Extracranial vascular malformations (hemangiomas and vascular malformations) in children and adolescents – diagnosis, clinic, and therapy

Abstract

The field of extracranial vascular anomalies is considered as special focus of pediatric otolaryngology and it has shown a rapid development during the last years. The reason for this interest is finally also due to the global acceptance of the classification introduced by the ISSVA (International Society for the Study of Vascular Anomalies). Hemangiomas are the most frequently observed vascular tumors. Today the systemic propranolol therapy is mostly used for therapy of hemangiomas requiring treatment. Increasingly, the topical application of beta blocker is discussed while the benefit in the head and neck seems to be limited. Vascular malformations are classified according to the morphology of the affected part of the vascular system in arterial, venous, arteriovenous, lymphatic, capillary, and combined vascular malformations. Conventional surgery, sclerosing therapy, and laser treatment are invasive options for the treatment of lymphatic malformations. The options for the treatment of venous malformations could be significantly improved during the last years. In this context, the use of Nd:YAG laser, the conservative treatment of the localized disseminated intravascular coagulation with low-molecular weight heparin, the re-discovery of bleomycin as effective sclerosing agent, and the improvement of alcohol-based embolization agents must be mentioned. Today the treatment with dye laser is the preferred therapy for capillary malformations and it is superior to other therapeutic options as for example photodynamic therapy. Arterio-venous malformations as representatives for high-flow lesions are the high-risk lesions. Frequently they are compared to malignant head and neck tumors, in particular when a curative treatment can no longer be assured because of diffuse or multifocal extent and when the disease shows a progressive course. The combined treatment of embolization and surgical resection and if necessary consecutive defect reconstruction have turned out to be appropriate for arterio-venous malformations. Incurable findings are still a major challenge. Despite the introduction of antiangiogenetic drugs in oncology, the medicamentous therapeutic approach could not be established for arterio-venous malformations up to now.

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Introduction

The interest in the field of extracranial vascular malformations is rapidly growing and turns out to develop significantly during the last two decades. The reason for this development is the increasing knowledge of the classification of vascular malformations and also the clearly improved repertoire of diagnostic and therapeutic possibilities. The diseases that are often called vascular anomalies as a summary of clinical symptoms can sometimes be classified as special focus of pediatric otolaryngology. This is not only due to the fact that according to their definition vascular malformations are already present at the time of birth even if they are not always clinically visible, but also to the fact that the group of infantile hemangiomas generally shows their complete clinical characteristics during the first months of life. Even if a significant part of patients, especially those suffering from vascular high flow malformations of the head and neck, reveal symptoms only as grown-ups and look for therapy, there is the majority of patients who become symptomatic as children and those whose clinical course can already be anticipated in childhood and thus adequate care can be assured.

With regard to partly fatal courses of patients suffering from advanced arterio-venous malformations it is especially the early diagnosis that is highly important, in particular in the context of recognizing the best time of

Table 1: Classification of vascular anomalies (according to [2])

Vascular anomalies	
Vascular tumors	**Vascular malformations**
Infantile hemangiomas	**Low-flow lesions**
Congenital hemangiomas (RICH – NICH)	venous
"Tufted Angioma"	capillary
Hemangio-endotheliomas	lymphatic
Pyogenous granuloma	mixed
Rare forms	**High-flow lesions**
	arterial – arteriovenous

RICH: Rapid Involuting Capillary Hemangioma
NICH: Non-Involuting Capillary Hemangioma

treatment. A precondition for this aspects is of course an adequate knowledge of the genesis, differential diagnosis, and the clinical course of those lesions.

In the majority of the cases the diagnosis of extracranial vascular malformations can already be made based on their properties by clinical examination and mostly even without the use of high equipment requirements. The imaging diagnosis is then applied for detailed analysis of the findings.

Often an inadequate terminology is the reason for insufficient treatment. One of the most evident errors may serve as prime example, that vascular anomalies are called hemangiomas without criticism. In 1982, Mulliken and Glowacki published a classification taking account of the biologic behavior of vascular lesions [1]. The essential point of Mulliken's and Glowacki's classification system was the strict differentiation between hemangiomas and vascular malformations which is still today of very practical use.

Classification and nomenclature

Vascular anomalies are subdivided into two main categories, i.e. vascular tumors and vascular malformations (Table 1). The classic representatives of vascular tumors are infantile hemangiomas. The congenital hemangiomas, epitheloid cellular hemangio-endotheliomas, so-called "tufted angiomas", pyogenous granulomas, and other rare vascular tumors are included in this category [2].

Vascular malformations, however, are subdivided according to the morphology of the affected area of the vascular system. The so-called Hamburg Classification that was established in 1988 divides vascular malformations into arterial, venous, arterio-venous, lymphatic, capillary, and combined vascular malformations. Those are subdivided into so-called extratruncular and truncular subtypes. Truncular forms arise from already differentiated vessels but extratruncular forms stem from the primitive embryonic vascular capillary network. The differentiation between extratruncular and truncular types takes in account the

level of the occurrence of malformations with regard to the developmental stage during embryogenesis. In the head and neck area, the extra-truncular type of vascular malformations is predominantly observed. Since 1996, the further elaboration of the Hamburg Classification is the established basis for the classification of vascular malformations accepted by the ISSVA (International Society for the Study of Vascular Anomalies) (Table 2) [3].

Hemangiomas

The term of "hemangioma" is reserved exclusively for classic, partly rapidly growing benign vascular tumors appearing in infants. Frequently also called "capillary" hemangioma, it never re-appears in adolescence nor in adults. The classic biological behavior of infantile hemangiomas consists of proliferation mainly shortly after birth with a natural tendency of spontaneous involution. The irregular parameter in this context is the time and the speed of the mentioned spontaneous involution. In most of the cases the regression of the hemangioma already starts in the second half of the first year of life. More rare subtypes such as the *rapid involuting capillary hemangioma* (RICH) and the *non-involuting capillary hemangioma* (NICH), both summarized in the term of *congenital hemangiomas* are only rarely observed in clinical routine. Until recently, the classic infantile hemangiomas of the head and neck were considered as potential therapeutic challenge, in particular when those showed a strong tendency of proliferation and associated complications such as ulceration, bleeding, obstruction of the sensory organs and of the aerodigestive tract, or facial disfigurement had to be faced.

The reliable, only histologic diagnosis of hemangiomas can sometimes be difficult. Up to date only one possible immune-histochemical marker has been described, the Glut-1 protein (glucose transport protein 1) which is typically expressed not only in classic infantile hemangiomas but also in the placenta. This knowledge seems to confirm the hypothesis of the genesis of hemangiomas stating

Table 2: Classification of the ISSVA (International Society for the Study of Vascular Anomalies) for vascular malformations (according to [3])

ISSVA-Classification
"The Hamburg Classification of congenital vascular malformations"

Type	Subtype
Predominantly *arterial* defects	**I. Extratruncular forms**
Predominantly *venous* defects	diffuse, infiltrating
Predominantly *arteriovenous* defects	limited, localised
Predominantly *lymphatic* defects	**II. Truncular forms**
Capillary malformations*	– Obstruction or Aplasia
Combined vascular defects	hypoplasia, aplasia, hyperplasia, stenosis, membrane, congenital spur
	– Dilatation
	localized (aneurysm)
	diffuse (ectasia)

Based on the consensus through the International Workshop on CVMs in Hamburg Germany 1988
* Modified through the Denver consensus meeting in 1992 and the Seoul consensus meeting in 1996

that fetal progenitor cells from the placenta might be the origin of infantile hemangiomas [4]. Further, hemangioma tissue contains estrogen receptors, and part of the concerned patients showed an increased endothelial growth factor (EGF) and an increased estrogen level.

