the procedure can be done in two stages: an early follow-up typically within 6 weeks will provide an initial assessment of the treatment outcome and will provide an opportunity for the physician to deal with any concerns the patients may present with. A long-term follow-up typically conducted at one year will provide a meaningful long-term assessment of the treatment outcome.

Ultrasound examinations should follow the same protocol as for the initial assessment, measurements obtained and flow characteristics assessed and any change to the pre-operative values reported. This should include: B-mode images of lesion, measurements of the size and flow, transverse dual image of the lesion to assess for compressibility, color Doppler images of the lesion and sample spectral traces in associated vessels and nidus.

Evaluation of surgical treatment of truncular anomalies

This assessment should document the residual malformation hemodynamic impairment. Specific anomalies defined in the pre-operative assessment should be followed and reported in the post-operative examination. Restoration of competence or new patterns of reflux should be documented in case of truncular VMs. In case of truncular AV shunts parameters derived from the Doppler curve should be compared with those acquired before the treatment.

Evaluation of endovascular interventions

Evaluation of the results of endovascular therapy is more complicated and should follow a set protocol. When assessing treatment success, compressibility of a previously treated (sclerosed/embolized) lesion may not be a reliable marker of success. Sclerosing agents typically

induce vessel wall fibrosis despite the presence of a patent lumen. Such non-compressibility is not indicative of complete vessel occlusion and endovascular fibrosis. Color Doppler should be utilized to assess residual flow in otherwise non-compressible lesions.

Hemodynamic consequences and residual venous abnormalities (abnormal Doppler signal, residual marginal vein, residual obstruction or dilatation) should be documented. Reduction of flow or new flow patterns should be documented and appropriately mapped. The effect on the size of the malformations depends on the biological interaction between the embolic agents, vessel wall and blood. This interaction is minimal with mechanical devices and maximal with ethanol and may cause organ enlargements which can last for weeks.

Venous malformation (VM) - ultrasound key points

General description ¹⁰⁵⁻¹⁰⁷

VMs are congenital anomalies of the venous system. These malformations may be classified as truncular or extra-truncular. VMs may be found in association with other CVMs such as LMs, CMs and AVMs or part of a generalized syndrome such as KTS.

Truncular malformations may present as agenesis, aplasia, hypoplasia, obstruction, duplication, dilatation, aneurysm or valvular agenesis of mature vessels. A vein may be defined 'hypoplastic' when its diameter is smaller than the corresponding artery in the standing position. Extra-truncular VMs present as phlebectatic lesions that infiltrate other tissues.

Ultrasound evaluation

Ultrasound assessment of VMs should achieve the following key procedural outcomes:

1. DIAGNOSIS, CLASSIFICATION AND MEASUREMENTS

Diagnosis of the anomaly as a VM and sub-classification to truncular vs. extra-truncular. Possible associated CVMs including AVMs or LMs should be identified and documented. Le-

sion size (depth, length and width) should be documented.

In the evaluation of extra-truncular VMs, B-mode examination is very important to define the size and to localize the lesion. Compressibility to determine patency or incompressibility due to thrombus or a previous treatment should be assessed.

In the evaluation of truncular VMs, aplastic, hypoplastic, obstructed, duplicated, dilated or aneurysmal segments have to be identified and incorporated in a venous incompetence map. Presence, size and competence of valves should be documented. Likewise, a marginal vein can be detected by ultrasonic investigation.

2. LOCALIZATION AND RELATIONSHIP TO REGIONAL STRUCTURES

The site of VM and the tissue plane involved (dermal, subcutaneous, intra-muscular, infiltrative, etc.) should be clearly identified. Near-by normal structures such as tendons, nerves and normal vasculature including arteries and veins should be identified.

3. PRE-OPERATIVE VENOUS MAPPING

Given the intimate relationship of VMs with the normal venous system, a complete venous mapping of both superficial and deep venous systems is required in the evaluation of extremity VMs. Anatomical distribution of the pathological vessels should be incorporated in the broader venous incompetence mapping of the venous system. Site and pathway of reflux should be determined. Relationship with the normal venous structures should be defined. Patency and competence of the deep venous system including variations in diameter compared to the contralateral side should be documented.

4. POST-OPERATIVE ASSESSMENT

Extra-truncular lesions can be treated with sclerotherapy. Successfully treated lesions demonstrate hyperechoic walls and no flow on augmentation. Flow may be difficult to induce and the lesion may not be fully compressible due to vessel wall induration that occurs following sclerotherapy. An anechoic or hypoechoic lumen

would suggest patency of the vessel lumen and may indicate the need for further intervention. Treatment should be deemed successful only when the lesion is non-compressible, appears uniformly hyperechoic on B-mode and shows no flow on Doppler examination.

Post-operative assessment of truncular malformations depends on the initial pathology and the initial aims of the surgical procedure. Post-operative venous incompetence studies should be compared with pre-operative evaluations to determine any new pathways of reflux (see below).

Infiltrating extra-truncular lesions

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

Truncular malformations - contribution to chronic venous insufficiency

Truncular malformations may contribute to CVI due to incompetence or obstruction/aplasia of the affected vessels. Presence of occluded segments (webs, hypoplasia) would result in hemodynamic impacts on their relevant venous systems depending on the location, extent/severity, and natural compensation through collaterals. CVI develops in the territory drained by such truncular vein. Stenosing truncular lesions produce venous obstruction leading to a reduction in venous drainage. In such cases, a detailed venous incompetence map demonstrating the pathway of reflux in both deep and superficial venous systems needs to be obtained.^{108, 109}

Truncular malformations - venous aneurysms

Jugular vein aneurysm of primary/congenital origin is a rare truncular anomaly and should be differentiated from a false aneurysm for example after a complication of neck abscesses. In 10% of cases, jugular vein aneurysms are bilateral. Only seldom they have a tendency to thrombose but are indicated for intervention when they cause compression of neighboring structures or cause cosmetic concerns.¹¹⁰⁻¹¹²

Popliteal vein aneurysms are relatively more frequent and usually detected after an episode of pulmonary embolism. These aneurysms may present alone or together with other VMs. These anomalies may be fusiform or saccular. The minimum size of a popliteal vessel to define an aneurysm is controversial. As proposed by Maletti,¹¹³ an aneurysm may be defined when the vessel size has reached three times the size of a normal vein. A diameter greater than 2 cm should be considered pathological. B-mode ultrasound allows the visualization of the aneurysm and provides size, extension and presence of complete or partial thrombosis.¹¹⁴⁻¹¹⁶ Unlike jugular venous aneurysm they have a tendency to cause venous thrombosis and consequently increase the risk for pulmonary embolism.

Ultrasound is also useful in the assessment of extracranial cerebral venous outflow.¹¹⁷⁻¹¹⁹ In addition to evaluation of aneurysms, stenosis, intraluminal obstructions and valve malformations of the jugular veins at the cervical level can be identified.¹²⁰⁻¹²²

Truncular malformations - the marginal vein

A frequent VM of the lower limbs is the persistence of the marginal vein which is an embryonic vessel which normally involutes and disappears before birth. Marginal vein is also known as lateral embryonic vein which includes sciatic vein as well. The persistence of the marginal vein may exist alone or may be associated with other anomalies of the deep venous system (e.g. hypoplastic femoral vein, absence/agenesis of the femoral vein): in this situation the therapeutic options are absolutely different¹²³ from those of the free standing marginal vein.¹²⁴⁻¹²⁶ This malformation may also appear alone or together with CMs and/or changes in soft tissues and bones.

Therefore, the diagnostic evaluation of marginal vein should be extended first to a thorough assessment of the deep venous system since the existence or absence of the deep vein is a most important fact concerning the therapeutic consequences. If a marginal vein is found with the absence of the deep vein, its management is totally different.

Hence, the first step should start with basic investigation of this anomaly including a detailed assessment of the deep veins and their hemodynamics in order to evaluate the risk to remove the vein itself. Because, when the deep venous system is structurally in hypoplastic condition, the blood flow might be re-routed from the deep system through these superficial vessels as natural compensatory mechanism.^{127, 128} The second step is to classify the marginal vein in four different types to drain into the normal/deep venous system according to the Weber classification as a road map for subsequent therapeutic strategy (Figure 1).¹²⁹ The third and final step is the pre-intervention mapping which should include the most dilated perforators.

Truncular malformations - the sciatic vein

A persistent sciatic vein is another abnormal/embryonic vessel remnant like marginal vein that should also disappear before birth but has failed to involute. Unlike the marginal vein, this vein is located deep in the thigh and has a course parallel to the sciatic nerve ending at the gluteal veins although incomplete form/ending can result in multiple channels. Sciatic vein may be connected with the popliteal vein or directly with the gemellar veins causing the reflux into the calf muscle veins with various symptoms mimicking sciatic pain. However, discomfort requiring treatment is rare.¹³⁰⁻¹³²

Sciatic vein infrequently exists with the marginal vein together as well as the deep vein aplasia/hypoplasia so that the increasing risk/probability of all three conditions of marginal vein, sciatic vein, and deep veins aplasia/hypoplasia combined cannot be overemphasized. The diagnostic assessment should be extended to an investigation to exclude/confirm not only the presence of sciatic vein but also marginal vein and deep vein aplasia/hypoplasia, as well.

