Progress toward understanding vascular malformations
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Introduction and outline of this thesis
Introduction

More than two decades ago Mulliken and Glowacki proposed a biological classification system to create some clarity in classifying vascular anomalies (figure 1). According to this classification, vascular lesions are differentiated into vascular tumors or vascular malformations (1). This classification system is currently the most accepted framework to classify vascular anomalies and was also accepted by the International Society for the Study of Vascular Anomalies (ISSVA) (2). Due to syndrome names and different nosology, the terminology describing vascular anomalies has been a source of confusion in the medical literature. Recently Hand et al has proven that this nosologic confusion is also widespread in standard genetic textbooks, and it is expected that many physicians still describe vascular malformations as being “hemangiomas, cavernous hemangiomas or venous angiomas” (3).

One of every three newborns has a vascular birthmark, but most of these fade away or remain small (4). A small proportion of babies are born with vascular anomalies that require referral to a center specializing in these anomalies. Vascular malformations should be differentiated from the much more common hemangiomas. Vascular tumors are divided into hemangiomas (by far the largest group), tufted angiomas, kaposiform hemangiomas and other rare tumors (5). Hemangiomas are the most common tumors during infancy. By the age of one year, approximately 8-10% of Caucasian children have at least one hemangioma (5-7). Most hemangiomas arise in the neonatal period, but subcutaneous and visceral hemangiomas may not manifest itself until the second or third months. Hemangiomas are further characterized by a proliferative phase, a stable phase and an involutary phase. By the age of 7 years 70% of hemangiomas are fully involuted, while at the age of nine years 90% have involuted. Histologically hemangiomas are composed of tightly packed sinusoidal channels, lined by rapidly dividing endothelial cells (5). Hemangiomas very seldom require treatment, but bleeding hemangiomas and lesions influencing function (eg. obstructing vision or breathing) may require intervention.

Vascular malformations are congenital lesions and are characterized by their structural defects. The endothelial cells have a normal turnover throughout their natural history (5). They are divided anatomically into capillary, venous, arterial or lymphatic malformations; or combinations. According to the flow in the lesion they can further be divided into high- or low-flow lesions. Any lesion with an arterial component is classified as a high-flow lesion. Trauma, hormonal change or sepsis may exacerbate progression of these malformations. Data on the prevalence and incidence is rare since many inconspicuous small capillary malformations are never presented and reported.
Figure 1: Classification of vascular anomalies (1)
In general the incidence is estimated to be between 0.3 and 2.1% with capillary malformations representing the majority of lesions (7-9). The distribution of vascular malformations appears to be variable in different parts of the world (7,10-12). With the biological classification suggested by Mulliken and Glowacki it is possible to make a clinical diagnosis in 90% of cases; in the other 10% some form of radiological intervention is needed for the diagnosis (5,8). Often patience is needed and with time (natural history) will it be possible to make a diagnosis in those patients where it was not possible to make a diagnosis at the first visit.

It is once that the diagnosis is made that the real problem arises. What is the best treatment for these lesions? In this day and age where our 'outside' is so important patients/parents present much earlier for advice and treatment. Internet is available to many people in the world, and many patients/parents are willing to spend hours looking for advice. It is possible for parents presenting with a young child inquiring about treatment options, to leave your outpatient clinic disappointed because treatment options are few, often unsatisfactory and with an uncertain outcome. When these patients inquire about the prognosis, we often have to inform them about the unpredictability of these lesions. Some patients / parents travel from clinic to clinic in the hope that some remedy or treatment cure will be offered. Often the patients/parents are explained that many muscles are involved by the vascular malformation (and sometimes bone), and that complete cure from the lesions will only be acquired with devastating mutilation of the affected part. Only then will these patients accept that no complete remedy is available.