The clinically based incidental observations of the effect of propranolol on hemangiomas gave new impulses for the pre-clinical research regarding the genesis of hemangiomas. It was astonishing how a drug that has been established in pediatric cardiology for more than four decades could develop also an anti-proliferative effect on those benign vascular tumors without being noticed. Wong and co-workers [5] could reveal that propranolol does not only induce apoptosis in endothelial cells from hemangiomas but also an early transformation of stem cells in hemangiomas into fibrous-fatty tissue. Isolated stem cells from hemangiomas are now also used for establishing animal models [6].

The therapeutic spectrum for the treatment of hemangiomas ranges from systemic or intralesional steroid therapy, the application of different laser systems (predominantly dye laser and Nd:YAG laser) to conventional surgery. It was the already cited report published by Léauté-Labrèze and co-workers [7] that revolutionized the therapeutic approach for hemangiomas requiring treatment. Their incidental observation was described as a clear response of hemangiomas on the application of beta blockers. Only shortly thereafter, further reports were published on the successful application of beta blockers [8], [9] and prospective and multicentric studies were initiated that were supposed to reveal the effect of propranolol in the context of prospective evaluation.

As the propranolol therapy can still be classified as off-label therapy, voices are getting loud more and more to criticize this negative view of propranolol. This becomes even more important as it can be doubted if there has ever been an on-label treatment for hemangiomas. The treatment results reported before 2008 taking into account different therapeutic modalities as for example the application of steroid or also interferon a cannot be considered as on-label as well. With regard to the mostly excellent treatment results and the low incidence of complications of propranolol application, the systemic propranolol therapy can nowadays be considered as first line therapy for problematic hemangiomas.

Even if this term of first line treatment can be justified in the context of the current state of knowledge, this does not automatically mean that propranolol or other beta blockers are the therapeutic option of first choice for all hemangiomas of the head and neck. It must be emphasized that the majority of circumscribed unproblematic hemangiomas that occur much more often in pediatric or dermatologic practices than in specialized angioma centers and that do not lead to significant functional or aesthetic impairment, are generally only observed. This approach is also called watch-and-wait can be considered as method of first choice for this subgroup (Figure 1).

Another aspect of the therapy with beta blockers is that this type of treatment only develops its effectiveness in the proliferation phase of the hemangioma and that the effect itself must be considered as early induction of the natural regression so that, when hemangiomas that typically lose their tendency to proliferate in the second six months of the first year of life and the involution phase starts independently from the individual involution speed, no further therapeutic effect can be expected after the application of beta blockers. At that time they should be classified as so-called non-responders. The same is true for the part of hemangiomas that do not respond to propranolol therapy at all. It must not be underestimated that there is a relatively large patient population where therapy with beta blockers is contraindicated because of

Figure 1: Course of spontaneous involution of a periorbital hemangioma without functional impairment

Figure 2: (a) Two-year-old girl suffering from residual hemangioma of the nasal tip after previous treatment with propranolol and dye laser. (b) Status after conventional surgical treatment via a modified trans-columellar approach.

several conditions, as for example cardiac arrhythmia, blood glucose dysregulation, or bronchial asthma.

Focal hemangiomas of the face, especially those in the area of the nasal tip or the eyelids are well-known not to respond to beta blocker treatment (Figure 2). Beside residual hemangiomas, focal hemangiomas are appropriate for conventional surgery after the beginning of regression. Recently, reports have been published about the successful application of locally applied beta blocker containing drugs for the treatment of hemangiomas. There are also reports on the use of timolol which is an unselective beta blocker that is admitted as topic gel in its genuine indication for the treatment of glaucoma. This preparation seems to be appropriate in particular for small and superficial hemangiomas. Long-term experiences are still missing but the effectiveness for the above-mentioned limited lesions in randomized clinical studies could already be confirmed [10]. While lesions of the head and neck that are appropriate for a possible treatment with locally applicable drugs are relatively rare, potentially the local therapy with beta blocker containing topics might be considered even for usually critical anatomic locations such as the hands and feet or the gluteal or genital regions, because already very superficial lesions may show ulcerations.

Vascular malformations

Two main aspects are basic for the differentiation of vascular malformations, i.e. the hemo-dynamic properties and the vascular morphologic characteristics. The low-flow type is represented by lymphatic, venous, and capillary malformations, those of the high-flow type are arterio-venous malformations.

Lymphatic malformations

The head and neck area can be defined as the region where lymphatic malformations (synonymous: lymphangiomas) are mainly located. Meanwhile it is established to classify lymphatic malformations based on their dominant morphologic properties into micro- and macrocystic types and so-called combined types. This differentiation meanwhile replaced the classification into capillary, cavernous, and cystic lymphangiomas [11]. Nonetheless, beside the primary morphology lymphatic malformations show important differences with regard to their location, their growth behavior, the symptoms they cause, and the response rate on different therapeutic options.

Microcystic lymphatic malformations mostly have an infiltrative character, they are rarely limited and often do not show a relevant response to sclerosing therapy. In contrast, macrocystic lymphatic malformations can be well defined and may be approached by conventionally surgical resection depending on the individual extent. They also show a better response to sclerosing therapy [12], [13], [14].

The knowledge of the above-mentioned particularities of lymphatic malformations, however, is not sufficient to always assure an adequate classification. It is desirable to have a further optimized specification of those lesions of the head and neck not only allowing a therapeutic decision and prognostic estimation but also a comparison of therapeutic results. De Serres and co-workers [15]

Figure 3: Course of the disease of an extended cervico-facial lymphatic malformation with involvement of the mandible. Multiple pretreatments with conventional surgery, laser therapy, and sclerosing. Female patients at birth (a), at the age of 2 (b); 5 (c), and 21 years (d).

were the first to introduce a staging system classifying lymphangiomas of the head and neck into five stages according to anatomic aspects (Table 3). Hereby the authors could show that the complication rate of the surgical therapy and the number of necessary therapeutic interventions is correlated to a more advanced stage – this observation could also be reported by other authors [16]. In this context the group around Wittekindt developed a morbidity correlated score system, the so-called Cologne Disease Score that aimed at establishing a comprehensive clinical estimation with regard to speech, swallowing, and breathing function as well as aesthetic aspect [17], [18]. In the head and neck region, the affection of the tongue plays a decisive role regarding function and prognosis. The involvement of the tongue, however, was neither included in the classification of de Serres nor in the Cologne Disease Score. In 2009, in order to compensate this deficit, Wiegand and co-workers introduced a staging for lymphatic malformations of the tongue classifying the affection of the tongue into the stage I–IV [19]. Stage I includes isolated superficial microcystic lymphatic malformations of the tongue, stage II describes lymphatic malformations affecting the tongue with muscle involvement (IIA: part of the tongue. IIB: entire tongue). The floor of the mouth is involved in stage III; and stage IV describes extensive microcystic lymphatic malformations involving the tongue, floor of mouth, and further cervical structures. The quintessence of the Marburg results revealed that a complete resection of the lesion

is only possible in stages I and IIa and that generally all other stages may not be appropriate for complete resection with organ preservation.

