Epidemiology of Vascular Anomalies

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Accurate epidemiological analysis of vascular anomalies is extremely difficult to afford for several reasons:

- First, majority of vascular malformations are indolent, unnoticeable, of minimal size, and harboring no progression or disappearing spontaneously. This group of patients will never report their « problems» to any physician and therefore the anomaly will not be registered. Typical examples are nuchal or frontal capillary malformations in neonates or small lymphatic malformations in the abdominal cavity.
- Second, diagnosis of vascular anomalies remains a challenge for too many specialists. Tremendous confusion exists with regard to the classification and treatment of vascular lesions. For a long time, vascular anomalies have been categorized using inconsistent terminology, such as "hemangioma", and a significant number of patients receive ineffective and potentially harmful treatments based on this misclassification. A first version of the International Society for the Study of Vascular Anomalies (ISSVA) classification was adopted in 1996 and allowed to classify vascular anomalies into two groups (tumors and malformations). Many subsequent revisions led to the 2014 ISSVA classification system, based on clinical, histological, histochemical, and radiological findings. With the improvement of molecular and genetic understanding, the updated classification ISSVA 2018 [1] incorporated the causative genes involved in many of these lesions, opening the era of precision medicine.
- Third, there is an urgent need to establish vascular anomalies registry (VAR), an organization for the systematic collection, storage,

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analysis, interpretation, and reporting of data on subjects with vascular tumors and malformations. These information may help to increase the knowledge on epidemiology and natural history of vascular anomalies, to design new clinical trials, and to more easily select cohorts for targeted therapies. Efforts should be done by the National Health Care provider system to promote these registries. Some examples of fruitful national and international registries are those developed for liver hemangioma, PHACES syndrome, multifocal lymphangioendotheliomatosis with thrombocytopenia, or generalized lymphatic anomalies and Gorham-Stout disease.

In order to accurately evaluate epidemiology of vascular anomalies, we will follow the current ISSVA classification and nomenclature.

96.1 Vascular Tumors

96.1.1 Epidemiology of Infantile Hemangioma and Congenital Hemangioma

As 30% of infantile hemangioma (IH) are noticed at birth and 70–90% appear during the first four weeks of life, epidemiological studies based on hospital data about the incidence of IH are not useful. The incidence of IH in the general newborn population ranges between 1% and 3%, but increases to up to 15% by one year of age, as shown in a report of 973 preterm infants. The male to female ratio was 1:1.4 [2]. IH incidence increases with decreasing gestational age and birth weight, with up to 23% for those born at <1000 g compared with 1–4% for term infants. Facial involvement seems to be less common in preterm infants. For every 500 g decrease in birth weight, the risk of IH increased by 40% [3, 4]. A prospective trial showed also that the number of lesions increased in preterm patients; 40% of preterm infants had 2 to 5 lesions vs 24.5% of term infants, and 7.5% of preterm infants had more than 5 lesions compared with 3% for term infants. Analysis of birth weight association alone showed that lower birth weight also correlated with increased numbers of IH lesions [5]. A positive family history also increased the risk of IH (33% vs 15% of controls) [3]. In an epidemiological study of IH in 118 twin pairs, being female, fair-skinned, Caucasian, and having a positive family history were found to lower the threshold for hemangiogenesis, wherein extragenetic factors can trigger the appearance of this most common tumor of infancy [6]. As in vitro fertilization (IVF) techniques significantly enhance incidence of IH, countries with expanded use of IVF may experience higher rates of IH incidence [7].

Three types of Congenital hemangioma (CH) exist, including rapidly involuting (RICH), partially involuting (PICH), and non-involuting congenital hemangioma (NICH), depending on the lesion evolution. As congenital hemangiomas proliferate already in utero, they are fully present at birth. The lack of GLUT1 staining in these tumors suggests that they are biologically distinct from IH. They are rarely seen (less than 5 cases per year in tertiary referral vascular anomalies centers), with unavailable accurate epidemiological data.