Vascular malformations can present with a wide spectrum of involvement and subsequent symptoms. Capillary malformations are often satisfactorily treated with pulsed-dye laser treatment, but treatment results of other deeper located vascular malformations are often unsatisfactory, with intervention often resulting in recurrences (2,13-17). After surgical intervention, lesions often reoccurred in a more aggressive way than before surgical therapy. For that reason, treatment options have been very conservative, with patients often instructed to "live with it". Momentarily two words dominate the rules of therapeutic management of all types of vascular malformations: a multidisciplinary approach and modesty (18).

Only by defining the etiology of the pathologic process will it be possible to understand the progression of these malformations, subsequently diagnose these lesions correctly, and to ultimately treat these patients effectively. Before the pathogenesis of the abnormal vascular system is understood, we must at least understand the embryology involved in the development of the normal vascular system. Medical students and (hopefully) physicians will often open an anatomy book to study the vascular system, relying on the consistency of the vascular
Chapter 1

Determinants. It is only once we realize that many blood vessels (with their proper diameter) are formed even before the heart of the embryo starts beating, that we really appreciate the real complexity of the embryology of the vascular system (19). Even when we look at embryology textbooks we start realizing how much is speculation (19). With molecular and genetic studies we are now able to study some of the mechanisms that control the development of the vascular system. Our quest to treat cancer has stimulated our will to understand the vascular system (angiogenesis), and since the 1970's our knowledge about that growth of capillary blood vessels has exponentially increased. Long term in vitro culture of capillary endothelial cells and the discovery that certain proteins are mitogenic for these endothelial cells has greatly increased our knowledge of the vascular system (20).

Aims and outline of this thesis:

Although the classification system proposed by Mulliken and Glowacki has provided much clarity at a time when there was a lot of confusion in the medical literature, this classification may oversimplify the ontogeny of these vascular anomalies. The medial telangiectatic nevus (nevus simplex or stork bites) is a vascular malformation that usually clinically disappears (21). Natural involution is thus involved in these lesions. Kaposiform hemangio-endotheliomas clinically have a phase characterized by proliferation, while the histological characteristics are those of a lymphatic malformation. The classification system further states that hemangiomas are neoplasmas and in such thus distinct from true structural deficits. Large face hemangiomas have been associated with the so-called PHACE syndrome (22). Here the hemangiomas are associated with posterior fossa arterial anomalies of the cerebrovasculature, (hemangiomas), arterial abnormalities, coarctation of the aorta, and eye abnormalities. There are other syndromes characterized by dysmorphology of hemangiomas, including those related to midline sternal cleft defects, usually associated with midline abdominal raphe (23,24). It is also known that sometimes there are patients in which clinical or histological characteristics of both vascular malformations and hemangiomas are seen (25). At present the biological classification system suggested by Mulliken and Glowacki is the best we have, and should not be discarded before a better classification system is universally accepted.

The first step to understand vascular malformations is to better understand the genesis of the normal vascular system. Next we should describe the molecular pathology involved in vascular malformations; this will hopefully lead us to categorize vascular malformations more accurately,
and subsequently treat them effectively. For that reason Chapter 2 is devoted to what our current state of affair is with regard to our understanding of vascular malformations. This comprehensive review not only describes our present understanding of the normal vascular system, but also describes the best known molecular mechanisms for the different vascular malformations.

The most common vascular malformations are capillary malformations (port-wine stains). These malformations are currently also the best treatable with pulsed-dye laser (PDL). The unpredictability of this treatment medium has made us search for the underlying pathology. Only by defining the pathologic processes involved will we be able to understand the reasons for the difference in response and in the long term introduce better treatment options, or even better, be able to prevent these lesions from developing. In the past certain genes have been identified to be causative for inherited vascular malformations eg. mucocutaneous venous malformations (TIE-2 gene) (26). Although a familial tendency has been described in the medical literature, a locus for capillary malformations had never been mapped (27). Chapter 3 is devoted to mapping a locus for an autosomal dominant disorder in a three-generation family that manifested itself with multiple cutaneous capillary malformations. It is likely that the genes involved in the familial cases of capillary malformations are also involved in the sporadic cases. In Chapter 4 we have summarized the present understanding of the pathology involved in capillary malformations. Although we do not want to describe the influence of PDL in capillary malformation treatment, it is inevitable to include some information about PDL in a discussion about capillary malformations. In this chapter we want to compare the histology of the normal skin to pathology involved in capillary malformations, and provide an overview of our current molecular understanding of capillary malformations.