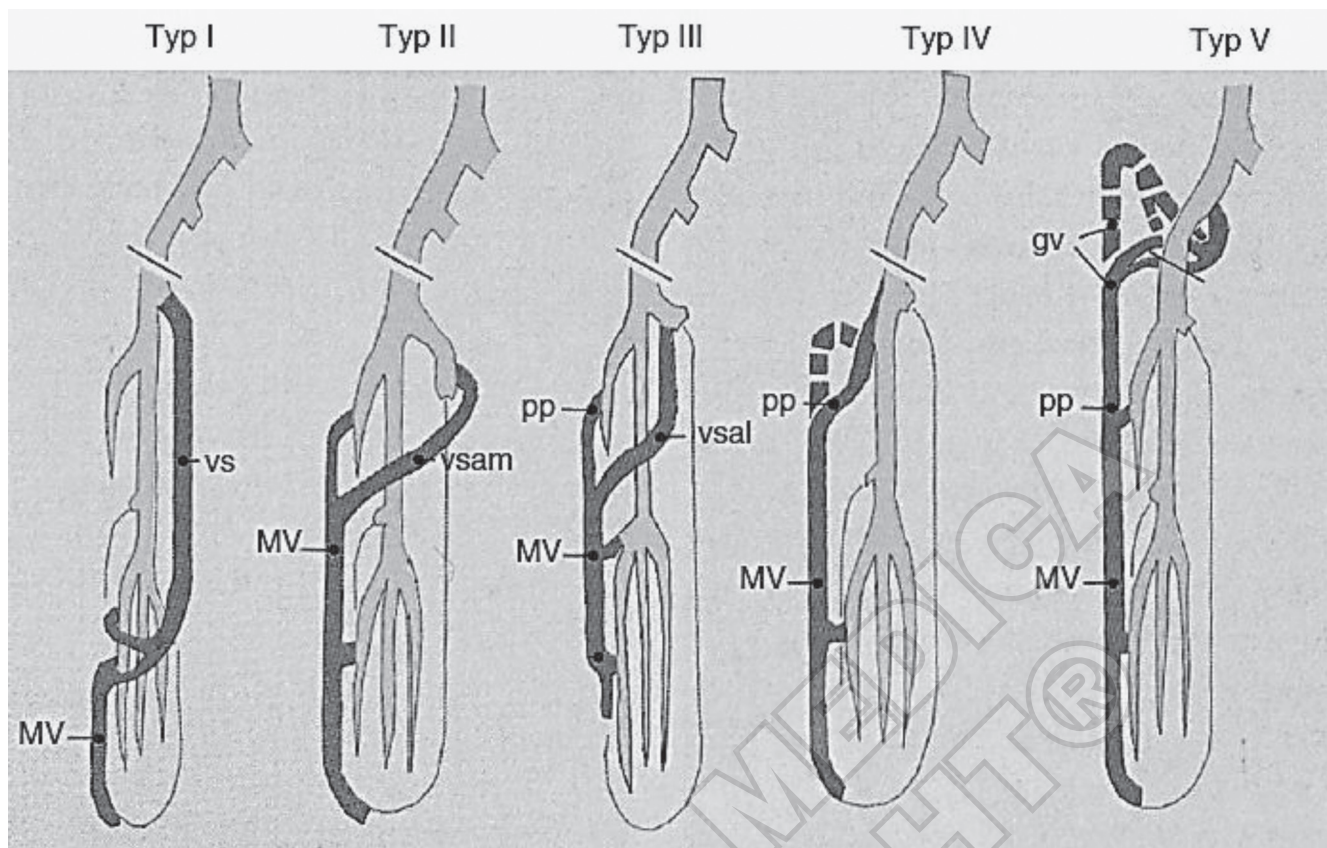


Figure 1.—Classification of the marginal vein according to Weber*
 MV, marginal vein; vs, great saphenous vein; vsam, medial accessory saphenous vein;
 pp, perforans vein to deep femoral (profunda femoris) vein; vsal, lateral accessory saphenous vein; gv, gluteal veins
 *Weber J. Invasive Diagnostik angeborene Gefaessehler (Invasive diagnostic of CVM). In: Loose DA, Weber J, eds. Angeborene Gefaessmissbildungen. Luenburg:Verlag Nordlanddruck GmbH, 1997;127–63

Lymphatic malformations (LM) - ultrasound key points

General description ¹³³⁻¹³⁵

LMs are anomalies of the lymphatic trunks and collectors. LMs may be classified into two categories of truncular malformations and extra-truncular lesions. LMs may exist alone or together with CMs, VMs, and AVMs or part of a generalized syndrome such as KTS.

Truncular LMs are caused by agenesis, aplasia, hypoplasia or hyperplasia/dilatation of the lymphatic vessels and clinically present as primary lymphedema. Extratruncular lesions present as macrocystic or microcystic lesions. Macrocystic lesions are defined as having a dimension greater than 2 cm while microcystic lesions are defined to have a dimension less than 2 cm. A key characteristic of LM is fluid overload to soft tis-

sues: lymphedema in truncular lesions and tissue displacement by infiltrating cystic lesions in extratruncular LMs. ¹³⁶⁻¹³⁸

Severe forms of LM have to be assessed carefully in order to exclude associated anomalies including bony involvement, presence of spindle cells, development of thrombocytopenia (suggestive of kaposiform lymphangiomatosis) and various syndromes with a significant lymphatic component: Hennekam Syndrome, Aagenaes Syndrome (cholestasis-lymphedema syndrome), Lymphedema-dystichiasis syndrome, CLAPO, ODELAID, or Turner Syndrome. (Appendix C & Appendix D)

Ultrasound assessment remains the main diagnostic tool in the assessment of LMs. Ultrasound evaluation should be complemented by lymphoscintigraphy which represents the gold standard in the study of the dynamics of lymphatic circulation in truncular lymphatic mal-

formations. Data obtained by ultrasonography are comparable with the data obtained by MRI. Recent advances in radiological lymphodynamic studies can soon improve our understanding of aberrant lymphatic flows, as well as their evolution and outcome. However, the genetic research to investigate on the aggressive behavior of certain lesions is still underway.

Ultrasound evaluation

Ultrasound assessment of LMs should achieve the following key procedural outcomes:

1. DIAGNOSIS, CLASSIFICATION AND MEASUREMENTS.

Diagnosis of the anomaly as a LM and subclassification to truncular vs. extra-truncular. Possible associated CVMs including VMs, CMs and AVMs should be identified and documented. Lesion size (depth, length and width) should be documented.

In the evaluation of extra-truncular LMs, B-mode ultrasound investigation may reveal the presence of anechoic/hypoechoic cysts. Doppler examination will reveal cavities containing fluid but without spontaneous flow. Augmentation and distal compression may cause turbulence in some larger cysts but no directional flow will be induced such as that seen in veins or extra-truncular VMs. Patients may need to be examined in both the sitting and supine position to assess variations in size especially when examining neck lesions. Microcystic lesions generate multiple interfaces and may present as a uniformly diffuse hyperechoic tissue.¹³⁹⁻¹⁴¹ In the evaluation of truncular LMs, assessment should include evaluation of skin, subcutaneous tissue and the associated lymphedema.

Ultrasound evaluation should include morphological assessment of cysts including presence of septae within the cystic cavity, measurement of cystic dimensions and the number of macrocysts. In extensive malformations where large surface areas are affected, it may not be practical to count and measure all lesions.

2. LOCALIZATION AND RELATIONSHIP WITH REGIONAL STRUCTURES

The site of LM and the tissue plane involved (dermal, subcutaneous, intra-muscular, infil-

trative, etc.) should be clearly identified. Ultrasound anatomy of normal skin and deeper layers is generally characterized by the first superficial hyperechogenic layer (the epidermis), the second low-echogenicity layer of "papillary" dermis and hyperechogenicity layer of the deeper reticular dermis, and the third layer of mixed-echogenicity of the subcutaneous layer, which is characterized by connective bands and nodule-like (adipose component) images.

Near-by structures such as tendons, nerves, normal vasculature including arteries and veins and presumably 'normal' lymphatic trunks should be identified.

3. PRE-OPERATIVE ASSESSMENT

Anatomical distribution of the cystic lesions, infiltration in other tissues such as inter-muscular spaces and subcutaneous fat and proximity to vital organs and structures such as airways and major vessels should be determined. Variations compared to the contralateral side should be documented. Pre-operative marking should determine the best pathway of approach for puncture to avoid inadvertent injury to other near-by structures. This is especially important when treating neck lesions.

4. POST-OPERATIVE ASSESSMENT

Extra-truncular lesions can be treated with embolization using agents such as Doxycycline, OK-432 or ethanol. Successfully treated cysts should no longer be visible on ultrasound. Pre-operative images and documentation of the location of the cysts is crucial in guiding the post-operative assessment.

LMs involving the neck

Macrocystic lesions predominately localize to the neck and can cause compression of the airways particularly at birth. In these cases, a pre-natal morphological ultrasound can plan an exit procedure for birth.^{142, 143} Communication with the thoracic duct or the right lymphatic duct and proximity to major neck vessels should be identified.

Truncular LMs and lymphedema

In truncular malformations, a high frequency probe >7.5 MHz can visualize the dermis, the

subcutaneous tissue, the presence of dilated lymphatics known as lymphatic lakes and the subfascial space. Flow in these lymphatic vessels cannot be visualized. It is also important to evaluate the echogenicity of the subcutaneous tissue in order to establish the grade of fibrosis.