96.1.2 Epidemiology of Kaposiform Hemangioendothelioma—Tufted Angioma

In the largest published series of patients, this rare tumor had a prevalence of approximately 0.91/100,000 children and an incidence of 0.071/100,000 children. It manifests in infancy in 93% of cases and neonates in 60% of cases. Overuse of the term Kasabach-Merritt phenomenon (KMP) to describe any low platelet count observed in a patient with a vascular anomaly has caused considerable confusion. It is now clear that KMP occurs with KHE and tufted angioma, and not with IH. KHE involves a spectrum of lesions from small, superficial tumors without KMP to large, infiltrative lesions with life-threatening complications including KMP. Large KHE lesions (greater

than 8 cm) or with retroperitoneum or mediastinal infiltration or extending into multiple anatomic regions confer an increased risk of KMP. Localized or disseminated coagulopathy is more commonly attributed to other vascular malformations [8].

96.2 Vascular Malformations

The epidemiology of vascular malformations remains not well-documented, with highly variable prevalence reported in the literature. The data are further challenged by the retrospective design and the fact that the disease classification and nomenclature have gone through a number of iterations over the years and disease definitions across studies may not be aligned. Vascular malformations are divided into slow-flow (venous, capillary, and lymphatic) malformations and in fast-flow (arteriovenous, AVM) vascular malformations. The 2018 ISSVA classification also incorporated gene mutations to vascular malformations. Alterations in PI3K-AKT-mTOR pathway (PIKopathy) are frequently detected in slow-flow while alterations in the RAS-RAF-MEK pathway (RASopathy) are more commonly detected in arteriovenous malformations (AVMs) and in some complex lymphatic malformations (CLAs) [9]. A report based on hospital registry in Denmark estimated an incidence of 5 per 100,000 for slow-flow vascular malformations and 0.4 per 100,000 for fast-flow vascular malformations (arteriovenous malformation, AVM). However, this study used a restricted set of International Classification of Disease-10 codes that do not well-map onto the ISSVA classification [10]. Recently, an Australian registry database evaluated prevalence of vascular malformations in a well-defined and isolated population using the ISSVA classification. In this study, the prevalence of slow-flow and fast-flow reached 1/1000 and 1/10,000, respectively [11]. Compared to other reports, the Australian registry seems to be more accurate than those available in the literature.

96.2.1 Venous Malformations

Venous malformations (VMs) represent the majority of slow-flow vascular malformation. Fraulin et al. reported that among 311 patients with vascular malformations, 39% had VMs, 31% capillary malformations, 14% slow-flow malformations, 12% lymphatic malformations, and 5% AVMs. The sex distribution was almost equal [12]. In the Australian registry, among 1233 patients with slow-flow malformation, 45% of patients had VM, representing an estimated prevalence of 45 per 100,000, with a median age at presentation was 10.7 years, ranging from 0 to 82 [11].

The frequency of VMs is probably underestimated as whole-body Doppler ultrasound examinations or magnetic resonance angiography are not routinely performed, and therefore many patients with intracranial, thoracic, or intra-abdominal aberrant venous development are not diagnosed early in life. Some true VMs such as testicular varicocele are very often incorrectly considered as acquired. « So-called » liver and vertebral hemangiomas, frequently seen in the adult population, are true VMs and not tumors.

More than 90% of VMs are sporadic and unifocal but around 1% of VM are inherited and multifocal. Genetically, VMs are typical PIKopathies: mutation in *TEK*, encoding TIE2 receptor, is observed in 60% of VMs and *PIK3CA* mutation in 20% [9]. *TEK*-related VMs encompass a range of phenotypes, including common VM (unifocal/isolated VM or multifocal sporadic VM), inherited multiple cutaneous and mucosal VM, and sporadic blue rubber bleb nevus syndrome. Glomuvenous malformation due to inherited glomulin mutations are more frequently inherited and account for 5% of VM [9].