Table 3: Staging of lymphatic malformations of the head and neck according to [15]

Staging of lymphatic malformations

Stage I: unilateral infrahyoidal

Stage II: unilateral suprahyoidal

Stage III: unilateral infra- and suprahyoidal

Stage IV: bilateral suprahyoidal

Stage V: bilateral infra- and suprahyoidal

Extended lymphatic malformations of the head and neck are an important therapeutic challenge because the possibility to cure the concerned individuals is very limited. Patients suffer from significant disfiguring lesions that may lead to enormous functional impairment because of the affection of the upper aerodigestive tract or even the orbit [20]. Often dysgnathia is observed in suprahyoid lymphatic malformations that is very difficult to correct [21] and that complicates the disease and therapy (Figure 3).

Up to day the exact pathogenesis of lymphatic malformations is not fully understood. It is supposed that already in the sixth embryonic week the development of lymphangiomas starts in the context of the formation of the jugular

sac which can be considered as a protrusion in the cervical mesenchyme. Two hypotheses are currently discussed regarding the genesis of lymphatic malformations. Basically it is a deficient connection of the lymphatic system to the venous system or an abnormal or insufficient network within the lymphatic system [22]. The hypothesis of the deficient connection of the lymphatic system to the venous system is more likely an indication for the fact that lymphatic and venous malformations go through some common stages in the context of embryogenesis. This assumption becomes even more probable when frequently combined lymphatico-venous malformations of the head and neck are observed.

Generally, invasive therapeutic options for lymphatic malformations can be divided into three categories, i.e. conventional surgery, sclerosing therapy, and laser treatment.

Conventional surgical therapy has its limits when microcystic lymphatic malformations have to be treated that involve larger anatomic areas. Often conditions are observed with severe functional impairment because of multiple conventional surgical interventions. This is especially true for extended lymphatic malformations with affection of the orbit and the cervical soft tissue and in particular for suprahyoid lymphatic malformations affecting the floor of the mouth and the tongue. The affection of the tongue and the floor of the mouth with consecutive protrusion of the tongue and resulting macroglossia is often initially treated by means of partial resection of the tongue and tissue reduction in the area of the floor of the mouth. Nonetheless, shortly after an intervention, many patients suffer from recurrent swelling of the tongue with occurrence of the initial symptoms despite radical surgery (Figure 4).

Figure 4: Recurrent protrusion of the tongue of a lymphatic malformation of the neck, the floor of the mouth, and the tongue of a 3.5-year-old patient. Status after resection of the lymphatic malformation from the area of the neck with subsequent partial resection of the tongue one year ago.

Not rarely the use of the CO_2 laser alone or in combination with the Nd:YAG laser is indicated for the treatment of microcystic hemorrhagic parts of lymphangiomas in the area of the mucosa or the tongue in order to achieve at least a medium-term improvement of the symptoms by vaporizing the lesions. The laser treatment itself is not curative but it can be considered as having very few complications and being not very invasive, and thus it is justified for a longer lasting symptom relief (Figure 5).

Various substances had been used for percutaneous sclerotherapy of lymphatic malformations such as hypertonic saline solution, concentrated dextrose or glucose solution, boiling water, fibrin glue, alcohol derivatives, bleomycin, doxycycline and Picibanil® (OK-432) [20]. The sclerosing agent Picibanil® (OK-432) is the most frequently used agent for sclerosing therapy of lymphatic malformations [14]. Comparable substances are bleomycin and doxycycline which could not be established as sclerosing agents of first choice in Europe. Picibanil® is a lyophilized mixture of streptococcus pyogenes of the group A which was treated with penicillin. Regarding the mode of action, it is assumed that the application of Picibanil® induces an inflammation reaction leading to fibrosis with consecutive shrinking (Figure 6). The agent is most effective in macrocystic lymphangiomas. In practice, however, it became obvious that it is not possible to treat advanced bilateral lymphangiomas exclusively with this method so that sclerosing therapy alone is often insufficient for this kind of lesions. The treatment of advanced cervico-facial lymphatic malformations is generally performed in a multimodal cascade [20]. After the initially performed conventional surgery of the pediatric patients concerned, sclerosing therapy and laser treatment are performed as additional interventions or as follow-up options.

Generally, in the context of therapeutic decisions the knowledge of the genesis and the biology of the lymphatic malformations should be present. It is important to understand those lesions as malformations of the lymphatic system in the true sense of the word and not as "tumors". The genesis of this disease is based on the malformation of the lymphatic system and not a tumorous proliferation of the lymphatic tissue. Unfortunately, often the situation must be faced that despite radical excision of a lymphangioma the adjacent areas subsequently develop a dilatation of the neighboring lymph vessels with formation of cystic lesions in the area of the mucosa or the soft part tissue because a much larger field of the lymphatic system had been affected than previously expected based on inspection or imaging diagnosis. With this background, decisions to perform an invasive treatment in children should be made in order to achieve the functionally best and for the psychosocial development best justifiable aesthetic result. It must be avoided to aim at a tumor-free situation at any price with acceptance of functional consequential damages.

Several modifications of therapeutic approaches for the treatment of lymphangiomas have been published up to now as for example the intralesional endoscopy for better morphologic assessment of those lesions but also for

Figure 5: Acute exacerbation of the lymphatic malformation of the tongue in a 9-year old patient. (a) Condition before and (b) status 9 months after vaporisation of the microcystic lesions with CO_2 laser.

Figure 6: Sclerosing therapy of a macrocystic lymphatic malformation located in the parotid region in a 14-month-old patient. (a) Initial findings. (b) Status 2 weeks and (c) 7 months after sclerosing with Picibanil®.

targeted endoscopically guided sclerosing therapy [23] and radio frequency ablation [24]. The optimal care for pediatric patients already starts in the prenatal phase because the majority of advanced lymphangiomas is already diagnosed in the context of prenatal ultrasound diagnosis. The so-called EXIT procedure turned out to be appropriate for securing the breathing during birth when lymphatic malformations with obstruction of the airways are found [20], [25]. Despite maximal therapy, many patients suffering from advanced lymphangiomas complain about secondary deformations such as significant dysgnathia or functional impairment of the tongue or the larynx. Not rarely, there is also a mediastinal or thoracic involvement in addition to the cervical findings (Figure 7) that requires the contribution of specialized pediatrics or pediatric surgeons or thoracic surgeons. So for the care of pediatric patients frequently many disciplines are involved such as maxillo-facial surgeons, pediatrics, speech therapists, orthodontists, and pediatric surgeons beside ENT specialists.
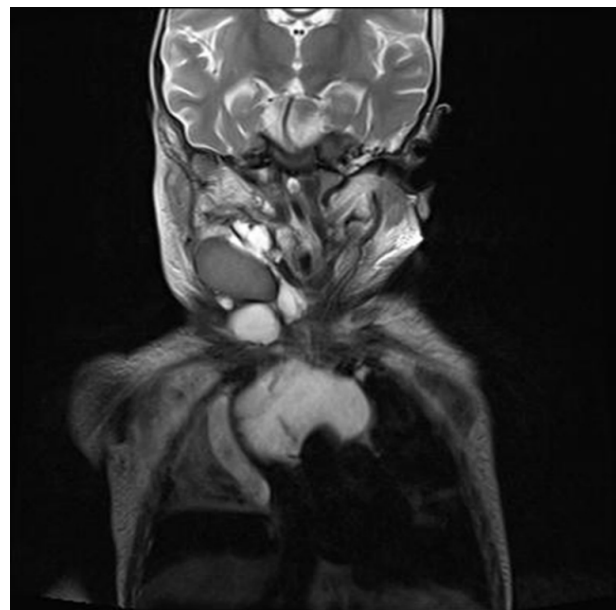