The evolution and treatment outcomes may be confirmed by the measurement of skin thickness. Skin elasticity may be assessed by compressing the tissue with the transducer to assess the progression of lymphedema. The ultrasound evaluation of subcutaneous tissue thickness is a useful parameter to evaluate lymphedema and its response to treatment. The suprafascial and the subfascial thickness of the edematous tissue is demonstrable through high resolution echography (and/or CT scan) and tissue compressibility.^{144, 145} These are useful measurements that allow periodic assessment of the response to therapy and are useful in monitoring a patient's progress and determining prognosis.^{39, 40}

In patients with lymphedema, thickening of the cutaneous, epifascial, and subfascial compartments has been sonographically observed. This contrasts with MRI observations, where the subfascial compartment was shown to be unaffected.¹⁴⁶ High frequency ultrasound (20 MHz) reveals characteristic patterns of cutaneous fluid localization in various types of edema.^{39, 40} In lymphedema, there is a distinctively uniform pattern of distribution. Ultrasound imaging has applications both in differential diagnosis and in therapeutic monitoring, although further refinement may become necessary to better characterize the spectrum of subcutaneous fibrosis that can be encountered in lymphedematous skin.^{7, 141, 147}

Arterio-venous malformations (AVM) - ultrasound key points

General description

AVMs are congenital anomalies of the arterial and venous systems. These malformations may be classified as truncular or extra-truncular. AVMs may be found in association with other CVMs such as VMs, LMs and CMs and can be part of a generalized syndrome such as the Parkes-Weber syndrome.

Extra-truncular AVMs present as anomalous

communications between the arterial and venous systems. Truncular arterial malformations are discussed below under 'Arterial Malformations'.

Ultrasound evaluation

Duplex ultrasound remains the first choice investigation amongst various non-invasive modalities in the initial clinical assessment and subsequent follow-up of AVMs. Ultrasound assessment of AVMs should achieve the following key procedural outcomes:

1. DIAGNOSIS, CLASSIFICATION AND MEASUREMENTS

Diagnosis of the anomaly as an AVM and sub-classification based on Do' criteria (see angiography below). Possible associated CVMs including VMs or LMs should be identified and documented. Lesion size (depth, length and width) should be documented. Presence or absence of nidus should be documented.

On B-mode examination, AVMs may present with a honeycomb appearance of multiple non-compressible vascular spaces. The surrounding soft tissue may appear hyperechoic. AV fistulas present with a single afferent artery and draining vein.

Spectral, color and power Doppler are very helpful to further define the flow characteristics in the afferent feeding arteries, within the nidus and in the efferent draining veins. Aliasing is a typical Doppler feature noticed within the nidus and represents turbulent flow.⁷ Ultrasonography of AVMs is characterized by multidirectional (high-flow Doppler signal with low-resistance arterial waveforms) blood flow, high amplitude arterial waveform with spectral broadening and arterialized venous outflow.^{101, 148} This is in contrast to VMs which demonstrate monophasic, biphasic or no detectable flow in 78%, 6% and 16% of cases, respectively.¹⁴⁹

Do's classification of AVM is based on the nature of afferent (single or multiple arteries or arterioles) and efferent vessels (single or multiple veins or venules) and the presence or absence of a nidus (see below). Although angiography is the best way to sub-classify AVMs, in superficial lesions, ultrasound can achieve a similarly accurate diagnosis.

Ultrasound examination can readily differentiate an AVM from a VM or LM. VMs (when not thrombosed or sclerosed) are compressible while AVMs (and LMs) are non-compressible. On Doppler examination, AVMs present with a pulsatile, high volume, low resistance flow.⁷ By contrast, LMs have no flow while augmentation is required to induce flow in VMs.

In most cases, ultrasound can also differentiate a vascular tumor from an AVM from. Vascular tumors are relatively homogeneous soft tissue masses. Active tumors are highly vascular and contain pulsatile blood flow and varying low flow draining veins. By contrast, AVMs are formed of multiple vascular channels with a honeycomb appearance and monophasic high flow characteristics in afferent feeding arteries.⁷

The differentiation from vascular tumors may not be straightforward in children and a RICH or NICH may be confused with an AVM. In adults, NICH can still be confused with an AVM. Such cases will require histological assessment to make a diagnosis.

Measurements should include measurement of the diameter of the vessels involved in comparison with the contralateral side.

2. LOCALIZATION AND RELATIONSHIP WITH REGIONAL STRUCTURES

The site of the AVM and the tissue plane involved should be clearly identified. The origin of the afferent vessels in the normal arterial system and the drainage into the normal venous system should be mapped. The extent of the arterialized flow within the venous system should be identified. Associated tissue hypertrophy or atrophy and in particular hypertrophy of the subcutaneous fat should be documented and reported on. Near-by normal structures such as muscles and nerves should be identified.

3. PRE-OPERATIVE ASSESSMENT

AVMs originate from feeding afferent arterial vessels and efferent draining veins. Given this communication with the normal vascular system, a pre-operative map is required to demonstrate the anatomical position of the anomaly and to map the flow from the arterial system into the venous system. Such ultrasound derived

map should be supported and complemented by MR angiographic information. The anatomical distribution of the pathological vessels should be incorporated in the broader arterial and venous mapping of the extremity or the region.

An important pre-operative consideration in the management of AVMs is to select the most suitable catheterization approach. The approach in general may be trans-arterial, trans-venous or trans-cutaneous. Ultrasound can play an important role in the selection process and puncture and catheterization is ultrasound guided. The pre-operative marking should identify the location of the nidus and the direction and location of the afferent and efferent vessels.

4. POST-OPERATIVE ASSESSMENT

AVMs are typically treated with embolization which may be complemented by surgical resection or sclerotherapy of the embolized lesion. The outcome depends on the type of embolic agent used. Ethanol will cause distortion of the tissue and scar formation that will appear hyperechoic on ultrasound. The most important parameter is flow which should be reduced or completely interrupted following the intervention.

Arterial malformations - ultrasound key points

Sciatic artery - truncular lesions

The persistent sciatic artery is an artery which runs parallel to the sciatic nerve and involutes before birth. This artery often degenerates to an aneurysmal dilatation and remains (because of the defective vessel wall structure) as an embryonic vessel remnant.

There are two variants for this malformation. First, the sciatic artery coexists with normal iliac-femoral arteries. Second, it may be accompanied and compensates for an aplasia of the iliac-femoral arteries. This lesion can easily be identified by ultrasound investigation. The symptomatology is related to the compression of the sciatic nerve, distal embolization and acute ischemia secondary to the thrombosis of the aneurysmal sac.¹⁵⁰⁻¹⁵⁴ Therefore, proper investigation should also include the appraisal of these findings.

Visceral vascular malformations

This unique anomaly can develop at any splanchnic vascular bed mostly as a truncular malformation. Amongst them, the splenic artery and renal artery aneurysms are well known.

Therefore, the alertness on various lesions as described below is mandated for the ultrasonographic evaluation of the abdomen whenever indicated with suspicion.

Visceral arterial aneurysm - truncular malformation

Arterial aneurysms involving the visceral organs in young patients are usually secondary to congenital defects of the arterial wall. They are usually asymptomatic until rupture and may be easily detected incidentally during routine ultrasound abdominal examination.

Renal vascular malformations

The ultrasound investigation allows detection and measurement of the size of the vessels involved. Doppler will assess the blood flow direction and velocity.¹⁵⁵⁻¹⁵⁷

Renal AVMs are uncommon.¹⁵⁸ Renal AVMs are classified according to their location as central or peripheral (for the renal hilum) or intraparenchymal. On B-mode ultrasound, hypoechoic cysts or tubular structures are evident.¹⁵⁹ With the use of color Doppler and pulsated Doppler high flow vessels are evident. The pulsating flow is also evident in the efferent vein. Small AVMs near the hilum might be difficult to visualize as they may be hidden by normal vessels.¹⁶⁰

Hepatic vascular malformations and vascular tumors

Due to the complexity of vascular structure, the liver is frequently involved by hemangioma as well as vascular malformations, mostly VMs. These lesions may cause important changes of the metabolism resulting in complete liver failure. Therefore, this unique hepatic lesion warrants appropriate knowledge to distinguish hemangiomas from various vascular malformations, especially on their dynamic course with times.

The most important differentiating factor in the evaluation of hepatic vascular anomalies is the age of the patient. The most common involvement in children is a HOI which remains the most common benign liver tumor in pediatric population. VMs, often mistakenly called "hemangiomas", are most common in adults.^{45, 47}

Recently, pediatric liver vascular tumors were reclassified based on the GLUT-1 expression to replace the old confusing term of hepatic infantile hemangioendothelioma. GLUT-1 positive expression is usually demonstrated in multifocal, and diffuse hepatic infantile hemangioma, which shares clinical and morphological features with cutaneous HOI. Multiple cutaneous and hepatic hemangiomas are also involved in 'diffuse neonatal hemangiomatosis'. Since the prognosis of hepatic hemangiomas has become much favorable with propranolol, proper evaluation with the ultrasonography is further mandated for proper management.¹⁶¹⁻¹⁶⁴

GLUT-1 negative vascular liver tumors occur in neonates with unique clinical, imaging and pathological features. They differ from diffuse hemangiomas in terms of earlier presentation as solitary masses with central necrosis, rapid involution and pathologic features showing a notable, often prolific, lymphatic component. Following the parallelism with cutaneous anomalies, the term hepatic congenital hemangioma has been suggested comparing their behavior with RICH described in skin and subcutaneous locations. The natural history for focal liver hemangiomas is spontaneous regression in the first year of life. However, shunts embolization or complete surgical excision is required only in case of serious cardiac failure.

