5 Epidemiologic Aspect of Congenital Vascular Malformation

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It is difficult to get exact epidemiologic data of congenital vascular malformation (CVM) due to confusing nomenclatures and definition of the CVMs in times past. Epidemiologic data available in the literatures often misguide the true incidence and prevalence of the CVMs.

Though CVM is caused by an embryonic developmental defect, it may not be clinically apparent from birth. To describe epidemiology of CVMs, we have to rely on the data of symptomatic patients with clinically apparent CVM.

Some CVM may remain quiescent throughout the remaining life. However, most of the CVM lesions grow along with age, and some of them show sudden expansion after certain events such as trauma, hormonal changes (puberty or pregnancy), or infection. We still don't know an exact mechanism to stimulate the dormant CVM lesion. Accordingly, an exact incidence of CVM cannot be estimated at the time of birth.

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European Surveillance of Congenital Anomalies (EUROCAT) is a network of population-based registries (http://www.eurocat-network.eu/aboutus/whocollaboratingcentre) for the epidemiologic surveillance of congenital anomalies covering about 30 % of all births in the European Union [1].

Even in the EUROCAT data, it is difficult to estimate an exact incidence of CVM because vascular malformation is not separately listed as a congenital anomaly but may be included in the skin anomaly, limb defect, or aortic coarctation.

According to the Bogota Congenital Malformations Surveillance Program (BCMSP) between January 2005 and April 2012, congenital anomalies at birth were detected in 1.66 % (4682 out of 282,523 births). They reported that the most frequent congenital anomalies were vascular anomalies (0.03 %), followed by hypospadias (0.028 %), and anorectal malformations (0.022 %). According to the report, 84 % of vascular anomalies were blood vessel origin and 15 % were lymphatic origin. Regarding to the anatomical distribution, craniofacial lesions were the most frequently diagnosed vascular anomalies after birth, followed by vascular anomalies at the extremities, thorax, and abdomen. However, they did not differentiate CVM from the infantile hemangioma [2].

Kennedy [3] also reported the overall incidence of CVM as 1.08 % (0.83~4.5 %) based on a comprehensive review of 238 studies on the

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literatures reporting more than 20 million births. Overall incidences of CVM were obtained from hospital records, birth certificates, and also retrospective questionnaires from intensive examinations of children. However, this study highlighted the variability in reporting methods due to differences in terminology and inconsistent diagnostic criteria.

Depending upon the embryological stage when the developmental arrest has occurred, the CVMs present different clinical characteristics. CVM lesions (extratruncular form) resulting from developmental errors during an earlier stage of the vasculogenesis have "evolution potential" even after birth while CVM lesions(truncular form) derived from the later stage of the vasculogenesis do not have such property but tend to accompany with main vessel abnormalities [4, 5].

Tasnadi [6] reported overall incidence of the CVM is 1.2 % based on a study carried on 3573 three-year-old children. According to them, infiltrating or localized venous malformation (VM) and/or arteriovenous malformation (AVM) is 0.45 %, capillary malformation (CM, port wine skin lesion) is 0.42 %, lymphatic malformation (LM)/primary lymphedema is 0.14 %, and mixed from CVM showing phlebectasia, nevus, and limb length discrepancy is 0.34 %.

Among venous predominant vascular malformations, Eifert et al. [7] also reported the prevalence of deep venous anomalies (truncular VM) among the VMs using duplex ultrasonography, venography, CT, MRI, and arteriography. Among 392 patients with CVMs, 65.5 % were confirmed as truncular VM with deep venous anomalies including phlebectasia, aplasia or hypoplasia of venous trunks, aneurysms, and avalvulia of deep vein system.

Among various types of CVMs, venous malformation (VM) is reported as the most common type of CVMs, which has been reported to occur in one of 5000–10,000 childbirths [8].

If we include clinically not significant capillary malformations (CMs), CM may be much more common than the VM which occurs in 0.3 % of childbirths [9].

However, VM is certainly the most frequent type of the CVMs requiring a medical attention.

VMs are present at birth but are not always apparent at birth. They typically become more prominent as the patient grows up, and the pronounced enlargement usually occurs from infancy to puberty; thereafter, less pronounced changes occur in adulthood [10].

Majority of LM is present at birth, with the remainder presenting by 2 years of age [11].

There are two common clinical types of pure lymphatic malformation (LM): lymphedema (diffuse LM) and lymphangioma (localized, macrocystic LM). Primary lymphedema is divided into three types by age of presentation: congenital familial lymphedema (Milroy's disease), lymphedema praecox (typically presents during adolescence), and lymphedema tarda (presents after 35 years of age). Macrocystic LMs (cystic hygroma) are usually visible at birth and may be detected by prenatal ultrasound examinations. They are frequently located on the neck, axilla, retroperitoneum, or mesentery. According to a review of 305 patients with lymphangioma in our group, their anatomic distribution was most prevalent at the head and neck (46.2 %) followed by trunk surface and extremity (44.6 %) and intra-abdominal or mediastinal (9.2 %) and showed male predilection by 1.4:1 [12].

