CONGENITAL VASCULAR MALFORMATIONS SHORT REVIEW

Contemporary Interpretation of Congenital Vascular Malformations: Extratruncular or Truncular lesions

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Abstract Due to the wide range of clinical presentations, degree of severity and its location, together with unpredictable clinical course and erratic response to treatment with high recurrence by its nature/pathogenesis, congenital vascular malformation (CVM) remains a most challenging and confusing diagnostic and therapeutic clinical entity. Indeed, old definition of the CVMs based on only the clinical findings and also the classification with name-based eponyms through the last century added more confusion and failed to provide proper information necessary for its advanced management. But Hamburg Classification and ISSVA Classification have been established to meet its mandate for the contemporary management through last two decades as new classifications. The role of old classification became obsolete, no longer needed for contemporary management of the CVMs since both new classifications were based on advanced knowledge of the anatomy, embryology and pathophysiology involved to the CVM pathogenesis as birth defects affecting entire vascular system: artery, vein, and lymphatics. Hamburg Classification can provide more safer clinical guide with its subclassification based on embryological characteristics of the CVM lesions depending upon the stage of embryogenesis when the developmental arrest occurs: 'extratruncular' type for the lesions originated from the 'early' classified with the potential for growth and proliferation to cause the recurrence and subsequent morbidity while 'truncular' type for the lesion from the 'late' stage with more serious hemodynamic impacts. This subclassification would give a role as the clinical histopathological classification to bridge to the future genetic classification till available. ISSVA Classification also provides a clear guideline for the differentiation between the vascular tumor, known as hemangioma, and vascular malformation which was further subgrouped based on the flow characteristics. Further, 'updated' ISSVA classification of 2014-2016 is a hybrid classification matching the anatomical and the genetic characteristics of many pathologies. Hence, correct understanding on these two classifications will be critical for proper management of every CVM lesion based on correct identification and confirmation of each CVM lesion on this embryological subtype.

Keywords congenital vascular malformation (CVM); Hamburg Classification; ISSVA Classification; embryological characteristics: 'extratruncular' type; 'truncular' type

Main Text

Following the first document/record on the vascular malformation involved to the scalp by Guido Guidi of France in the 16th century - personal physician of King Francis I of France- for the first time in Western history, there have been numerous records on various shapes/ appearances of the vascular malformation through many centuries[1].

Nevertheless, till the 17th Century when William Harvey introduced a new concept of blood circulation in 1628 through "Excercitatio anatomica de motu cordis et sanguinis in animalibus", abnormal circulation such as arteriovenous (AV) connection to cause AV malformation (AVM) had no place to belong/classify as a disease entity.

Table I: ISSVA Classification of CVM
Overview table of ISSVA classification 2018, modified

Vascular Anomalies

Vascular Tumors	Vascular Malformations

	Simple	Combined	Of Major Named Vessels	Associated with Other Anomalies
Benign	Capillary malformations	defined as two or more vascular malformations found in one lesion	abnormalities in the origin/course/number of major blood vessels that have anatomical names	syndromes in which vascular malformations are complicated by symptoms other than vascular anomalies
	Lymphatic malformations			
Locally aggressive or Borderline	Venous malformations			
	Arteriovenous malformations *			
Malignant	Arteriovenous fistula *			

But, based on such monumental discovery of blood circulation system, numerous vascular malformation cases were documented through the next two - 18th and 19th- centuries; one legendary document by two French physicians, Klippel and Trenaunay (1900) along the turn of the last century became the beginning of 'name-based eponyms' to open the era of 'angiodysplasia' based on the 'old' concept.

Indeed, before the modern technology was available for modern diagnosis of the congenital vascular malformations (CVMs), most of the conditions were named after the physicians who described first entirely based on the clinical findings alone (e.g. Klippel and Trenaunay Syndrome).

Such old nosology and terminology of CVMs with no proper information on etiology, anatomy, and pathophysiology, failed to provide appropriate defining of critical characteristics among the CVMs. This old classification of 'angiodysplasia' era based on clinical presentation alone was unable to provide proper anatomical and pathophysiological information that is required for proper advanced evaluation, diagnosis, and treatment, only adding more confusion.

Old classification with a lack of such critical information (e.g. vascular malformation versus vascular tumors/hemangioma) often misguided to make the status further worsening with mistaken terminology (e.g. cavernous/capillary hemangioma versus infantile/neonatal hemangioma).

Indeed, this group of birth defects with anomalous vascular structures presents various conditions of vascular defects anywhere in the (peripheral) vascular system: artery, vein, and/or lymphatics, as the outcome of defective development during various stages of embryogenesis with different characteristics.