VMs are the most common hepatic vascular anomalies in the adult population. Liver hemangiomas do not exist by definition after puberty, and the diagnosis of epithelioid hemangioendothelioma has to be considered in the adult patient with a hepatic vascular tumor.

Blebs, spurs, webs and membranes due to a truncular anomaly may be found in the vena cava at the confluence site of the hepatic veins. These cause inadequate outflow of the hepatic veins resulting in hepatic vein outlet obstruction, known as primary Budd-Chiari syndrome.¹⁶⁵⁻¹⁶⁷

In HHT (Osler-Rendu-Weber disease), AVM/AV fistula is known as the most common finding

among various CVMs. In this case, high velocity profile in the hepatic artery with a pulsatile flow in the portal branch is detected with an inversion of the flow direction. Portal hypertension secondary to splenic AVM lesion can be detected. Porto-systemic shunts, intra- or extra- hepatic, may be detected by color Doppler examination and the shunt fraction may be measured.¹⁶⁸⁻¹⁷⁰

The Panel recommends (Duplex) Ultrasound examinations as the basic non-invasive test to define the hemodynamic and anatomic features of the malformation. The examination has to be complete and in case of limb involvement both limbs should be investigated. The examination should be performed in orthostatism and clinostatism. (GRADE 1B)

Hemangioma of infancy (HOI)

The diagnosis of HOI is usually clinical but ultrasound is required to make the precise organ assignment and the precise classification of the stage which is obligatory for the indication if this hemangioma needs a treatment or is a candidate for spontaneous regression, which is the majority.

HOI in the early phase (stage 1 and 2) are characterized by the presence of a highly vascular soft tissue mass demonstrating high velocity flow patterns during the proliferated phase followed by a lesser vessel density and hyperechoic tissue due to the fat degeneration during the regression phase (Table III). It is normally not hypoechoic but relatively hyperechoic as it con-

tains fat. The vessels are hypo- or anechoic but the bulk of the mass is not.

Congenital hemangiomas may be lobulated and the vessels have a palisading architecture. Ultrasonography is therefore, a non-invasive imaging technique very useful for differentiating hemangiomas and VMs as the first-line imaging study for the children.^{97, 171} 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.^{6, 20}

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.^{6, 20}

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 cm², 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 hemangioma.^{6, 20}

Therefore, an ultrasound study of a child being assessed for a hemangioma should provide the following information:^{6, 20}

TABLE III.—Correlation of clinical presentation and Color Coded Duplex Sonography (CCDS) characteristics of HOI.

Stage	Clinic	CCDS
S I Prodromal phase	red/white spot; teleangiectasia blurred swelling	loss of skin structure, structure less, low echo space no signs of pathological vessels
S II Initial phase	loss of typical skin structure increasing of thickness and induration	hyposonor center at the edges beginning hypervascularization
S III Proliferation phase	cutan bright red infiltration, flat spreading subcutaneous growth of thickness infiltration of surroundings, even organ borders possible early central ulceration	increasing Intratumoral hyperperfusion center vessel density nutrition tumor vessels drainage veins with arterial flow profile
S IV Maturation phase	pale and livid color decreasing of growth possible late ulceration over drainage veins	declining central vessel density increasing ectatic drainage veins declining arterialization of the drainage veins central increasing hypersonore
S V Regression phase	hypopigmentation, wrinkled skin/ teleangiectasias surroundings subcutaneous drainage veins subcutaneous palpable induration	circumscribed hypersonore area loss of typical tissue structure nearly no central tumor vessels residuals of supplying tumor arteries residuals of ectatic drainage veins

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.

B-mode

— Gross ultrasonographic 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.

— 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.).

— Compressibility of vascular channels and presence/absence of thrombus within the channels.

— Evidence of previous treatments (hyper-echoic walls/segments), sclero-thrombus, and surgical scarring should be identified and commented on.

— 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 according to the stage of hemangioma.

Other observations

Comments should be made regarding:

— Whether the lesion is unilateral or bilateral.

— If the underlying tissue shows hypertrophy or atrophy.

Magnetic resonance imaging (MRI)

MRI is the procedure of choice after ultrasound evaluation for the assessment of all CVM: MRI has a better spatial resolution/definition and a wider field of view than ultrasound; it also presents an intrinsic capability to visualize blood flow and characteristics of tissues without using ionizing radiation.^{172, 173} However, both have the possibility of multiplanar acquisition.

In the investigation of vascular anomalies equipment with high power (at least 1.5 Tesla) should be used in order to have a better contrast and spatial resolution which allows to detect also small anomalies.¹⁷⁴⁻¹⁷⁶

Disadvantages of MRI are that they may be lengthy, noisy and potentially frightening examination for children, especially in younger age groups where consequent sedation for MRI is required.¹⁷³

Each vascular anomaly has unique MRI feature as summarized in Table IV.

A typical CVM imaging protocol consists of spin echo (SE) or fast spin echo (FSE) T1-weighted sequences axial to the lesion generally with fat suppression in order to highlight the lesion; images obtained after gadolinium injection are useful to distinguish LMs and VMs which have similar images in normal and in angiographic acquisition. SE sequences can also identify signal voids representing arterial feeders.^{172, 173, 177}

T2-weighted images (FSE with fat suppres-

TABLE IV.—MRI imaging features of vascular anomalies.

Vascular pathology	MRI imaging features
Hemangioma of infancy (HOI)	In the proliferating phase appearance of a well lobulated mass with low signal intensity on T1W images and high intensity in T2W images; presence of flow voids in SE T1W images, no perilesional edema and early homogeneous enhancement Involuting phase: fat replacement with high signal on T1W images and decreased enhancement
Venous malformations (extratruncular)	Lobulated sometimes septated mass with low signal intensity in T1W images, high intensity in T2W images, flow voids in T2W fat saturation images (phleboliths), slow gradual enhancement in delayed with contrast media
Lymphatic malformations (extratruncular)	The same characteristics of the venous malformations. No enhancement in microcystic malformations. Septal and rim enhancement in macrocystic malformations
Capillary	Skin thickness lesion
Arterio-venous malformations (extratruncular)	Enlarged feeding arteries and draining veins. Flow voids in T1W SE sequences; early enhancement of arteries nidus and draining veins

sion or in alternative short tau inversion recovery -STIR- images) in at least two planes has been found most sensitive and specific for detection of the extent and depth of the lesion because of a generally bright signal intensity lesion over a low signal intensity fat, muscle, and bone background; these sequences can also show the content of the malformation.^{172, 177}

Some authors also proposed the use of bright blood gradient recalled echo (GRE) sequences, to identify high flow vessels as rounded and hyperintense signal voids; the use of these sequences, however, is not essential and has been progressively abandoned.¹⁷⁸⁻¹⁸⁰

The presence of signal voids on T2-weighted images is suggestive for hemosiderin, dystrophic calcification or phleboliths typical for VMs.¹⁷²

Magnetic resonance angiography (MRA) techniques are complementary to the conventional MRI sequences; traditional Time-of-Flight (TOF) and Phase Contrast techniques have now abandoned in the study of CVM, preferring contrast enhanced MRA (CE-MRA).¹⁷⁴ CE-MRA uses 3D T1-weighted sequences with fat suppression: the contrast medium (gadolinium chelates) is injected in a peripheral vein causing a shortening of T1 relaxation times.¹⁷²

Although many techniques have been described for CE-MRA, time resolved 3D-MR digital subtraction angiography is best suited for evaluating vascular anomalies. With this technique a serial acquisition of less than or equal to 10 second duration are performed in rapid succession. At least one acquisition will certainly coincide with the arterial phase and at least one will coincide with the venous phase of enhancement. Of course for optimal visualization, temporal resolution must be maximized: improvement of data processing techniques can generate 3D images every 2 seconds.¹⁷²

Compared with conventional angiography, the CE-MRA has the advantage of being able to perform multiplanar reconstructions, does not use ionizing radiation and is much less invasive. The disadvantages of CE-MRA are related to the fact that spatial resolution and the area of interest are influenced by a high time resolution; MRA also lacks the selectivity that may instead provide a selective catheterization.¹⁸¹

The Panel recommends MR imaging as a major non-invasive test together with ultrasonographic evaluation. MR has a better spatial resolution al-

lowing a wider field of examination. This examination allows to highlight various anatomic components according to the magnetic stimulation of the organs. It gives the best evaluation of organ involvement by the malformation. (GRADE 1B)

Extratruncular venous malformations (VM)

MRI and MR venography (MRV) are 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.^{6, 20}

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. They usually show low to intermediate signal in T1-weighted sequences and high contrast in FSE T2-weighted or STIR sequences, where the vascular malformation is highlight from the surrounding fat. In case of thrombosis or hemorrhage heterogeneous signal are seen in T1-weighted images. VM lesions may be localized or diffuse and have usually lobulated margins.

A slow filling of the malformation is visible with the use of contrast medium.¹⁷⁷ This characteristic of the VMs is important in the differentiation with the LMs and other cystic lesions which do NOT have any contrast enhancement after gadolinium injection.

The morphological features of VMs correlate with the success of the sclerotherapy.¹⁸² Well defined margins and dimensions less than 5 cm are predictive of good results after ethanol therapy.