More often, LM is combined with other forms of CVM such as VM, CM, or AVM.

Lee et al. [13] made a review on the subtypes of the LM separately among 1203 CVM patients. Predominant LM lesion accounted for 32.6 % of all patients with CVM which included 271 (69 %) patients with truncular LM and 122 (31 %) patients with extratruncular LM lesions. Of 122 patients with extratruncular LM, 89 (73 %) had the macrocystic type with a predilection for the head, neck, and thorax. Of the 271 patients with truncular LM, 247 (91 %) patients showed lymphatic channel aplasia or hypoplasia and a predilection to occur in the lower extremity. LM lesion presented as combined with VM in 9 % of 1203 CVM patients.

Table 5.1 shows the demographic features and distribution of CVM lesions according to the type of CVMs.

When we reviewed our registered 2971 CVM patients at Samsung Medical Center (SMC), VM

Table 5.1 Demographic features and anatomic distribution of CVM lesions in 2971 CVM in SMC (1992–2015)

	Number of CVM patients (%)				
	VM or venous predominant	AVM	LM or lymphatic predominant	CM only	Subtotal (%)
No (%)	1576 (53 %)	502 (17 %)	861 (29 %)	32 (1 %)	2971
Age[a], mean, year	7.0	13.8	10.3	1.6	
Male/female	1: 1.2	1: 1.2	1: 1.1	1: 1.3	
Anatomic distribution					
Extremity Lower Upper	921(58 %) 667(42 %) 254(16 %)	274(55 %) 155(31 %) 119(24 %)	439(51 %) 339(39 %) 100(12 %)	14(44 %) 11(34 %) 3(9 %)	1648(55 %) 1172(39 %) 476(16 %)
Head and neck	416(26 %)	169(34 %)	249(29 %)	12(38 %)	846(28 %)
Trunk[b]	139(9 %)	57(11 %)	124(14 %)	1(3 %)	321(11 %)
Multiple	100 (6 %)	2(0.4 %)	49(6 %)	5(16 %)	156(5 %)
		119(24 %) 2(0.4 %)	53(10 %) 41(7 %)		3(9.4 %) 5(16 %)

Patients with AVM involving CNS or pure arterial malformation were not included in this table
Abbreviation: *VM* venous malformation, *AVM* arteriovenous malformation, *LM* lymphatic malformation, *CM* capillary malformation
[a]Age at the initial presentation
[b]Trunk indicates chest, abdomen, and pelvis

or venous predominant CVM was the most common type of CVM (53 %). Among the VM patients, the lower extremity was the most frequently affected site (42 %), followed by head and neck (26 %), upper extremity (16 %), trunk (9 %), and multiple site involvement (6 %). Among extremity VM patients, 93 % was extratruncular and 13 % was truncular form VM (see Table 15.2).

LM and lymphatic dominant CVM comprised of 29 % of all CVM patients. It was also most prevalent in the extremities (51 %) followed by head and neck (29 %) and trunk (14 %).

AVM accounted for 17 % of CVM patients and most frequently found in the extremities (55 %) followed by head and neck (34 %) and trunk (11 %) (Table 5.1).

AVM is known as the least common type of CVMs representing approximately 10–15 % of all clinically significant CVM lesions [14]. Among them, "extratruncular" form comprises the vast majority of AVM lesions. Most of the current data regarding the incidence and prevalence of AVMs include AVM lesion affecting CNS [15, 16]. Epidemiologic data of AVM lesion affecting CNS is beyond the scope of this chapter; therefore, we excluded AVM affecting CNS from the SMC data.

Regarding the age of an initial presentation, we found that patients with AVM or LM presented at later age than patients with VM or CM. And male/female ratio was close to 1:1 in general.

AVMs are also known to occur with equal frequency in males and females. About half of the AVM lesions are recognizable at birth, and 30 % become clinically apparent during childhood. They have a predilection to the head and neck area than in other locations [17].

AVM lesions take dynamic clinical courses so that Schobinger classified AVM lesions into four stages based on the clinical features: Stage I (quiescence), Stage II (expansion), Stage III (destruction), and Stage IV (decompensation) [18].

Significant numbers of the CVMs are also known to remain mixed forms of CVM (e.g., Klippel-Trenaunay syndrome and Parkes Weber syndrome).