96.2.2 Capillary Malformations

Epidemiology of capillary malformations (CM) presents significant differences when data compilation is performed at birth or later in life. Many patients with evidence of capillary anomalies in

the neonatal period will experience significant improvement of their birthmarks, remaining unnoticeable after puberty. In opposite, it is frequent to see patients with progressive darkening of CM not remarkable at birth. The birth prevalence is reported to be 0.3%, with Salmon patches being reported in up to 40.3% of infants [13]. In a single report, a total of 900 consecutive newborns delivered at the Nehru Hospital in India, over a period of 7 months, were examined for presence of skin lesions within 48 hours of birth. Salmon patches were noticed in 28.4% of newborns [14]. Incidence rates of 13.8% and 22.3% have been reported in two additional studies [15, 16]. The sex distribution appears equal.

The most important issue in the clinical management of CM is to consider their high rate of association with other vascular anomalies, genetic mutations, and syndromes. Recognizing different patterns of CM in the skin is of paramount importance. Capillary malformation-arteriovenous malformation (CM-AVM), Klippel-Trenaunay (KTS), or Sturge-Weber syndrome (SWS) are among the most characteristic diagnoses with anatomical areas involved by CM.

- CM-AVM is characterized by the presence of multiple CMs mostly localized on the face and limbs, and with AVMs and/or arteriovenous fistulas. CMs occurring in this syndrome are lighter in color, often smaller in size compared to classic CMs. They can be surrounded by a halo, and they are even confounded with *café-au-lait* lesions or mastocytosis. CM-AVM inheritance is linked to 2 genes alterations: *RASA1* and *EPHB4*. Prevalence of CM-AVM is estimated at 1/20,000 for *RASA1*-CM-AVM and at 1/12,000 for *EPHB4*-CM-AVM [17, 18].
- Klippel-Trenaunay Syndrome (KTS) is a vascular malformation syndrome comprising varying involvement of cutaneous capillaries, veins, and lymphatics with hypertrophy of soft tissue and bones of the affected limb. This syndrome is also referred to as capillary-lymphatic-venous malformation (CLVM) with hypertrophy. The estimated incidence is between 2–5/100,000 and is found equally in both sexes. KTS is associated with an activating mutation of *PIK3CA* [19]. KTS is a clinical diagnosis made by the presence of at least two of the three classic findings of localized cutaneous capillary malformations, venous anomalies, and limb hypertrophy. The presence of arteriovenous malformations is a separate entity named as Parkes-Weber syndrome.
- Patients with Sturge-Weber syndrome (SWS) characteristically have facial CM, also known as port-wine birthmark, a leptomeningeal vascular malformation, abnormal blood vessels in the eye, and glaucoma. The most common somatic mutation underlying SWS affects *GNAQ*. The incidence is of 1/20,000–1/50,000 infants, with no known sex or racial predilection [20].

96.2.3 Lymphatic Malformations

ISSVA classifies lymphatic malfromations (LMs) into macrocystic, microcystic, and mixed macro- and microcystic malformations. The estimated incidence of LMs varies between 1/6000 and 1/16,000 births and accounts for 15% of pediatric vascular anomalies in a referral pediatric institution [21].

Around 5% of LMs are diagnosed prenatally, 30% during the neonatal period and 65% by the age of 2 years [22]. However, some may only become apparent if they grow or become symptomatic. Furthermore, a large number of small thoracic or abdominal LMs remain asymptomatic and therefore undiagnosed. Nomenclature is also confusing and many patients receive different diagnosis, such as lymphodysplasia, lymphangiectasia, lymphangioma, and lymphoedema for similar entities, while others receive diagnosis such as hemihypertrophy or overgrowth syndromes when suffering from central lymphatic channel disorders. *PIK3CA* mutation is observed in around 80% of LMs [9].

CLAs are multifocal or cause defects in the central collecting lymphatic channels. They include generalized lymphatic anomaly (GLA), Gorham-Stout disease (GSD), kaposiform lym-

pangiomatosis (KLA), and central conducting lymphatic anomalies (CCLA). They are rare diseases with overlapping and variable clinical features, making their diagnostics and management challenging. PIKopathy and RASopathy have been reported in these entities [23]. There is often a female predominance, with female to male ratios estimated between 2.5 and 10 [24].