Figure 7: Cervical and thoracal involvement of a lymphatic malformation in a 3-year-old patient (imaging performed by the University Department of Diagnostic and Interventional Radiology, UKGM GmbH, Marburg, Germany)

Time and again, of course also because of the despair regarding missing treatment success, medicamentous therapy for the treatment of lymphatic malformations is postulated. Some experts also recommend the long-term application of broad spectrum antibiotics in order to control at least infection or inflammation associated growth. Also the application of immunomodulators or immunosuppressants such as Rapamycin that is discussed in analogy to the experiences made with the treatment of lymphangiomatosis [26]. Recently, the successful application of Sildenafil for the treatment of lymphangiomas was reported [27]. This short communication about the possible successful application of Sildenafil was not further pursued by the involved experts despite initially promising results. One reason might be the warning published immediately by the FDA (Food and Drug Administration) regarding the application of Sildenafil in its initial off-label indication for pulmonary hypertension in pediatric patients. Further, the therapeutic effect was meanwhile questioned critically for the four published cases. Based on the current knowledge, also the application of Rapamycin is not always recommended because of the possible adverse effects, especially immunosuppression.

Venous malformations

As main type of low-flow malformation of the head and neck, venous malformations must be mentioned. They are the most frequently occurring malformations in humans and according to the definition they are also present at birth. At that time, however, they are mostly small and inconspicuous. Frequently they appear as superficial and circumscribed livid alteration [28] that manifest in their full clinical characteristics in the third or fourth decade of life. Frequently a slow increase in size up to the adult age can be observed. Venous malformations can often be well controlled with current therapeutic means. Beside the aesthetic impairment, frequent clinical manifestations are dysphagia, dysphonia, foreign body sensation, valsalva induced swellings, and often exacerbations due to thrombophlebitis or phleboliths causing stasis [28], [29].

An intracranial involvement cannot always be excluded, especially in cases of very extended venous malformations of the head and neck so that MRI does not only serve for local determination of the depth but also for excluding venous intracranial dysplasia.

Histologically, those anomalies are dysplastic, abnormal, venous vessels (Figure 8) that may appear as extratruncular malformations without or as truncular malformations with connection to regular vessels. Frequently the histologic evidence of smooth muscle cells is only found rudimentarily, the thin endothelial layer lies on a thinned out basal membrane. Morphologically, those lesions vary from enlarged post-capillary venules to cystoid cavernous dilatations. Especially in the area of the orbit, also encapsulated vascular malformations are often found consisting of dysplastic venules and veins that were described as

so-called cavernous hemangiomas, which is incorrect according to current criteria [30]. For venous malformations in particular of the trunk or the extremities, already inherited subtypes are known that explain at least part of the pathogenesis of venous malformations. The exact origin that might explain the mentioned morphologic alterations is not fully known, and there are only few research groups focusing on this issue. Already in 1996, Vikkula and co-workers were able to identify a genetic anomaly of the receptor tyrosinkinase TIE2 in the context of family studies that impair the interaction of smooth muscle cells with endothelial cells [31].
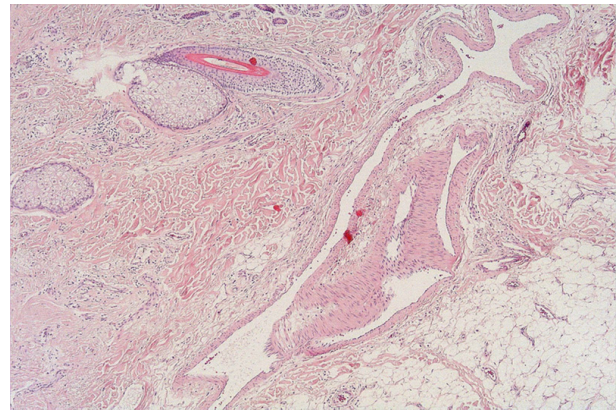

Figure 8: Venous malformation. →Dysmorphic, ectatic, venous tissue with affection of the subcutaneous fatty tissue and the skin (H&E, x5).

Beside the soft tissue of the neck and face, venous malformations of the head and neck mainly manifest in the mucosa of the upper aerodigestive tract [28] which explains the most frequently observed symptoms. The involvement of the visible parts of the oral cavity, as for example the lips or the tongue, may lead to mental stress of the patient (anxiety, restriction of intimate activities, but also limited hygiene of the mouth and the teeth). Additionally, the mentioned complaints as well as dysphagia, dyspnea, pains, obstructive sleep apnea, and in rare cases even hemoptysis justify an invasive treatment.