Extratruncular lymphatic malformations (LM)

The MRI appearance of LM is variable in relation to the size of the cysts. Microcystic LMs usually appear as diffuse areas with low signal in T1-weighted and high signal intensity on T2-weighted sequences.¹⁸¹ These cysts are too small to be individually identified on MRI. The microcystic LM may appear completely avascular or show a mild enhancement.

The macrocystic LM instead are characterized for the presence of cysts and septa well defined. The cysts have low signal intensity on T1-weighted sequences and appear markedly hyperintense on T2-weighted images. It is often possible to recognize a fluid-fluid level within the cyst, due to the presence of blood or proteins. The presence of flow voids or areas of intralesional enhancement are not typical of LM.¹⁸¹

The septa and the walls of the cyst after injection of contrast present a mild enhancement. The cystic spaces do not show enhancement and this behavior helps to differentiate them from the VMs. Sometimes, however, an enhancement of the cyst can be detected after treatment (both surgical and percutaneous) or in the case of mixed formations (lymphatic-venous).¹⁸¹ PET scan and/or CT scan is indicated in cases of chylous reflux.

Truncular lymphatic malformations (LM): primary lymphedema

MRI with or without contrast is indicated for further detailed evaluation of tissue overgrowth, pelvic pathology, obstructing lymph drainage or malformations among the patients with a combined form of vascular malformations (e.g. KTS).^{183, 184}

In lymphedema, the images reveal a characteristic distribution of edema within the epifascial compartment, disclosing a honeycomb pattern along with thickening of the skin. In venous edema, both the epi- and subfascial compartments are affected, while in lipedema, there is fat accumulation without fluid.^{185, 186}

MRI is also helpful in the identification of lymph nodes, enlarged lymphatic trunks, and in the differentiation of the various causes of lymphatic obstruction in secondary lymphedema. The anatomic information derived from MRI may complement the functional assessment provided by lymphoscintigraphy. At times, these complementary sources of information are necessary to establish the diagnosis and to make the requisite therapeutic decisions.¹⁸⁷

Extratruncular arterio-venous malformations (AVMs)

AVMs have a significantly different appearance on MRI than their low-flow counterparts

(VMs).^{188, 189} On MRI, an AVM appear as ill-defined alteration in the context of soft tissue, of variable signal intensity in both T1- and T2-weighted images, with enlarged blood vessels in the presence of both afferent arteries (feeding artery) and efferent veins dilated without a mass that can be viewed with respect for the distinct levels.^{173, 177}

The blood vessels in AVMs cause linear or rounded signal voids in the T1-weighted SE sequences that correspond to signal hyperintensity in the GRE sequences.^{172, 181} The "nidus" is heterogeneous, characterized by a tangle of multiple empty signal in T1-weighted sequences in the presence of dysplastic veins, well highlighted in the T2-weighted sequences.¹⁷⁷ Thickening of the skin, increasing amount of fat tissue and muscle atrophy in proximity to the AVM can also be present.

The AVM can affect bone causing hypoplasia, cortical thinning and demineralization; direct involvement of the bone is identified by the presence of intraosseous high flow vessels.^{181,177, 178}

Surrounding tissue signal alterations (representing edema) can be detected with MRI. This aspect can be confused with the presence of a mass: such relief is often found when the AVM is localized in the context the muscle sheath; in this case the differential diagnosis between an AVM and a vascular tumor (rhabdomyosarcoma, hemangiopericytoma, angiosarcoma) can be extremely difficult.

Elements useful in the diagnosis of AVM are therefore represented by the presence of fat within the lesion, muscle atrophy and absence of surrounding edema.¹⁹⁰

CE-MRA is used to identify a dilation of arteries and veins, an early visualization of the draining veins and to provide details of vascular anatomy useful for the treatment or angiography.¹⁷²

Post treatment evaluation

The effect of a treatment on vascular malformation may be measured according to the size or the flow reduction. In extratruncular flow malformation, the treatment can be the injection of sclerosing agents or surgical excision in low flow malformations and transarterial embolization in high flow malformation. The biological response to sclerotherapy with all agents is long

and the scarring process may last some months. In these cases the evaluation of the results and the indication for further treatment is based on the injection of gadolinium which allows detection of the perfused area.¹⁹¹

Hemangioma of Infancy (HOI)

MRI plays no role in the diagnostic of HOI and may be only required in uncertain and in deep localizations where ultrasound is not possible. But in cases of KHE and NICH, MRI is important to detect soft tissue and bone infiltration and to guide biopsy.

So MRI is the second non-invasive test for differential diagnosis of hemangioma and VM although it is NOT as critical as ultrasound. MRI may be indicated for diagnostic confirmation when the ultrasound findings are not clear. This investigation allows to better define the anatomy and the vascularization of the lesion, so distinguishing hemangiomas and VMs. In many cases, MRI and ultrasound with color flow imaging are complementary.^{177, 178, 192}

The characteristics of the tissue involved differ according to the biologic phase. In the proliferating phase, HOI appears as lobulated well defined mass, hyperintense in T2-weighted images and intermediate intense in T1-weighted images. Typically, prominent draining veins will be identified along both central and peripheral and some smaller arterial high-flow vessels are seen. There is intense, uniform, diffuse enhancement following intravenous administration of gadolinium chelates. Usually there is no perilesional edema.¹⁰⁰ In the presence of edema it is useful to make a biopsy of the tissue in order to exclude sarcoma.¹⁸⁸

Involuting hemangiomas presents more varied and heterogeneous appearances with increasing amount of fibrous tissue, fat and an increased signal, evident in T1 sequences with less vascular enhancement.

Congenital hemangiomas

MRI findings are similar to those of HOI but an increased venous component, vascular aneurysm and arterio-venous shunting may be present^{174, 188} For the RICH, ultrasound is sufficient but in progressive NICH and KHE, an addi-

tional MRI is beneficial. In case when Kasabach-Merritt-Syndrome (KMS) should develop, the signal becomes much more intense with interstitial edema same as ultrasound. The reduction of these signs correlates with the normalization of the coagulopathy although the thrombocytopenia can remain for long time.^{193, 194}

Computed tomography (CT)

Although MRI is preferred for assessing CVM, CT may replace or complement MRI in some cases: CT is an alternative to MRI in those patients with respiratory or cardiac failure because of the velocity in the images acquisition. Of course it is useful in patients who have contraindications to sedation with MRI and is preferable to MRI in imaging vascular anomalies of bowels and lungs.¹⁷³

In addition, it presents fewer artefacts compared to MRI in patients with embolization coils or metallic clips.

Compared to MRI, CT may better define both alteration in bony architecture and identify phleboliths or other dystrophic calcifications.¹⁷⁷ If there is a CVM (in particular in high flow vascular lesion) bone involvement, CT may provide additional information to MRI.

The adverse effects are represented by the exposure to ionizing radiation and the necessity to use contrast medium to visualize the vessels. The problem of the exposure to ionizing radiation is of particular importance in pediatric age, regarding CT's potential for carcinogenesis.

On CT, VMs often appear hypodense or heterogeneous lesions which enhance slowly from the periphery after the injection of contrast.¹⁹¹ 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.¹⁹⁵⁻¹⁹⁷

LMs shows fluid-filled, low-attenuation masses occasionally with fluid-fluid levels and peripheral contrast enhancement of the wall.¹⁹¹

Contrast enhanced CT of AVMs, with bolus tracking technique (CT-angiography; CTA) to ob-

tain an optimal study of arterial vessels, reveals numerous enlarged feeding arteries with rapid contrast shunting into enlarged draining veins without significant intervening tissue enhancement that usually would be seen within a normal capillary network. Contrast-enhanced CT of AVMs is significantly more informative than in other vascular malformations because it provides a distinct three-dimensional data set for accurate mapping and measurement of arterial, nidus, and venous structures and assessment of flow patterns for interventional radiologic or surgical planning which is possible especially due to the many post-processing options.¹⁸⁸

VMs are heterogeneous lesions which enhance slowly from the periphery after the injection of contrast.¹⁷² In AVMs, the afferent artery, the efferent veins and the nidus are well defined.

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.¹⁹⁵⁻¹⁹⁷

CT with intravenous contrast enhancement has been used for the differential diagnosis of hemangiomas and VMs.¹⁹⁸ Yet CT involves significant exposure to ionizing radiation making it less useful, although CT gives superior resolution for osseous lesions.^{6, 20}

Standard MRI is not a good technique for precisely demonstrating the nidus or arterio-venous connection. Instead, CTA provides much better anatomical information, sometimes showing the arterial and venous anatomy in excellent detail, but is inferior in all aspects to the newer technique of CE-MRI.⁷

Even considering that CTA may give more precise anatomical detail than MRI, particularly in small blood vessels, the benefits of clinically justified CT examinations should always outweigh the risks for an individual child, and referral to a center that performs CE-MRI^{100, 199} should be considered as well.⁷

MRI should remain as the option of choice in the diagnosis of high flow vascular anomalies for this special group. Only when dealing with a specific AVM in a critical area difficult to treat, CT is indicated, though extremely rare.⁷

We recommend CT scan as useful test especially with the contrast medium presenting excellent spatial and temporal resolution. Its principal indications are thoracic and visceral malformations as well as AVM with bone involvement. (GRADE 1C)

Conventional radiological assessment: plain X-ray and bone scanograms

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 objective criteria for further management.^{6, 20}

Conventional radiologic techniques are addressed to discover bone involvement in CVMs. Bones may be elongated, shortened, deformed, thickened or thinned because of osteolysis.^{173, 200} The pathological cause is related to ischemia of the osteoblasts representing a growth stimulation or to compression of the bone by the surrounding structures or vein and lymph stasis.²⁰¹⁻²⁰³

Calcification in the soft tissues is a hallmark of VMs. Multiple enchondromas are typical of Maffucci syndrome and they have the tendency to progress to malignancy.