Hence, the CVMs remained the most confusing vascular disorder through the last century, keeping its notorious reputation as an 'enigma' among the vascular disorders. And a new classification system was mandated to provide accurate anatomo-patho-physiologic information/ status of the CVMs with standardized definition as the outcome of the developmental arrest during various stages of embryogenesis.

Modern diagnostic and therapeutic technology provided appropriate basis for new contemporary

classification as a new guideline for better understanding of this complex problem replacing old terminology/ classification of the CVMs[2-4].

A consensus workshop was held in Hamburg 1988 gave a new momentum to seek advanced classification to replace the old name-based eponyms and meet the mandate for the contemporary management of the CVMs with more logical classification with appropriate differentiation of anatomic, pathophysiologic, and clinical presentations among various CVMs.

Prof. Edmondo Malan (1964) proposed a new classification to distinguish the different venous, arterial and other associated malformations for the first time[5-8], which gave a momentum for subsequent two new classifications: Hamburg Classification[9-12] and ISSVA* Classification[13-16]. And the name-based eponyms (e.g. Parkes Weber syndrome) are no longer essential for the contemporary management of the CVMs. *ISSVA: International Society for the Study for Vascular Anomaly

Indeed, Mulliken et al. proposed another new concept with a new classification system for 'vascular anomaly' as a whole following the Hamburg Consensus workshop. This new classification was later adopted by ISSVA (International Society for the Study of Vascular Anomalies) officially as the ISSVA Classification (1996), accommodating both vascular malformations that are developmental aberrations and vascular tumors that proliferate[17-20].

Hence, ISSVA Classification (Table I) defined the vascular tumor and vascular malformation under the name of "vascular anomaly". ISSVA classification of 2014-2016 is a hybrid classification matching the anatomical and the genetic characteristics of many pathologies. In this classification there is no differentiation between truncular and extratruncular forms although much beneficial to guide surgical and endovasal therapy more successfully. Genetic features, however, are important for target therapy though this kind of the therapy is restricted to few pathologies.

Eponyms in the ISSVA classification is based on the genetic issues: similar phenotypes are caused by different genotypes. It elicits that the cause of the malformation is genetic (germinal or mosaicism) and the anatomical characteristics are fundamental for a surgical or end-vascular treatment.

Hamburg Classification (Table II) has made more specific verification of the vascular malformation with subclassification based on its embryological background while limited its scope only to the vascular malformations.

Table II - Hamburg classification of congenital vascular malformations (CVMs)

Primary classification*	
	Arterial malformation
	Venous malformation
	Arteriovenous malformation
	Lymphatic malformation
	Capillary/Microvascular malformation
	Combined vascular malformation:
	Hemo-lymphatic malformation
Embryological Subclassification**	
	Extratruncular forms (former 'angioma')
	Diffuse, infiltrating
	Limited, localized
	Truncular forms
	Obstruction and/or Stenosis
	Aplasia; Hypoplasia; Hyperplasia
	Membrane; Congenital spur
	Dilatation
	Localized (aneurysm)
	Diffuse (ectasia)

** Modified based on the consensus on CVM through the international workshop in Hamburg, Germany 1988 and Seoul, Korea 1995.*
***Developmental arrest at the different stages of embryonal life: earlier stage – extratruncular form; latter 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.*

Accordingly, the CVM is classified first to arterial malformation (AM), venous malformation (VM), lymphatic malformation (LM), capillary malformation (CM), and arterio-venous malformation (AVM) based on its (pre)dominant vascular components; although the majority of the CVMs exist alone as an independent form, infrequently the CVM may exist as a combined form affecting more than one vascular system as a mixture of various CVMs, classified separately to hemo-lymphatic malformation (HLM)[21-24]. Therefore, the CVM exists either alone as one single type of (pre)dominant lesion or mixed

condition with other CVMs, locating anywhere within the body in various numbers, shapes, extents/ degrees, and condition.

But they also identified two different groups with the morphological differences among the lesions, one involving the main vessel trunks often with a direct communication (“truncular" form) and another occurring peripherally as separate defects (arteriovenous angiomas). Indeed, all the CVM lesions were found to belong to one of two distinctive characteristics originated from the embryological background as subclassified by Hamburg Classification, which is critical for their management despite such extensive variety of the lesions[25, 26].

Through the workshop, Belov et al. re-introduced an old embryologic term: “extratruncular” to stop the confusion generated by old term of “angioma” (c.f. hemangioma). They borrowed the term: 'extratruncular' from old embryology school (Sabin F.R. 1917) and successfully replaced old term: angioma to clear the confusion on the group of the vascular tissue clusters originated from the 'early stage' of embryogenesis.

These 'angiomatous' lesions were re-described as “extratruncular” lesion based on their distinctively different morphology from “truncular defects” and this new term 'extratruncular' successfully replaced the often-misleading old term “angioma”.