Especially for venous malformations, the therapeutic possibilities could be optimized during the last years. Regarding the manifestations in the head and neck area, pathophysiological knowledge could be included in the treatment planning. Conventional surgical approaches to advanced venous malformations are potentially threatening and associated with a high risk of bleeding and postoperative morbidity. With this background, the increasing distribution of laser treatments has gained an important value for venous malformations. The Nd:YAG laser system which has been applied in otolaryngology for more than twenty years now has turned out to be a reliable instrument for the treatment of venous malformations in the area of the mucosa [32] (Figure 9). Long-term results of Nd:YAG laser application for the treatment of venous malformations of the upper aerodigestive tract show a nearly negligible incidence of complications. Especially bleedings that are otherwise associated with conventional surgical techniques rarely occur during laser
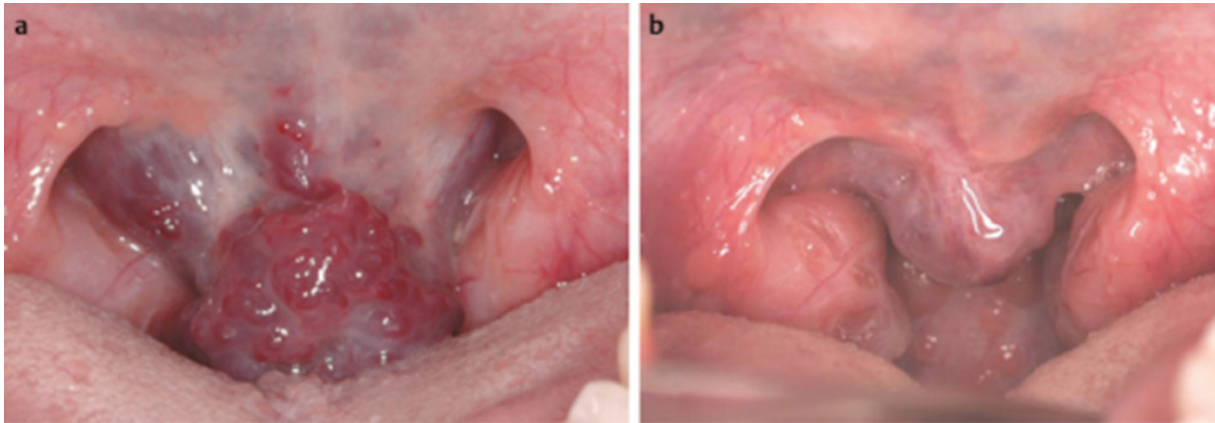
Figure 9: Venous malformation of the uvula and the soft palate in a 11-year-old female patient (a) before and (b) 4 months after therapy with Nd:YAG laser in non-contact mode
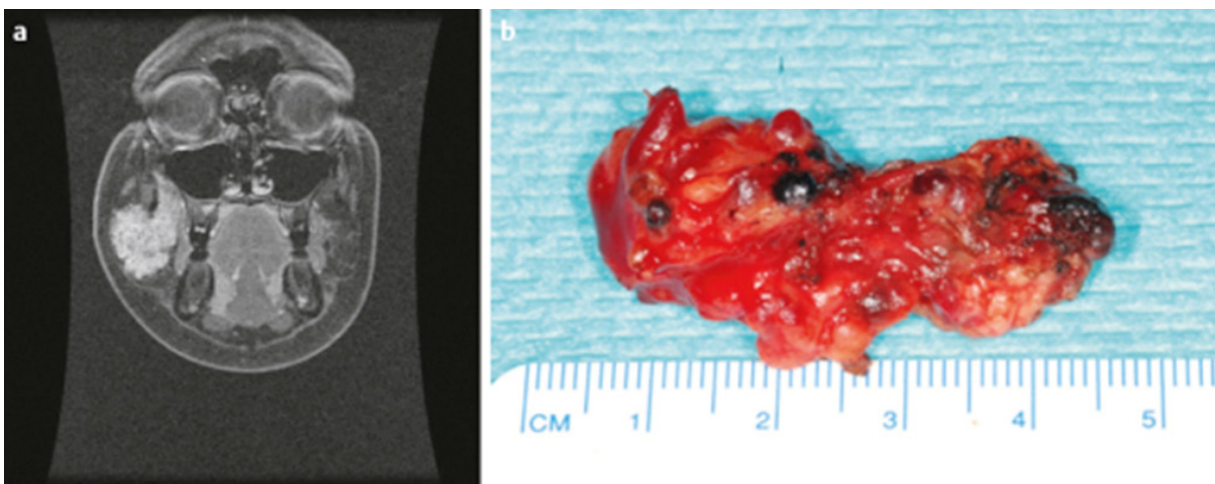

Figure 10: Venous malformation in the area of the buccal soft parts in a 14-year-old patient. (a) Preoperative findings of MRI and (b) specimen of a complete extirpation via an enoral approach.

treatment. However, this does not mean that conventional surgery has lost its significance for the treatment of venous malformations. Regarding the involvement of cervical or facial soft tissue, the laser application is clearly limited. A conventional surgery can then be recommended when extended venous malformations of the parotid region or in the area of the deep cervical and facial soft tissue must be treated (Figure 10). In addition of high surgical expertise open surgery requires extra efforts due to the use of additional instruments to increase the treatment safety. Beside transoesophageal echocardiography for prophylactic detection of possible air embolism, autologous blood transfusion systems to avoid life-threatening bleedings are meanwhile standard in the operating room for the treatment of extended venous malformations.

As already mentioned in the introduction, an improved understanding of the pathology of venous malformations contributed to an optimized treatment and to an increased therapeutic safety. It is well-known that vascular, in particular venous malformations can be associated with a so-called localized coagulopathy. It is explained by the local, i.e. in the lesion itself, consumption of coagulation factors, especially fibrinogen. In particular distinct venous malformations have increased D-dimers in the serum which cannot be explained by other origins, so it is a progress of a localized to a disseminated intravascular coagulation. Additionally, a reduced fibrinogen level of the serum can be observed in relevant disseminated intravascular coagulation [29], [33]. The increased d-dimers level results from a pathologic activation of the coagulation cascade within the lesion. An abnormal blood flow meets an abnormal endothel and causes the genesis of microthromboses and thus indirectly the consumption of coagulation factors. This fact is observed additionally and independently from the disturbances of the coagulation system and the thrombocyte function identified in some vascular malformations. An additive disturbance of the thrombocyte aggregation increases the risk of intra-, peri-, and postoperative bleedings. So a detailed analysis of the primary hemostasis is obligatory especially for patients with extended venous malformations [34]. The localized coagulopathy that is found in patients with venous malformations can be treated successfully up to a certain level by applying low-molecular heparin. Furthermore, a surgical intervention is performed directly in the area of the malformed vessels and this fact alone already bears the risk of bleeding in affected patients.
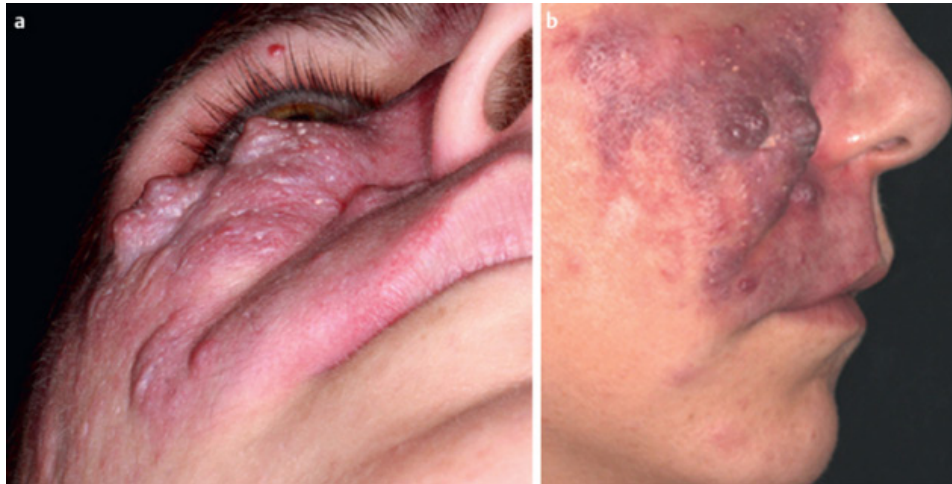
Figure 11: Nodal development and increasing pigmentation in an 32-year-old female patient with naevus flammeus of the midface