The Panel recommends Plain X-rays as an essential test in detecting bone pathology related to CVMs. Bony changes including lengthening, shortening, enchondromas and vanishing bone syndrome should be identified. These images are also useful in detecting calcifications (phleboliths) in soft tissues as a hallmark of VMs. (GRADE 1B)

Invasive diagnostic evaluation

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

Basic diagnosis of CVMs is generally sufficient with proper combination of the non- to minimally invasive tests and “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 which are important for options of treatment.^{6, 20}

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.^{6, 20}

Direct puncture phlebography is also very useful to identify a large efferent vein of extratruncular lesions.^{125, 204} These veins can be treated in advance to allow more effective therapy with reduced risk of recurrence, with subsequent embolotherapy or sclerotherapy.^{6, 20}

There is no role for diagnostic angiography in the diagnosis or follow-up of low-flow vascular malformations; angiography should be reserved only in AVM as a road map to further define the lesion and plan proper treatment. To minimize radiation exposure, these techniques are usually performed at the time of treatment in young patients.^{200, 205}

These studies include:

- Selective and superselective arteriography
- Percutaneous direct puncture phlebography

Therefore, once the intervention is decided, the level of propaedeutic to the therapy should be elevated to pre-therapeutic mapping of the lesions including the angiographic classification of extratruncular VMs (Table V) and also AVMs (Figure 2) proposed by Puig¹⁰³ and YS Do *et al.*,¹⁰⁴ respectively. These classifications have a

TABLE V.—Angiographic classification of venous malformation.

Angiographic classification of venous malformation by YS Do <i>et al.</i>	
	Description
Type 1	Isolated malformation without peripheral drainage
Type 2	Malformation that drains into normal veins
Type 3	Malformation that drains into dysplastic veins
Type 4	Malformation that represents a dysplasia

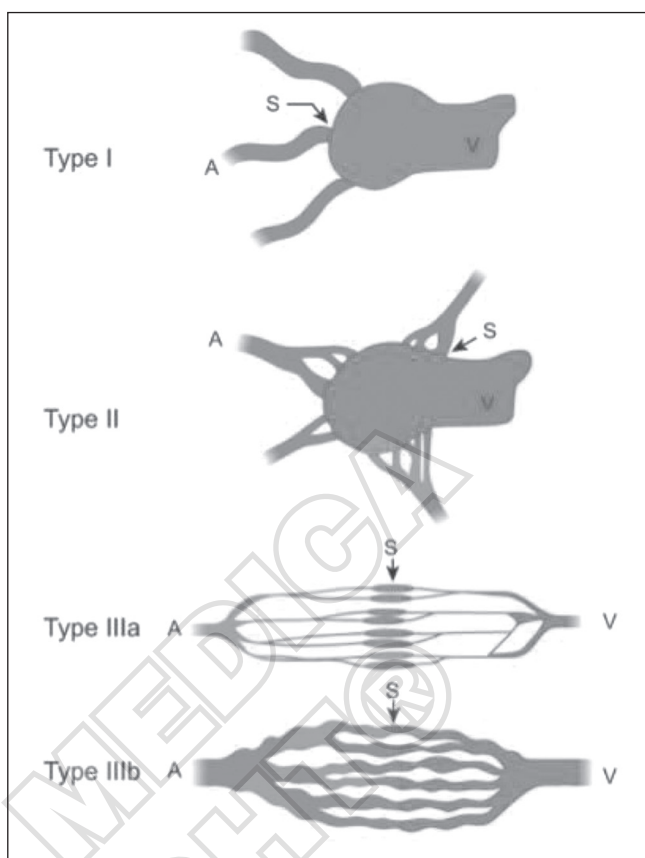


Figure 2.—Arteriographic classification of AV malformation.

great importance as predictive measurement for the results of intravascular therapy.

Phlebography

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).^{97, 103, 206}

From a diagnostic standpoint, phlebographic evaluation of patency and anatomic variations of the deep venous system deserves special consideration in addition to phlebographic classi-

fication of the VM. 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.^{6, 20}

Ascending phlebography is rarely required for the diagnosis of a vascular malformation. The role of ascending phlebography is limited to the diagnosis of truncular venous disease and in particular of obstructive pathology. It is important to evaluate the patency of the deep veins in presence of dilated superficial veins and hypoplasia or aplasia of deep veins according to the non-invasive investigations.^{125, 204, 207} Technical skills are required to avoid incorrect results of phlebography, as preferred abnormal outflows may sometimes simulate absence or main vein stenosis.

The main advantage of this procedure is that the imaging can be performed in orthostatism. Descending phlebography is indicated to avaluia and in pelvic, sciatic, and visceral malformations. Direct puncture venography is related to the treatment of extratruncular VM lesions. With this procedure it is possible to visualize the outflow drainage of the malformation and it is possible to distinguish four types according to the drainage veins.

We recommend direct puncture phlebography for the evaluation of the venous outflow of the lesion. It helps in understanding the success probability of a vascular surgical procedure or sclerotherapy. (GRADE 1A) We also recommend retrograde phlebography to evaluate deep venous incompetence in the lower limbs, visceral and pelvic malformations. (GRADE 1B)

Arteriography

The use of arteriography has been replaced by MRI and CT scan for the management of the CVM in general but it still remains as the gold standard for the ultimate assessment for the AVMs and warranted for the planning of the treatment of an AVMs which were already studied with non-invasive diagnostic tools.

It is necessary to have panoramic and superselective pictures in order to highlight the feeding arteries to lead to the nidus. It is possible to adopt

an arteriographic classification of AV shunts in order to guide the therapy as mentioned in details above.¹⁰⁴

We recommend arteriographies as pre-operative invasive investigations. They should be reserved for the patients who need a therapy and should be performed by the centers which deliver this therapy. (GRADE 1B)

Lymphography

Invasive tests are seldom needed for the actual diagnosis of LMs but are occasionally needed for differential diagnosis. Further studies with invasive tests such as direct puncture percutaneous lymphangiography can be generally deferred to later stages if there is a need for refining the diagnosis or if surgical or other invasive therapeutic measures are considered. Otherwise, these should be reserved for road-mapping in subsequent therapy if needed.

Conventional oil contrast lymphangiography, especially if coupled with CT scan, is still advantageously employed in selected patients with chylous dysplasia and gravitational reflux disorders in order to define more clearly the extension of the pathologic alterations and sites of lymphatic and chylous leakage. These are the only diagnostic investigations that can clearly demonstrate pathologies of chylous vessels, chylous cyst and thoracic duct in cases of chylothorax, chylous ascites, protein losing enteropathy, etc.^{39, 40, 208, 209}

For most instances, lymphography has been replaced by lymphoscintigraphy in the diagnosis of lymphedema. There is a revival in the use of lymphography in case of lymphoceles, and pathology of chylous reflux. In this case a direct puncture of inguinal nodes is made under ultrasound and lipiodol infused. The procedure causes the inflammation of the lymphatic pathways and may be curative.^{210, 211}

Nuclear Medicine Evaluation

Whole body blood pool scintigraphy (WBBPS)

WBBPS using Tc99 is a very useful tool to detect the presence of a vascular malformation.

With a single examination it is possible to check the presence of a vascular malformation in the whole body. Their strength is the possibility to investigate whole anatomic structures in one examination. It gives some quantitative data on the blood trapping of the lesion and this allows the possibility to assess the results of treatment.²¹²⁻²¹⁴

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 the evaluation of therapy to assess the progress of treatment and the natural course of the VM lesion with some numerical values.²¹⁵⁻²¹⁷ It can exclude the LM where the absence of an abnormal blood pool over the lymphatic lesion is the typical finding.^{6, 20}

WBBPS is also an excellent optional test for the AVM evaluation as well. But it is rather more useful for the screening of hidden CVM lesions throughout the body and also for a qualitative analysis of the AVM lesion along the course of the multisession therapy as a cost-effective measure. It is an excellent tool for the routine follow-up on the progress of treatment and its natural course as well when TLPS is not feasible/available.⁷

We recommend Whole body blood pool scintigraphy as a very useful tool to detect the presence of a vascular malformation throughout the body. (GRADE 1B)

Transarterial lung perfusion scintigraphy (TLPS)

Scintigraphy is not an essential examination necessary for the diagnosis of AVM and/or CVM in general but remains an option for a secondary investigation only in selected cases. TLPS^{7, 57, 91} has a unique role in determining the degree of AV shunting by the AVM lesion within an extremity.²¹⁸

TLPS has a special value to detect and assess a micro-AV shunting lesion, which is often difficult with conventional techniques. Micro-AVMs frequently exist in the combined form of CVM, the hemolymphatic malformation (HLM), and its delayed or overlooked diagnosis with subsequent progress beyond the optimum time for the interception can be avoided with TLPS alone.^{7, 57}

TLPS allows not only to quantify the AV shunt

present in a malformation^{66, 67} but also provides quantitative measurement of the shunting status during therapy. TLPS may replace the substantial role of traditional arteriography as a follow-up assessment tool for extremity AVMs.