A substantial number of angiogenesis-related genes (i.e., *TIE2*, *VEGFR-3*, *RASA1*, *KRIT1*, *MGC4607*, *PDCD10*, glomulin, *FOXC2*, *NEMO*, *SOX18*, *ENG*, *ACVRLK1*, *MADH4*, *NDP*, *TIMP3*,

Notch3, *COL3A1*, and *PTEN*) have been identified in the pathogenesis of vascular malformations to provide a new base for further scientific epidemiological evaluation; however, more insight is required on the involved molecular mechanisms, which may lead to the development of therapeutic strategies for treating Klippel-Trenaunay syndrome (KTS) [19].

At the moment, there is no racial, demographic, or environmental risk factors for CVMs have been identified to date.

References

1. Loane M, Dolk H, Garne E, Greenlees R. Paper 3: EUROCAT data quality indicators for population-based registries of congenital anomalies. Birth Defects Res Part A Clin Mol Teratol. 2011;91(Suppl 1):S23–30. doi:10.1002/bdra.20779.
2. Correa C, Mallarino C, Pena R, Rincon LC, Gracia G, Zarante I. Congenital malformations of pediatric surgical interest: prevalence, risk factors, and prenatal diagnosis between 2005 and 2012 in the capital city of a developing country. Bogota, Colombia. J Pediatr Surg. 2014;49(7):1099–103. doi:10.1016/j.jpedsurg.2014.03.001.
3. Kennedy WP. Epidemiologic aspects of the problem of congenital malformations. In: Persaud TNV, editor. Problems of birth defects. Baltimore: Publisher University Park Press; 1977. p. 35–52.
4. Belov S. Anatomopathological classification of congenital vascular defects. Semin Vasc Surg. 1993;6(4):219–24.
5. Lee BB, Laredo J, Lee SJ, Huh SH, Joe JH, Neville R. Congenital vascular malformations: general diagnostic principles. Phlebology/Venous Forum R Soc Med. 2007;22(6):253–7.
6. Tasnadi G. Epidemiology and etiology of congenital vascular malformations. Semin Vasc Surg. 1993;6(4):200–3.
7. Eifert S, Villavicencio JL, Kao TC, Taute BM, Rich NM. Prevalence of deep venous anomalies in congenital vascular malformations of venous predominance. J Vasc Surg. 2000;31(3):462–71.
8. Vikkula M, Boon LM, Mulliken JB. Molecular genetics of vascular malformations. Matrix Biol J Int Soc Matrix Biol. 2001;20(5–6):327–35.
9. Eerola I, Boon LM, Mulliken JB, Burrows PE, Dompmartin A, Watanabe S, Vanwijck R, Vikkula M. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. Am J Hum Genet. 2003;73(6):1240–9. doi:10.1086/379793.
10. Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations: part I. J Am Acad Dermatol. 2007;56(3):353–70. quiz 371-354 doi:10.1016/j.jaad.2006.05.069.
11. Redondo P. Classification of vascular anomalies (tumours and malformations). Clinical characteristics and natural history. An Sist Sanit Navar. 2004;27(Suppl 1):9–25.
12. Whang DB, Lee SH, Lim SY, Lee SG, Seo JM. Surgical treatment of difficult cervicofacial lymphangioma in children. J Korean Assoc Pediatr Surg. 2015;21:1–7. doi:10.13029/jkaps.2015.21.2.1.
13. Lee BB, Laredo J, Seo JM, Neville R. Treatment of lymphatic malformations. In: Mattassi R, Loose DA, Vaghi M, editors. Hemangiomas and vascular malformations. Milan: Publisher Springer-Verlag Italia; 2009. p. 231–50.
14. Lee BB, Baumgartner I, Berlien HP, Bianchini G, Burrows P, Do YS, Ivancev K, Kool LS, Laredo J, Loose DA, Lopez-Gutierrez JC, Mattassi R, Parsi K, Rimon U, Rosenblatt M, Shortell C, Simkin R, Stillo F, Villavicencio L, Yakes W. Consensus document of the International Union of Angiology (IUA)-2013. Current concept on the management of arterio-venous management. Int Angiol J Int Union Angiol. 2013;32(1):9–36.
15. Jackson JE, Mansfield AO, Allison DJ. Treatment of high-flow vascular malformations by venous embolization aided by flow occlusion techniques. Cardiovasc Intervent Radiol. 1996;19(5):323–8.
16. Al-Shahi R, Warlow C. A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. Brain J Neurol. 2001;124(Pt 10):1900–26.
17. Kohout MP, Hansen M, Pribaz JJ, Mulliken JB. Arteriovenous malformations of the head and neck: natural history and management. Plast Reconstr Surg. 1998;102(3):643–54.
18. Schobinger R. Proceeding of ISSVA congress, Roma; 1994.
19. Delis KT, Gloviczki P, Wennberg PW, Rooke TW. Driscoll DJ (2007) Hemodynamic impairment, venous segmental disease, and clinical severity scoring in limbs with Klippel-Trenaunay syndrome. J Vasc Surg. 2006;45(3):561–7.