The therapy of low-molecular weight heparin which is usually applied as pre-treatment prior to surgical interventions in patients suffering from extended venous malformations and confirmed disseminated intravascular coagulation is increasingly applied in the conservative treatment of acute symptom exacerbations on the floor of local thrombophlebitis or stases [29], [33]. Even this measure can be considered as a progress in the care of patients. The rediscovery of Bleomycin as potential sclerosing agent for venous malformations could be made based on reported and reproduced results from China [35]. So it is easy to understand that increasingly the intralesional application of Bleomycin as alternative for the treatment of venous malformations is favored [36]. Nonetheless the possible toxicity must not be neglected. The life-time dose of 400 mg should not be exceeded and the treatment has to be performed under strict monitoring of the pulmonary and renal functions. In cases of renal or pulmonary pre-existing disease, therapy with Bleomycin must not be indicated. If alternative treatment options are present, such as for example laser therapy or the possibility of waiting up to the adult age, pediatric patients should not be treated with Bleomycin or the indication to perform this type of therapy has to be made with careful attention. Another treatment optimization of venous malformations is the improvement of alcohol based embolization agents. While pure alcohol is an extraordinarily effective sclerosing agent for the treatment of venous malformations, the embolization or sclerosing is sometimes associated with a high morbidity and mortality rate. The reason for this is the systemic and local toxicity of alcohol. However, after the development of new agents with improved viscosity during the last years that contributed significantly to the safety of sclerosing therapy, alcohol based sclerosing agent is being increasingly applied. Ethanol gel or ethyl cellulose ethanol (e.g. Sclerogel®) is more frequently applied for the treatment of venous malformations also in the head and neck region [37]. This measure, however, should only be applied under angiographic control also in cases of direct puncture because of the mentioned toxicity of the alcohol.

Capillary malformations

Probably the most important differential diagnosis of venous malformations is made for the capillary malformations. Typically, this subtype of low-flow lesions manifests as naevus flammeus, or port-wine stain, with an incidence of 0.3% of all newborns [38]. The etiology is currently still unclear; often a disturbed innervation of the affected capillaries with ectasia because of the reduction of the vascular tonus is discussed beside the wall morphologic anomaly [39].

The term of capillary malformation comprises a broad spectrum of cutaneous manifestations such as the so-called salmon patch or angel's kiss, the naevus anemicus, the naevus roseus, or also the telangiectasia that are known in the area of the mucosa and the skin in cases of Morbus Osler patients (hereditary hemorrhagic telangiectasia, HHT) [40], [41].

The following will focus on the naevus flammeus as main representation of capillary malformations. Naevi flammei can be located directly above deep arterio-venous malformations and in this context they may be associated with syndromes like the Sturge-Weber-Klippel-Trenauny syndrome [42]. Especially in case of periorbital naevi flammei the above-mentioned syndrome must be considered as it required further diagnosis. In those cases ophthalmologic complications based on choroidal involvement as well as neurologic symptoms (seizure disorders) due to associated leptomeningeal vascular anomalies would have to be excluded or examined directly after birth. Naevi flammei can also be associated with non-vascular malformations, e.g. the Proteus syndrome or pigmento-vascular phacomatosis [43].

Nearly always naevi flammei appear initially as superficial non-raised spots (maculae) from birth up to adolescent age. There is a tendency to gradual hypertrophy so that during the course of time a nodal transformation and an increased pigmentation are regularly observed [44] (Figure 11). Part of the patients can develop soft tissue hypertrophies in addition to cutaneous manifestation. As prime example for this phenomenon the hypertrophy of

the lower lip can be mentioned that is often observed in capillary malformations of the lower face (Figure 12).

Figure 12: Hypertrophy of the lower lip in a 15-year-old female patient with complicated course of a capillary malformation. Status after multiple pretreatments with dye laser and Nd:YAG laser, conventional surgery, and correction of the scars.

Because of primarily cutaneous manifestation and the apparently external affection of the patients, the extracutaneous manifestation of naevi flammei is often not in the center of interest. Based on its characteristics, the vascular malformation, however, is not limited to the borders of the dermis (Figure 13). The mucosa of the upper aerodigestive tract or the cervical soft parts can possibly be affected in addition to the cutaneous manifestation and cause functional symptoms according to the location of the malformation [44], [45], [46], [47]. The oral mucosa, the gingiva, the tongue, the larynx, the nasal mucosa, the cervical soft tissue, the parotid gland, and the auditory canal are possible, clinically relevant locations of manifestation in the head and neck as recently analyzed in the own patient population [48]. Extracutaneous manifestations sometimes lead to significant complaints in addition to the only aesthetic impairment. Those complaints include painful cervical or parotid swellings, globus pharynges, dysphonia, dysphagia, gingival bleeding, epistaxis, nasal obstruction, recurrent otitis, and the mentioned macrocheilia. Those manifestations require an individualized treatment such as conventional surgery, laser treatment, speech therapy, periodontal treatment, and local care of the ear. The broad spectrum of potential manifestations in the head and neck makes clear also in cases of naevi flammei how necessary a close interdisciplinary cooperation between dermatologists who mainly treat the patients initially and specialized otolaryngologists in order to achieve an optimal care also for this group of patients who suffer from extracutaneous and extracranial capillary malformations.
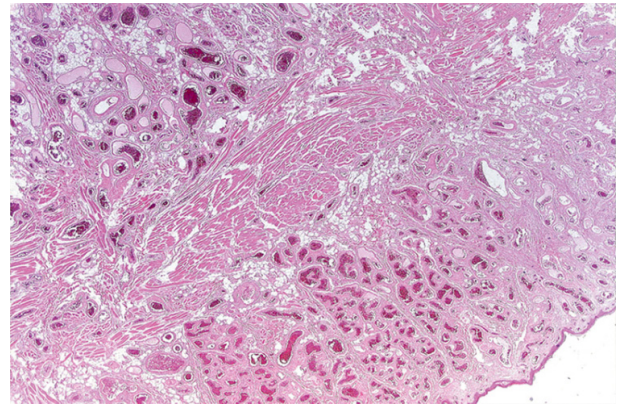

Figure 13: Histologic specimen of a capillary malformation of the lower lip with involvement of fatty, muscular, and glandular tissue (→ dismorphic capillary vessels) (H&E, x2,5)

The above-mentioned tendency to hypertrophy and nodal alterations suggests introducing therapy already in childhood in cases of naevi flammei. The manifold psychological stress of the patients must not be underestimated so that therapeutic intervention are often necessary [49], [50].

The therapy by means of pulsed dye laser (PDL) can be considered as favored therapy for capillary malformations because the effectiveness is proven and it is superior to other therapeutic modalities like photodynamic therapy or flash light therapy. Modifications such as the application of longer wavelengths or impulse durations due to improved possibilities of simultaneous cooling of the surfaces the success rates could be increased by the safe application of higher energy doses [51]. Treatment by means of dye laser generally required several sessions while the most significant effects in the sense of discoloration is already achieved in the first 3–5 sessions [52]. In this context it must be mentioned that especially in early childhood the treatment is often performed under general anesthesia.