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.^{7, 57}

The Panel recommends transarterial lung perfusion scintigraphy to quantify the AV shunt in an AVM when indicated. (GRADE 2B)

Radionuclide lymphoscintigraphy (LSG)

LSG is a functional study that complements the anatomical information provided by lymphangiography. There are no standardizations nor is there a gold standard as of yet.^{39, 40, 219-222}

LSG, performed with injection of 99mTc-labeled human serum albumin or 99mTc-labeled Sulphur Colloid subcutaneously into the first and second web-space of the toes or fingers, is the test of choice to confirm or exclude lymph vessel pathology as the cause of chronic limb swelling.^{39, 40}

Movement of the colloid from the injection site, transition time to the knee, groins or axilla, absence or presence of major lymphatic collectors, number and size of vessels and nodes (e.g. popliteal nodes), the presence of collaterals and reflux, symmetric activity with the opposite side are recorded and used for interpretation.²²³ Semi-quantitative assessment has been reported, and most recently, the technique of quantitative assessment of transit time from the foot to the knee was also validated²²⁴⁻²²⁸

LSG represents the main examination to evaluate the lymphdynamics of the limbs. This will be recorded in rest, after exercise, and one hour of daily activity. With this examination it is possible to detect the presence of deep and superficial lymphatic vessels and the presence or absence of reflux.^{7, 55, 59} In patients with genital and abdominal lymph leakage there is an indication for SPECT examination to visualize the intraabdominal lymph node status.⁵⁷

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).²²⁹⁻²³¹

LSG remains the gold standard for lymphatic

function evaluation since the LSG is the only test that can clearly indicate lymphatic function. Radionuclide lymphoscintigraphic findings provide the proper clinical and/or laboratory staging that may be essential for proper clinical management.

LSG, along with clinical evaluation, is the most essential component for the diagnosis of chronic lymphedema.^{39, 40}

LSG is extremely useful for identifying the specific lymphatic abnormality and has largely replaced conventional oil contrast lymphography for visualizing the lymphatic network. LSG can easily be repeated with minimal risk. Data and images obtained from the study identify lymphatic (dys)function, based on visualization of lymphatics, lymph nodes, and dermal backflow as well as semi-quantitative data on radiotracer (lymph) transport.^{39, 40}

However, the LSG has not been standardized with regard to the various radiotracers and radioactivity doses, different injection volumes, intracutaneous vs. subcutaneous injection site, epi- or sub-fascial injection, number of injections, different protocols of passive and active physical activity, varying imaging times, static and/or dynamic techniques.²²³

The Panel recommends lymphoscintigraphy as the most essential non-invasive test for a morphodynamic evaluation of the lymphatic circulation. (GRADE 1B)

Laboratory Tests

Coagulation Studies in Venous Malformations

Coagulation disorders occur at a high frequency in patients with extensive VMs and may result in potentially severe thrombo-embolic events and hemorrhagic complications.^{6, 20} Extensive VMs are often associated with a 'localized intravascular coagulopathy' (LIC). LIC is due to stagnant flow in extratruncular lesions resulting in a cycle of ongoing intravascular thrombosis and fibrinolysis. Secondary hypofibrinogenemia (von-Willebrand-Juergens-syndrome) may follow resulting in spontaneous hemorrhage.

The pathogenesis of LIC in VMs is different from that of KMS associated with certain vascular tumors²³²⁻²³⁴ although both coagulopathies

are closely linked.^{235, 236} The differentiation between the two coagulopathies is critical as the 'early detection' of KMS is warranted before it progresses to severe coagulopathy with multi-organ failure. KMS never develops in GLUT-1 positive HOI but in KHE or tufted angiomas. Progressive NICH accompanies the highest risk.^{36-38, 51-53}

Currently, there are no evidence-based guidelines to advocate screening for coagulopathy in patients with potentially life-threatening VMs. It is important to follow an accurate diagnostic algorithm for coagulopathies associated with especially extensive VMs involving large surface areas, muscle involvement and/or palpable phleboliths.^{6, 20}

Assessment of the coagulation profile and D-dimer levels is indicated in patients with extensive VMs. 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 thrombophlebitis or thrombo-embolic events. D-dimer can detect a sign of consumptive coagulopathy which is common among VMs.²³⁵

Elevated D-dimer among the symptomatic VMs has a unique value for the clinical assessment of the severity of the VM lesions although D-dimer in general is highly non-specific. D-dimer levels may also assist in the diagnosis of occult lesions and help differentiate GVMs and LMs (normal D-dimer levels) from other multifocal venous lesions.²³⁷ Therefore, in addition to imaging studies, plasma D-dimer representing a direct measurement of endogenous fibrinolysis as a biological marker should be evaluated in the diagnosis and follow-up of VMs.

Patients with *extensive* VMs or *high risk* lesions in particular should undergo the following laboratory tests:^{6, 20}

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

The Panel recommends D-dimer measurements to detect elevated values linked to the presence of VMs, platelet count and fibrinogen levels in Kasa-

bach Merritt syndrome often associated with kaposiform hemangioendotheliomas. (GRADE 1B)

Histology

Biopsy should be reserved to make an accurate diagnosis and is mostly required when the lesion is suspected to be a tumor. Biopsy in particular may be required to differentiate between AVMs, NICH and vascular sarcomas. Histologic differentiation between HOI and congenital hemangiomas may be required and can be facilitated by GLUT-1 staining of HOI which persists also after regression. Biopsy may also be required to differentiate between GVM and BRBNS. GVM are lined by cuboidal glomus cells that stain positive for smooth muscle actin and myosin and is histologically differentiable from BRBNS.^{82, 83, 161-164}

Recently, immunohistochemistry has been used in the study of hemangiomas and supports a new classification of the pediatric liver vascular tumors based on the expression of GLUT-1 as a substitution of the old and confusing term of hepatic infantile hemangioendothelioma:

GLUT-1 positive expression is usually demonstrated in multifocal, and diffuse hepatic infantile hemangioma, which shares clinical and morphological features with cutaneous infantile hemangioma. Diffuse neonatal hemangiomatosis is a disorder characterized by multiple cutaneous and hepatic hemangiomas.

Therefore, timely identification of GLUT-1 expression is crucial for children with hepatic hemangiomas in view of improved management before reaching to the liver transplantation. In the last 5 years propranolol has dramatically changed the scope of children with hepatic hemangiomas. Prognosis is currently considered as favorable and those previously considered as unfortunate patients are not anymore candidates for liver transplantation.¹⁶¹⁻¹⁶⁴

The Panel recommends biopsy to be reserved only for unclear cases. (GRADE 1B)

Endoscopic evaluation

Endoscopic examinations are recommended when vascular anomalies are suspected to involve intra-cavity organs. This is usually performed when investigating causes of occult bleeding.

CVMs located on the face and neck often require early pharyngo-laryngo-tracheoscopy as the possible associated mucosal involvement may result in bleeding, infection or respiratory complications. Conventional imaging techniques may not be precise enough to detect such lesions. Endoscopic identification and destruction of the lesion may be achieved during the same session.

Malformations located in the pelvic cavity and lower extremities often need procto-sigmoidoscopy, urethroscopy, and/or vaginoscopy (colposcopy) for early detection before bleeding occurs. This is especially true in patients with KTS which accompanies a high incidence of gastrointestinal and genitourinary involvement.

Arthroscopy is indicated to assess lesions involving the knee as small lesions are frequently not detected by conventional imaging techniques. Accurate assessment is required for subsequent laser coagulation. Patients with BRBNS need regular esophago-gastro-duodenoscopy and complete colonoscopy due to the high risk of gastrointestinal mucosal involvement that can cause severe bleeding.

HOI with perioral/intraoral localizations may require an early pharyngo-laryngo-tracheoscopic evaluation for an early detection of accompanied subglottic or tracheal hemangioma before clinical symptoms occur. The vulvar lesion often needs a vaginoscopy/colposcopy and urethroscopy, while perianal lesion needs a proctoscopy.

Genetic testing and family screening

Germline and somatic mutations have been identified in a number of vascular anomalies. Germline mutations were identified when practitioners observed a familial occurrence of some vascular lesions, and blood samples from these individuals enabled researchers to identify these mutations. Sporadic syndromes are thought to occur due to mosaic distribution of somatic mutations that are detected from studies of affected tissue.^{27-31, 238-242}

Why, how and when to test patients and families for potential genetic mutations?

Why to perform genetic testing: identification of germline mutations may be important for a number of reasons. There may be a strong family history of affected individuals (e.g. HHT).

However, certain vascular anomalies occur

with variable penetrance, such that parents of the proband patient may harbor a genetic mutation without overt expression of the disorder (e.g. GVM). If these parents are interested in further offspring (and the genetic mutation has been identified), prenatal genetic testing can be offered.

