Progress toward understanding vascular malformations
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Summary, conclusions and future perspectives
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Vascular malformations have been, and are still among the most poorly understood entities in medicine. The Latin appellation for capillary malformations (port-wine stain) is *nevus flammeus* and it connotes the superstition that the mother was frightened by fire during pregnancy (1). Since medieval times there has been considerable stigma surrounding these anomalies. In the Middle Ages the newborn babies' skin abnormality was sometimes seen as a sign of the mother's wrongdoing (sin) during the pregnancy (1). Montaigne (1533-1592), a skeptical essayist, had no doubts about the origin of these congenital stains: "We know by experience that woman impart the marks of their fancy to the bodies of children they carry in their womb" (2). Until a classification of Mulliken and Glowacki was introduced in 1982, terms like hemangioma's, venous angioma's, cavernous angioma's, or cavernous hemangioma's were used interchangeably for lesions that were in fact vascular malformations. Since the biological classification was introduced, there has at least been a way to differentiate vascular anomalies into two groups: vascular tumors (mostly hemangiomas), and vascular malformations. Since 1982 there have been some fundamental improvements in our understanding of these anomalies. With recent improvements in especially our molecular understanding increasing rapidly, this thesis is an attempt to summarize some important improvements of recent years. This thesis is not a comprehensive review of our knowledge applicable to vascular malformations, and the interested reader is referred to specialized books.

It is obvious that some information supplied in chapter 2 is already out-dated. It was also not possible to include all the available information in an overview as was proven by the commentary of Michael Cohen in *Plastic and Reconstructive Surgery* © (3). With treatment options for cancer stimulating research in vascular development (angiogenesis), new information is found regularly. In January 2003 Medline had ± 20 000 "hits" for TGF-beta, and nearly 8 000 for VEGF. Despite this abundance of information we want to summarize some fundamental improvements in our understanding with regard to vascular malformations. Only some factors will be discussed, and referral to the Internet is suggested for a complete and more recent update.

After capillary malformations, venous malformations are the most common vascular malformations. The incidence is unknown, but is estimated to be between 1/5000 and 1/10 000 newborn babies (4). In chapter 2 the mutation found at R849W (chromosome 9) in familial venous malformations was described, but a different mutation, Y897S, has also been found in the same kinase domain (5). The signalling cascade of the TIE-2 receptor is complex, and the exact explanation of the phenotype caused by the mutant TIE-2 receptor is not fully explained. It
is suggested that the mutation causes changes in control of the endothelial cell cycle leading to a relative deficiency of smooth muscle cells (4). It is still unclear how the mutation exactly results in the phenotypic effects and more research is being performed.

Glomuvenous malformations (GVM) are venous malformations with "glomus cells" around the convoluted venous-like channels and are subgroup of venous malformations (4). Usually it is possible to differentiate clinically between these lesions and venous malformations (6). GVM are raised, bluish-purple, have a cobblestone surface and are very painful on palpation. In contrast to other venous malformations, GVM are rarely encountered on mucous membranes and are nearly never intramuscular. Venous malformations are blue lesions, encountered on the mucosa and intramuscular. In contrast to the nodular appearance of GVM, venous malformations are often flat. Hyperkarotosis is another way to differentiate between GVM and VM. This is found with GVM, while it is not seen in venous malformations. Postural emptying is also not possible with GVM, while this is well known for venous malformations. Genetic studies have supported the clinical and histological difference seen between venous malformations and glomuvenous malformations. It is suggested that 78% of GVM are inherited, while only 2% of venous malformations are inherited. The VMGL0M has been identified as a locus on chromosome 1 as mentioned in chapter 2. Characterization of additional families with inherited GVM enabled Irrthum et al to narrow the region to single 1.48-Mbp YAC (7). There are no known genes for vasculogenesis is this region, and it is suspected that the mutated gene could be novel factor regulating vasculogenesis / angiogenesis. It should be interesting whether this gene works in conjunction with the TIE2 gene or if it acts in TIE2 signalling, because VM have a relative deficiency of smooth muscle cells and GVM have a variable abundance of modified smooth muscle cells (3).

Chapter 3 is devoted to mapping the locus for an autosomal dominant disorder in a three-generation family that manifested itself with multiple cutaneous capillary malformations. It is possible that the multifocal nature of these lesions might be a clue to a familial predisposition.