The success rates in the facial area vary while the naevi flammei located in the central face usually do not respond as well as latero-facial lesions. A main reason for this observation is the relatively thick skin in the centro-facial region [53]. Also the severity of pigmentation plays a decisive role for dye laser treatment. Dark or livid lesions and parts that lie deeply in the dermis respond comparably poorly. In summary, most patients experience partial discoloration, a complete discoloration is given with max. 20% of the cases, the part of non-responders amounts up to 30% [54]. Those patients are then often offered a treatment with other laser systems, flash light therapy, or photodynamic therapy. A Cochrane analysis dated 2011 confirmed the value of dye laser therapy [55]. Nonetheless complete discoloration is only achieved in a minority of the patients so that also in this field further therapeutic improvements are expected.

Arterio-venous malformations (AVM)

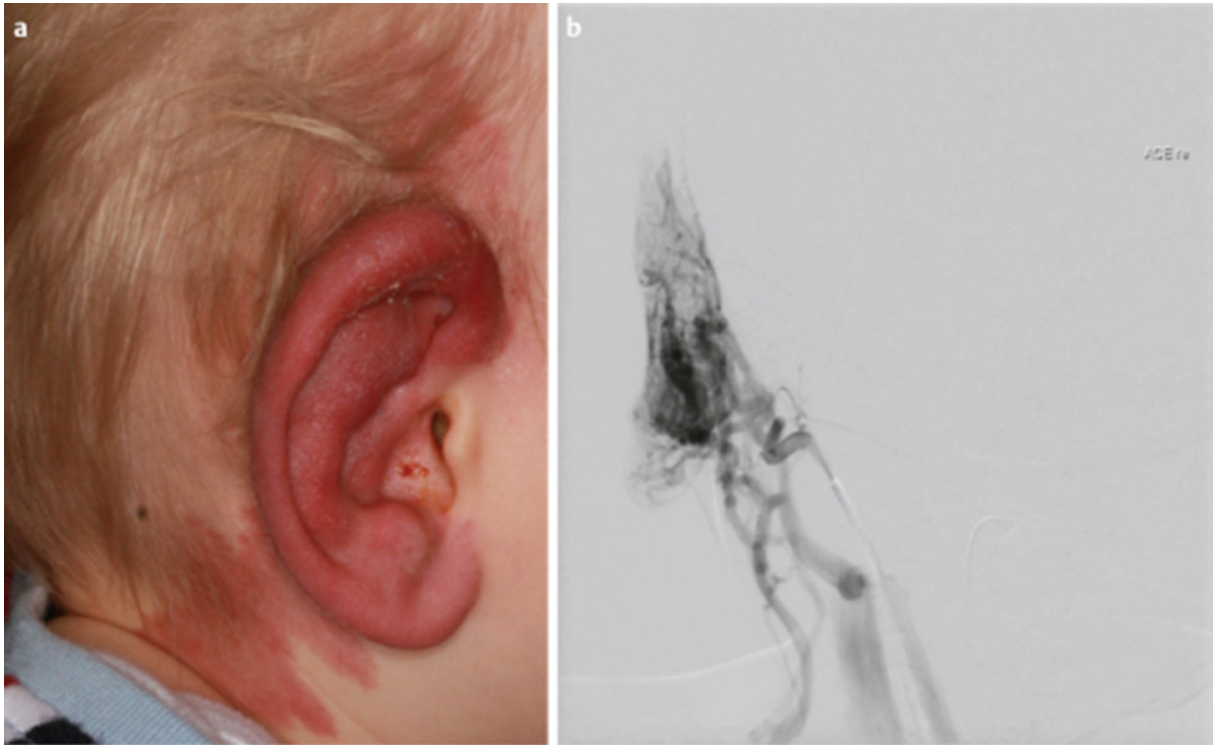Extracranial arterio-venous malformations (AVM) are the main representatives of the group of high-flow lesions of

Figure 14: (a) Arterio-venous malformation of the auricle of a 13-month-old male patient that was inefficiently treated with propranolol based on the assumption that it was a hemangioma. (b) Angiography showing an arterio-venous malformation.

the head and neck [11]. They belong to the most important challenges within the field of vascular anomalies. Further they are considered as the most risky subtype of vascular malformations. Arterio-venous malformations are much rarer than low-flow lesions. Even if their origin can be considered as congenital and according to the definition they are already present at birth, AVM often remain inconspicuous for many years so that the diagnosis is not found and is only made later in adolescence of adult age. In infant or child age there is often a hypervascularlized area. Very often those lesions are confused with capillary malformations (naevus flammeus) or misinterpreted as hemangiomas (Figure 14).

The actual genesis of AVM seems to occur in the fourth to sixth week of pregnancy [56], [57]. The exact pathomechanism of arterio-venous malformations is still unknown; in malformed areas, because of deficient sphincters or crosslinking abnormal capillaries seem to form a direct high pressure to low pressure connection between an artery and a vein. This central area of an AVM is called nidus and describes its origin in the narrower sense. In contrast to hemangiomas, AVM show a clear tendency to expand during lifetime. This expansion proliferates frequently and leads to a destruction of soft tissue and bones so that original borders can no longer be identified. It is often associated with severe bleeding, functional impairment and aesthetic deformities depending from the stage.

AVM may occur singularly or as part of a syndrome. Examples for syndromal diseases that are associated with extracranial AVM are the Wyburn-Mason syndrome, the Parkes-Weber syndrome, and the Cobb syndrome. The Wyburn-Mason syndrome is a disease of the central nervous system, associated with vascular malformations that are described as so-called angioma racemosum which is mainly due to history. In this context, abnormal connections are formed between the retina and the central nervous system of the patient. Frequently, the patients are affected by vision disorders to complete blindness and cranial nerve disorders. Also the extracranial involvement in the sense of a manifestation in the area of the face is characteristic and it often leads to disfiguration of the patient and repeated bleedings [57]. Patients with Parkes-Weber syndrome suffer from AVM of the extremities and are characterized by growing disturbances in the sense of gigantism. In many cases the patients additionally have a naevus flammeus of the affected region [58]. The Cobb syndrome is described with a connection between the capillary malformation of the skin and a deep AVM in the area of the spinal cord, the neighboring muscles and the bony areas of the spinal cord [59].

The so-called Schobinger classification can be considered as the first trial to subdivide arterio-venous malformations. In this context, the AVM are classified in four categories (I–IV). Category I, also called resting phase, is a stage of AV malformation that is mostly found in pediatric patients – it is an asymptomatic finding accompanied by a local erythema and overheating of the affected area. Stage II is characterized by growth with infiltration of deep subcutaneous structures. The lesion is associated with palpable pulsations and audible bruit. Stage III additionally shows dystrophic skin alterations in the sense of ulcerations, pains, bleeding, superinfections, and necrosis.

Table 4: Modified classification of arterio-venous malformations of the head and neck according to [61]. The extension on the surface refers to aesthetic units as applied in facial surgery [68].