They also borrowed the term: 'truncular' (Woolard H.H. 1922) for the group of lesions directly involved to the 'named' vessels as the outcome of defective development during the 'later' stage of vascular trunk formation[27-29].

Based on the consensus through the Hamburg workshop, the Hamburg Classification was formulated as a new system further to subclassify the CVM lesions based on these unique embryological characteristics of the CVMs as an outcome of the developmental arrest in the vascular system in two different stages of angiogenesis: 'extratruncular' and 'truncular' lesions.

Extratruncular form of the lesions are the result of the developmental arrest occurred in the 'earlier' stage of embryonic life (the reticular stage) where the primitive vascular structures are still in the “reticular network stage” before evolving into mature structures through the later stage of vascular trunk formation (pretruncal stage): “prematured/pretruncal embryonic lesion”. The (endothelial) cells present in this remnant of primitive network, retain the mesenchymal cells (angioblasts) characteristics of mesodermal origin maintaining its ability to proliferate. With this unique evolutional potential, this embryonic tissue remnant takes often unpredictable biological behavior.

When the condition/milieu should meet with adequate stimulation by various intrinsic (e.g., menarche, pregnancy) and extrinsic (e.g., trauma, surgery) mechanisms, it grows steadily with high risk of a recurrence after suboptimum management in particular.

Extratruncular lesion presents as amorphous vascular clusters in clinically diffuse infiltrating condition; it exists independently with no direct involvement of matured vessels. It therefore, gives a mechanical impact to the surrounding tissues/organs in addition to its hemodynamic impact to its belonging vascular system.

Nevertheless, an infiltrating extratruncular lesion is far more complicated than a truncular lesion because of this unique embryologic characteristic with a higher risk of progression and has more destructive potential than the truncular lesion in general.

Truncular form of the lesions are the defect occurred during the 'later' stage of the fetal development while the vascular trunk is formed (truncal stage), following the reticular stage of vascular development: “matured lesion”. Truncular lesion therefore, presents as a variety of the conditions as the outcome of defective vessel trunk formation: obstruction/dilatation of the formed vessel (e.g. vein web, venous aneurysm), or aplasia, hypoplasia, and/ or hyperplasia of the vessel development (e.g. agenesis/ rudimentary deep vein).

Truncular lesion also lost the embryonic characteristics of the mesenchymal cells (angioblasts) through normal maturation process of the vessel wall and no longer has its potential to grow with no risk of recurrence (cf. extratruncular lesion). But it has generally more serious hemodynamic impact in varying degrees of severity depending upon the involved vascular system (e.g. marginal vein, popliteal vein aneurysm, iliac vein stenosis)

A fetal (truncal) vessel, which failed to go through a normal involution process and remain after the birth (e.g. sciatic vein, marginal vein), also belongs to this truncular lesion as one of the defective developments along the last stage of embryogenesis while the vessel trunk is matured[30, 31].

Therefore, this embryological subtype based upon the different embryological stage when the defective development occurs, would result in a wide range of clinical presentation with unpredictable clinical course, erratic response to the treatment with high risk of recurrence and morbidity. Precise identification of the subtype of CVM lesion, either extratruncular or truncular, will remain critical to any CVM lesions before consideration of any treatment strategy.

However, all these truncular lesions cause potentially much more serious hemodynamic impact to the involved vascular system (e.g. marginal vein, fistulous AVM,

primary lymphedema) although they no longer carry the risk of recurrence and/or continuous growth[32-35].

Hence, the treatment strategy for the extratruncular lesion should be based on the risk of 'recurrence' as an embryonic tissue remnant while the 'truncular' lesion should give the priority on its hemodynamic impact for the management in view of potentially serious hemodynamic consequences (e.g. suprahepatic IVC occlusive disease)[36, 37].

Although the last version of the ISSVA classification did not include the differentiation between truncular and extratruncular defects, this subclassification would give additional benefits as the clinical histopathological classification to bridge to the future genetic classification till widely available for proper target therapies for selected pathologies which are approved by FDA.

ISSVA classification, however, also retains quite a few old name-based eponyms but to highlight the concomitant pathologies (e.g. pulmonary and hepatic av shunts in Rendu Osler syndrome; pleural effusion in yellow nail syndrome) and not for the classification of the vascular defect per se.

Conclusion

'Extratruncular' lesion of CVM maintains embryonic characteristics of "evolutional potential" originated from the mesenchymal cells to grow when the condition is met as the outcome of developmental arrest in 'earlier' stage of embryonic life.

But 'Truncular' lesion originated from the 'later stage' no longer possesses this potential while it accompanies potentially serious hemodynamic impact to affected vascular system -arterial-venous-lymphatic system.

Hence, their management principle and strategy should be fundamentally different between the extratruncular lesion and truncular lesion.

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