We have mapped a locus for an autosomal dominant disorder in this family to chromosome 5q13-22. This was the first time that a locus was demonstrated in capillary malformations. Since this publication one other study has demonstrated a locus in the same area, and it is expected that with time the gene(s) will be found (8). Our described locus spans 49cM between the markers D5S647 and D5S659 and includes several candidate genes. As indicated in the next chapter, abnormal neural development is possibly the major cause of the capillary malformation. Several genes involved in neurogenesis are located in this area. These include the FER gene shown to be involved in neurite outgrowth, and EFNA5 protein involved in axon guidance. Further refinement of the present linkage region and subsequent mutation analysis should allow
detection of the causative gene. Recent studies are indicating that the clear-cut differences we make between hemangiomas and capillary malformations by using the classification suggested by Mulliken and Glowacki, may not be so clear-cut as we think (9).

In Chapter 4 we have summarized the present understanding of the pathology involved in capillary malformations. It is clear from this summary that there is still a considerable amount of information to be gained from thorough histological (electron microscopy) studies. It seems that the pathology of the capillary malformations is located in the post-capillary venules and small venules, and that our definition of port-wine stains being capillary malformations is wrong. One important pathological characteristic detected in “capillary malformations” so far is the decreased neural innervation. It thus seems legible to describe these lesions as a neural malformation as well. It is even possible that all vessel deformation is secondary to the neurological pathology, and that capillary malformations are pure neural malformations with vascular dilatation being secondary. Further studies on capillary malformations should concentrate not only on the vasculature, but should also include studying the innervation of the dermal vasculature. Although histological studies have demonstrated that the ectatic part involved in capillary malformation is confined to the venular part, we know little about the real innervation of the arteriolar part and further research will have to clarify this aspect. Angiogenesis is also an essential process of nerve regeneration. Endoneural vascular supply provides access for hematogenous macrophages and oxygen / nutrients to enter the damaged nerve, essential for the outgrowth of neurites (10). It is surprising how little we know about the influence that VEGF has on neural development. The role of VEGF in angiogenesis of the nervous system is unquestionable, and the concept that VEGF also has direct neural effects is gaining more experimental support (10). With the common developments of the vascular system, nervous system and lymphatic system it seems logical that future investigations on capillary malformations will concentrate on the “genesis” as a whole and not only on vasculo- and angiogenesis.

Although a thorough 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. In Chapter 5 we provide an overview as to why MRI is currently the best modality to investigate vascular anomalies if intervention is anticipated, but this chapter also discusses some of the limitations of MRI. Although clinical characteristics can often differentiate between different types of vascular malformations, MRI is often needed to delineate the involvement of vascular malformation. Chapter 5 also summarizes some differences in high- and low-flow lesions concerning MRI and ultrasonography. Although no single imaging technique answers all our questions, the exact reason for requesting an investigation
should determine the choice of investigation. A decision-tree to help determine the composition of vascular birthmarks on the basis of MRI characteristics is further suggested. Even with contrast enhancement given to differentiate between lymphatic- and venous malformations, it is sometimes difficult to differentiate between these lesions. Clinical characteristics are important since venous and lymphatic lesions can sometimes occur together, making an attempt to differentiate between these anomalies by only looking at the MRI very difficult.