Options include chorionic villus sampling, amniocentesis, or pre-implantation genetic testing with in vitro fertilization of an unaffected embryo. Identification of the PTEN mutation requires counselling regarding the necessity for early and consistent surveillance for early detection of malignancies. Additionally, affected patients can be educated about their chances of having affected offspring. (Appendix C and D)

Identification of somatic mutations may have implications for new therapies. In many cases, discussion with a specialist in human genetics and/or genetic counsellor is recommended. In the USA, many insurance plans require prior authorization for this testing, which may be costly. Some research laboratories are interested in patient/family blood and/or tissue samples for genetic studies. Updated information regarding available tests and laboratories which perform them is available at the GeneTests website: <http://www.genetests.org/>

Follow-up assessment

Follow-up is necessary to evaluate the natural evolution of the pathology and/or the therapy results. The follow-up assessment may be carried based on non-invasive investigations (MRI and ultrasound). A temporary enlargement of the malformation lesion may be normal reaction after intravascular therapy. The results may also be evaluated using WBBPS.

We recommend follow-up evaluation to evaluate the natural evolution of the pathology and/or the therapy results. The follow-up shall be based on non-invasive investigations (MRI and ultrasound). (GRADE 1B)

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Received on April 19, 2014; accepted for publication on May 20, 2014.

Epub ahead of print on October 6, 2014.

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

Grading Recommendations According to Evidence¹ (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 studies	Weak recommendation, best 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

Appendix B. Abbreviations

AVM	Arteriovenous Malformation
CM	Capillary Malformation
CT	Computed Tomography
CVM	Congenital Vascular Malformation
CW-Doppler	Continuous Wave Doppler
DUS	Duplex Ultrasound
GLUT-1	Glucose Transporter-1
GVM	Glomovenous Malformation
HHT	Hereditary Hemorrhagic Telangiectasias
HOI	Hemangioma of Infancy
KHE	Kaposiform Hemangioendothelioma
KTS	Klippel-Trenaunay Syndrome
LM	Lymphatic Malformation
MRI	Magnetic Resonance Imaging
NICH	Non-involuting Congenital Hemangioma
RICH	Rapidly Involuting Congenital Hemangioma
VM	Venous Malformation

Appendix C. Genetic Mutations in Vascular Anomalies

Syndrome Clinical Manifestations	Genetic Mutation (Reference)
Cutaneous and/or Cutaneomucosal Venous Malformations	Tie-2 activating mutation Germline mutation Wouters <i>et al.</i> , 2010
Hereditary Hemorrhagic Telangiectasia (HHT) Multifocal arteriovenous malformations Punctate small AVMS in skin, mucous membranes; larger AVMS in lungs, liver, and brain Epistaxis, gastrointestinal and intra-oral bleeding	HHT1 - Endoglin HHT2 - ALK-1 (ACVRL-1) HHT + juvenile polyposis MADH4 Germline mutation McDonald <i>et al.</i>
PTEN Hamartoma Syndrome Arteriovenous malformation/thyroid disorders/tricholemmas/cancer predisposition	PTEN mutation Germline mutation Tan, <i>et al.</i> 2007;Blumenthal <i>et al.</i> , 2008 (3, 4)
Arteriovenous malformation/capillary malformation Arteriovenous malformation with multiple cutaneous capillary malformations	RASA-1 mutation Germline mutation Germline mutation Glomulin Gene mutation
Glomuvenous malformation Multifocal nodular, or plaque-like and segmental, variable color (pink, purple, dark blue)	
CLOVE Syndrome Congenital Lipomatous Overgrowth (fatty truncal mass), Vascular Malformations, Epidermal nevi +/- renal, orthopedic anomalies	PIK3CA somatic mutation Kurek <i>et al.</i>
Capillary malformation	GNAQ somatic mutation Shirley <i>et al.</i>
Proteus Syndrome	AKT1 somatic mutation Lindhurst <i>et al.</i> 2001&2013 (9, 10)
Capillary Malformation Microcephaly	STAMBP (Signal-Transducing Adaptor Molecule Binding Protein) 2p13.1 McDonnell <i>et al.</i> 2013 (11)
Lymphedema	Many genes – see below Connell <i>et al.</i> 2013 (12)

Appendix D. Genetic Mutations in Lymphedema Syndromes

Syndrome	Clinical Features	Genetic Information (Reference)
Turner Syndrome	Short stature, broad chest, widely spaced nipples, skeletal and endocrine abnormalities, congenital lymphedema, infertility	XO
Noonan's Syndrome	Lymphedema, characteristic facies webbed neck, cardiac skeletal, ophthalmologic, hematologic, neurologic abnormalities	Sporadic or autosomal dominant genetic heterogeneity mutations of genes involved in RAS-mitogen-activated protein kinases (MAPK) signal transduction pathway PTPN11 (Protein-Tyrosine Phosphatase, Nonreceptor-Type, 11) 12q24.1 SOS1, RAF1, KRAS, MEK1 (MAP2K1), NRAS, BRAF, SHOC2, CBL Tartaglia, <i>et al.</i> (13, 14)
Klinefelter Syndrome	Tall stature, sparse facial and body hair, taurodontism, lymphedema, gynecomastia, microorchidism, sterility, autoimmune disorders, emotional and learning disorders.	XXY
Primary congenital lymphedema		Autosomal Recessive Chr 5q35.3 Flt4 (VEGFR3 mutation) Ghulamkarpour, <i>et al.</i> (15, 16)

Syndrome	Clinical Features	Genetic Information (Reference)
Hereditary Lymphedema Type IA Nonne-Milroy Lymphedema Milroy Disease Primary Congenital Lymphedema;PCL	Early onset lymphedema	Autosomal Dominant, or sporadic (de novo) Chr 5q35.3 Heterozygous mutations in kinase domain of VEGFR3 Ghalamkarpour, <i>et al.</i> Karkkainen, <i>et al.</i> Irrthum, <i>et al.</i> (16-18)
Lymphedema type IB (LM-PH1B;611944) locus on chromosome	Onset occurred in early childhood, maximum manifestations at puberty, lower limb lymphedema	Autosomal Dominant Chr 6q16.2-q22.1 Malik, <i>et al.</i> (19)
Hereditary lymphedema, Type IC	early onset, between 0 and 20 years of age, lower limb lymphedema, then upper limb	Chr 1q41-q42 GJC2 gene mutation (Gap Junction Protein, Gamma-2;Connexin 47) Ferrel, <i>et al.</i> (20)
Primary non-syndromic lymphedema (Meige disease;Lymphedema Praecox) Hereditary lymphedema type I	peripubertal onset lymphedema Female predominance	Familial however gene mutation not yet identified
Recessive primary congenital lymphedema	pubertal or later onset lymphedema	VEGFR3 mutation Ghalamkarpour, <i>et al.</i> (16)
Lymphedema-Distichiasis Syndrome	lower-limb lymphedema, often asymmetric, peripubertal onset, distichiasis (anomalous eyelashes - double set or a single hair), cardiac defects, cleft palate, extradural cysts, and photophobia, early onset varicose veins	Autosomal Dominant Chr 16q24.3 FOXC2 Brice, <i>et al.</i> , Fabretto <i>et al.</i> , Fauret <i>et al.</i> , Mellor, <i>et al.</i> (21-24)
Hypotrichosis-lymphedema-telangiectasia (HLTS)	Leg lymphedema, telangiectasias	Autosomal recessive or dominant Chr 20q13.33 SOX18 Irrthum, <i>et al.</i> , Downs <i>et al.</i> (25, 26)
Microcephaly Lymphedema Chorioretinopathy Syndrome	Microcephaly, microphthalmos, +/- non-inflammatory chorioretinopathy, +/- mental retardation, lymphedema	Autosomal Recessive Chr 10q23.33 KIF11 (Kinesin Family Member 11) Ostergaard, <i>et al.</i> , Hazan, <i>et al.</i> (27, 28)
Emberger Syndrome	Myelodysplasia (+/- monosomy 7-)à acute myeloid leukaemia (AML), primary lymphedema, +/- warts, deafness, mild hypotelorism, webbed neck, thin fingers	Familial reports Chr 3q21.3 GATA2 Mansour, <i>et al.</i> (29)
Epidermodysplasia verruciformis (WILD Syndrome)	Warts, cell-mediated Immunodeficiency, Lymphedema, anogenital Dysplasia	Human Papilloma Virus-associated Kreuter, <i>et al.</i> (30)
Lymphedema-lymphangiectasia-mental retardation (Hennekam) syndrome	Lymphedema, lymphangiectasia, developmental delay, flat face, flat, broad nasal bridge, hypertelorism, glaucoma, dental anomalies, hearing loss, renal anomalies	Chr 18q21.32 CCBE1 gene (Collagen And Calcium-Binding EGF Domain-Containing Protein 1) Hennekam <i>et al.</i> , VanBalkom, <i>et al.</i> , Alders, <i>et al.</i> (31-33)
Yellow nail syndrome	Chronic sinusitis, bronchiectasis/pleural effusion, yellow nails (distinctive appearance from lymphedema-associated yellow nails)	N/A
Lymphedema-cholestasis syndrome (Aagenaes syndrome)	Severe neonatal cholestasis, chronic extremity lymphedema	Chr 15q Bull <i>et al.</i> , Fruhwirth <i>et al.</i> (34, 35)
Osteopetrosis, lymphedema, hypohidrotic ectodermal dysplasia, and immunodeficiency (OL-HED-ID)	osteopetrosis, lymphedema, hypohidrotic ectodermal dysplasia, immunodeficiency	Chr Xq28 Nemo (NF-Kappa-B Essential Modulator) Gene Mutation Roberts <i>et al.</i> (36)
Stewart-Treves syndrome	Lymphangiosarcoma in chronic lymphedema	Durr, <i>et al.</i> , Komorowski, <i>et al.</i> (37, 38)

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