Primary lymphedema is often associated with syndromes (Noone-Milroy lymphedema, Hennekam, Noonan) and has an autosomal pattern of genetic transmission. In around 30% of primary lymphedema, mutations have been reported, including mutation of *FLT4*, the gene encoding VEGFR3. In addition to genes mutated in primary lymphoedema, an increasing number of genes are associated with nonimmune hydrops fetalis (NIHF), which may be associated with primary lymphedema. Multiple primary lymphedema phenotypes are possible, related to the organ affected by the failure of the lymphatic system such as lung effusions, intestinal lymphangiectasia with chylous ascites, chylothorax, and numerous embryonic edemas under the term of NIHF [25]. Autopsy studies suggest that approximately 0.5–1% of infants who are stillborn or die in the neonatal period have thoracic lymphatic disorders. Furthermore, this condition carries a poor prognosis with a mortality rate ranging from 50% to 98%, with an incidence of congenital chylothorax being about 1/10,000–15,000 pregnancies and a male to female ratio of 2:1 [26].

In any case, terminology, again, remains the most important problem when trying to accurately characterize different lymphatic disorders from infancy to elderly.

96.2.4 Arteriovenous Malformations

Population-based data suggest that the annual incidence of discovery of a symptomatic AVMs is approximately 1/100,000 individuals; the number of asymptomatic AVMs is thus underestimated, but is more frequently observed in disease such as Hereditary Hemorrhagic Telangiectasia (HHT). Brain AVMs occur in young adults, with morbidity and death occurring in 30–50% and 10–15% of patients, respectively. The annual risk of a first-ever intracerebral hemorrhage from an unruptured brain AVM is about 1%–3%. The hazard risk for bleeding in previously ruptured AVMs is 3.2 [27].

The incidence of pulmonary AVMs is around 1/50,000 cases. They occur twice as often in women compared to men. Approximately 10% of cases are diagnosed in infancy or childhood, followed by an increase in incidence through the fifth and sixth decades. About 70% to 75% of patients with pulmonary AVMs are diagnosed with HHT, and nearly 15% to 35% of patients with HHT are diagnosed with a pulmonary AVM [28].

In the skin, AVMs are easily recognized both clinically and by ultrasound examination, but despite their congenital origin, they are infrequently noticeable at birth. In addition, AVMs are commonly misdiagnosed in infancy and childhood as CM because the lesion is not yet pulsatile. Enjolras observed progression of AVM during childhood in 84% of patients [29].

As for CM, their frequent presentation with associated anomalies makes epidemiological data more difficult to compile.

- AVMs commonly occur in HHT (also named Osler-Weber-Rendu disease) in the pulmonary, respiratory, gastrointestinal, and cerebral circulations. The reported incidence in the U.S. is 1–2 cases per 100,000 individuals annually. The overall prevalence is estimated to be approximately 1–2 cases per 10,000 population. However, the prevalence may be underestimated because many cases may be asymptomatic. The frequency may vary considerably between populations. HHT is driven by alterations in genes *ACVRL1, ENG,* and *SMAD4* [30].
- In CM-AVM, AVMs typically arise in the skin, muscle, bone, spine, and brain. Symptoms from intracranial AVMs/AVFs appear early in life. Life-threatening complications of these lesions can include bleeding, congestive heart failure, and/or neurologic consequences.

– Parkes Weber syndrome consists of multiple micro-AVFs associated with a cutaneous capillary stain and excessive soft-tissue and skeletal growth of an affected limb.

In summary, a tremendous effort is still needed in order to improve vascular anomaly classification and nomenclature. Unified criteria for the development of uniform diagnostic and therapeutic protocols are mandatory. Appropriate data compilation from vascular anomaly centers around the world through well-managed international registries will be the only way to progress in our understanding of vascular anomaly epidemiology.

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