Historically surgical treatment options for vascular malformations have been poor. In the past the MR characteristics differentiation between high- and low-flow lesions have been well described, but there is little detailed information available that accurately delineates the vascular malformation. In Chapter 6 we not only define the MRI characteristics of high- and low-flow lesions, but further provide more detailed information regarding the extent of local involvement and describe associated features of the tissue adjacent to the vascular malformation in the lower extremity. We retrospectively reviewed 40 MRI’s of 34 patients with low-flow lesions and 6 patients with high-flow lesions. Of the 34 low-flow lesions 23 (67.6%) had muscle involvement, while 4 high-flow lesions had muscle involvement. When the different muscle compartments were compared, it was seen that 80% of the lesions in thigh involved at least the anterior compartment, while 86.6% of lesions located at the leg had at least the posterior compartment involved. The angiosome concept is used to explain this phenomenon. The zones between angiosomes (anastomotic vessels = choke vessels) are not between muscles, but within them. It is possible that in the past only resection of the visible vascular anomaly was performed. The resection probably ended at the end of the muscle – subsequently not at the end of the angiosome. It is expected that the residual vascular malformation reacted in an aggressive way because of the change in blood dynamics. This study further indicates that 61% of patients with muscle involvement had more than three muscles involved. Twenty-five percent of patients also had bone involvement. It is thus unlikely that surgical intervention alone will be curative when treating these patients. This observation is further enhanced by the 20% of patients having multifocal lesions. A substantial amount of patients with associated muscle involvement also had associated muscle atrophy, again indicating that even if it is possible to resect the vascular malformations, it is imperative to look at the remaining muscles (although assessing the precise function of these remaining muscles is difficult). Our study also included 11 low-flow lesions with subcutaneous hypertrophy. Five of these lesions had no associated subcutaneous vascular malformations. It is possible that this aberrant fat is associated with the vascular malformation, much like some pure capillary malformations are associated with limb hypertrophy. Further studies are needed to clarify these observations. The angiosome concept should also be tested at other locations e.g. head and neck, and the upper extremity/hand.
Previous studies have characterized the radiological skeletal alterations seen with vascular malformations, but there is a paucity of information with regard to the clinical characteristics of patients with vascular malformations with associated osseous involvement. Chapter 7 describes the clinical characteristics of 18 patients with osseous involvement associated with vascular malformations on the lower extremity. Despite some reports indicating that vascular malformations with associated osseous involvement are rare, the contrary seems true with our study. Twenty percent (18/90) of our group of patients with vascular malformations of the lower extremity had osseous involvement, of which 15 patients had low-flow lesions, and 3 had high-flow lesions. As seen in table C and D in chapter 7, pain was the most common reason for presenting to a physician, together with a disparity in leg length. Of the six patients with an intra-osseous lesion, none initially complained of pain, while 10 of the 12 patients with reactive bone changes initially complained of pain. This pain could possibly be explained by tension caused by periosteal lifting. Only 50% of the patients with symptoms of knee hemarthrosis had intra-osseous extension. Although the other patients all had ligamentous involvement in the knee, this was often very subtle on the MRI. Chapter 7 focuses only on the 18 patients with osseous involvement visible on the MRI, and no mention or comparison is made of the symptoms of the patients without osseous involvement. Further studies should identify if any difference exists.

Once a diagnosis is made and some radiological visualization has excluded any therapeutic intervention, unfortunately many patients are send home without a satisfactory curative treatment solution. These patients are often told to "live-with-it" and for example, often elastic stockings and analgesia are prescribed for lesions located on the extremities. With the exception of capillary malformations (port-wine stains), the adverse psychosocial effects of vascular malformations has not received much attention in the medical literature. This in comparison to the well described physical morbidity. Due to this paucity of information we conducted a quality of life study with the MOS Short Form Health Survey Questionnaire (SF-36™) in Chapter 8 in patients with vascular malformations located primarily on the lower extremity who presented to us over a ten year period. Several possible predictors were also examined. This first study on health related quality of life in patients with vascular malformations of the lower extremity suggests that patients with vascular malformations located primarily on the lower extremity do not have a considerable decreased quality of life when compared to the general Dutch population. Our study population group report more bodily pain and worse vitality than a general Dutch population sample. Because the mean age of our VM patients is lower than that of the reference population, and since SF36-scores are negatively associated with age, this might have resulted in a slight underestimation of the difference in quality of life scores. Regarding other dimensions of health related quality of
life as assessed with the SF36, no differences were observed between both groups. The total explained variation in the quality of life of patients with vascular malformations on the lower extremity by the selected characteristics is small. Influence of patients wearing orthopedic shoes, elastic compression stockings, and those with hand and lower extremity involvement can explain some of the decrease in quality of life. Since the number of patients studied was small, insufficient statistical power to detect significant associations might have attributed. In addition, it suggests that quality of life is influenced by many more factors than the selected ones in the present study, but because of the heterogeneity of these anomalies it seems that it will be difficult to describe characteristics specific for these anomalies. It is reasonable to assume that the patients' quality of life is a result of a complex interaction of disease outcome, personal traits, coping behavior, social support, and the quality of care received. More studies are needed to investigate the quality of life in patients with vascular malformations. When we look at our study, it is possible that patients with for example predominantly hand involvement will have a worse quality of life than patients with predominantly lower extremity involvement. Further studies should be conducted to clarify this question.

Management of patients with vascular malformations encompasses the whole spectrum of care of patients. Most centers treating these patients have teams consisting of a spectrum of medical specialties. Although most vascular malformations are not life-threatening, it is also most often not a curable disease. Two words dominate the rules of therapeutic management of all types of vascular malformations: a multidisciplinary approach and modesty. Education is essential and patients should be educated in the natural history of the malformation and of the limitations of the current treatment methods.
References