Although a molecular description will provide us with a nice diagnosis, the most important question is whether treatment is possible. To answer that question an accurate description of the tissues involved is necessary. As mentioned earlier, 90% of vascular anomalies are diagnosed clinically, but sometimes radiology can be necessary to diagnose these anomalies. Although ultrasonography is cheap and easily available, it is notoriously operator dependent, but is currently the simplest method to make a definite diagnosis (28). In Chapter 5 we provide an overview as to why MRI is currently the best modality to investigate vascular anomalies, to see the extent of involvement or when intervention is anticipated. Although MRI is currently the best modality that we have to study vascular malformations, it also has some limitations which will also be discussed. We further suggest a diagnostic flow-chart developed on the basis of MRI features, designed to help determine the composition of a vascular birthmark.
Historically surgical treatment options for vascular malformations have been poor (2,13-17). In an attempt to investigate why vascular malformations may respond so badly to surgical intervention, the MRI characteristics of a group of patients who presented at our vascular anomalies clinic is described in Chapter 6. Although previous studies have described the characteristic differences between high- and low-flow vascular malformations, there is little detailed information available delineating the vascular malformation (29). This study is performed to provide more detailed information regarding the extent of local tissue involvement, and subsequently describe associated features of the tissue adjacent to the vascular malformation in the lower extremity.

In a retrospective study on 356 hemangiomas and 224 vascular malformations, Boyd et al found that hemangiomas are not often associated with osseous involvement, while vascular malformations in general are often associated with osseous changes (30). This study includes patients with bone hypertrophy/hypotrophy without visible bone involvement (31% of patients had bone changes). There is also no differentiation between patients having upper- or lower extremity involvement, since only the “extremities” are differentiated from the “head and neck” group. Since that article there have been some reports on osseous involvement associated with vascular malformations, but little attention is given to the clinical symptoms and signs of patients with vascular malformations and associated bone involvement (31,32). In an attempt to assess the osseous involvement in the lower extremity, we conducted a study on all the patients that presented at our vascular anomalies clinic over the last ten years. Chapter 7 focuses on the clinical and radiological characteristics of the patients with vascular malformations of the lower extremity with osseous involvement.

Once a diagnosis is made and radiological visualization has excluded any therapeutic intervention, unfortunately many patients are sent home without a curative solution. These patients are often told to “live-with-it” and if necessary elastic stockings and analgesia are prescribed. In the medical literature capillary malformations have received attention on what the psychological impact of the malformation may be (33,34). Currently most quality of life studies are focused on capillary malformations presumable because they are the most common vascular malformation; they occur often in the face and are often treatable with pulsed-dye laser. Very little is known of the psychological impact vascular malformations located on other parts of the human body have on patients. In an attempt to clarify some of these questions, we conducted a study in Chapter 8 to investigate what the influence of vascular malformations located on the lower extremity on everyday living would be.
In Chapter 9 we provided the summary and conclusions of this thesis and provided some ideas and directions for further research.

**Summary of main questions of thesis**

- What is our present understanding of how the normal peripheral vasculature develops, and how is this knowledge applicable to help us better understand vascular malformations?
- Is it possible to find a locus for capillary malformations?
- What is our current understanding of the pathology involved in capillary malformations?
- How can MRI be utilized to describe the composition of vascular birthmarks?
- Can MRI characteristics of vascular malformations of the lower extremity help us to better understand these lesions?
- What are the clinical characteristics of patients with vascular malformations of the lower extremity with associated osseous involvement?
- Do patients with vascular malformations of the lower extremity have a worse quality of life compared to patients without vascular malformations?

**References**