Classification	Description
T1	Includes 1 cervico-facial subunit
T2	Includes 2 cervico-facial subunits
T3	Includes ≥3 cervico-facial subunits
T4	Bilateral/multifocal disease
D1	Skin and/or subcutaneous involvement
D2	Subcutaneous and muscular involvement
D3	Subcutaneous, muscular involvement and cartilaginous or ossal involvement
D4	Skull base or intracranial involvement
S0	Resting
S1	Proliferation (pulsation, rapid growth)
S2	Destruction (ulceration, bleeding, pain)
Grade I	T1–2 D1 S0, T1 D1 S1, T1 D2 S0
Grade II	T1 D3 S0, T2 D1–2 S1–2, T2 D2 S0
Grade III	T1 D3 S1–2, T3 D1-2 S0, T2 D3 S0–2
Grade IV	T3 D3 S0–2, each D4, each T4

Schobinger finally described stage IV with continuing ulcerations and bleedings, associated with cardiac decompensation [60]. This classification that was presented in the 1970ies was and is still applicable in a limited way for head and neck AVM. For example, no patient suffering from AVM was observed in our patient population having consecutive cardiac decompensation associated with stage IV according to the Schobinger.

With this background, Richter and Suen modified the classification of arterio-venous malformations of the head and neck considering additional parameters. The modified version does not only include the extension but also the infiltration into the depth and the growth behavior [61]. This classification takes into account the tumor extension concerns the surface (T1–T4), the depth (D1–D4), and the general growth behavior of the malformation subdivided into the qualities of "resting", "expanding", and "destroying" (S0–S2) (Table 4).

In summary, the introduction of such a classification is appropriate because clinical studies on the subject of AVM of the head and neck are mostly based only on retrospective analysis of patient data. So the hope was to find a classification system that helps to better understand and compare the therapeutic results from those evaluations. However, no statement can be made if the mentioned classification will turn out to be useful at long-term.

Extracranial AVM are a rare entity. There are no data on the incidence of AVM. Viesser and co-workers [62] showed that AVM make only 4.7% of the total collective of 1,131 patients suffering from vascular anomalies. Up to now neither gender-specific nor race-specific particularities could be assessed.

The first diagnosis is often made only after an acute increase in volume or after occurrence of bleedings. Frequently, hyperemia is found in the area of the affected skin or mucosa, in this stage a Doppler sonography could confirm the presence of a high-flow lesion. The rapid growth of a normally stable vascular anomaly should always lead to the suspected diagnosis of arterio-venous malformation. Liu and co-workers [63] could show that the progression of arterio-venous malformations occurs most frequently in adolescence. On the average, their patients were 12.7 years old at the time of first diagnosis. Most studies dealing with extracranial malformations, however, report about patient collectives with ages ranging from 20 to 50 years when the AVM are most frequently diagnosed.

Up to now, no case could be identified where an arterio-venous malformation spontaneously disappeared. The progress itself is irregular, it can occur gradually or rapidly. A massive growth frequently requires a surgical with or without previous embolization. Without such a measure, critical findings nearly always lead to destruction of the tissue, functional impairment, ulcerations, and blood loss. In the head and neck area, bleedings from AVM of the soft tissue are rather rare in children, an involvement of the maxillary bone, however, can be the source of massive bleedings at the time of second dentition or in the context of dental treatment.

Furthermore, AVM can be divided into focal, uni- or multifocal, and also diffuse vascular malformations. The focal
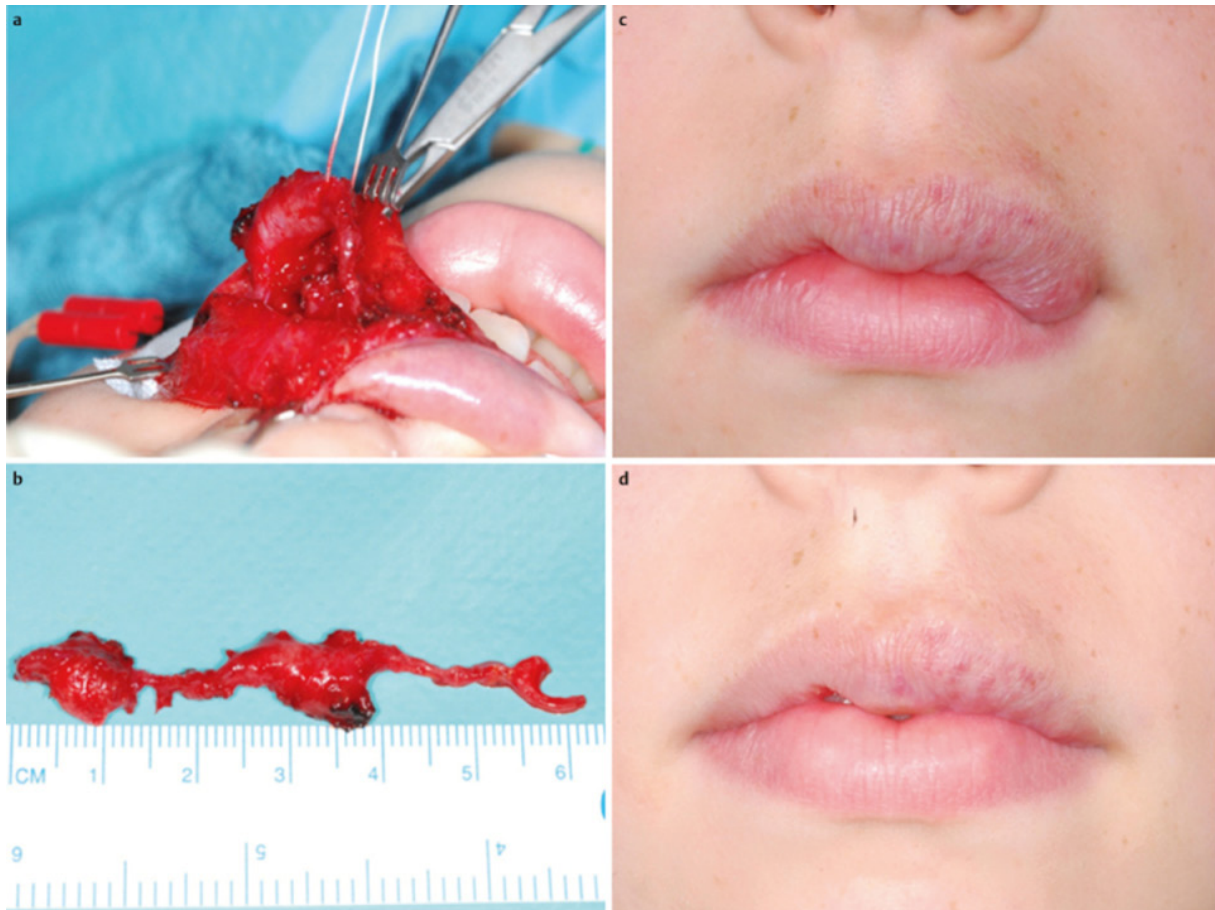
Figure 15: Treatment of a focal arterio-venous malformation of the lower lip by means of excision in a 13-year old female patient. (a) Surgical approach. (b) Resected tissue. (c) Preoperative status and (d) condition 3 months postoperatively.

AVM show a well delineated nidus which in its simplest form consists of one single arterial feeder with corresponding venous drainage. Those focal AVM are mostly accessible for surgical therapy and could ideally be diagnosed and treated already in childhood (Figure 15).

Diffuse AVM that already go beyond the limits of topographic units and where also with the background of incomplete previous treatments the arterio-venous nidus can no longer be identified are mostly observed in adult age. They are more difficult to treat and have a significantly higher recurrence rate after resections.

Theoretically, arterio-venous malformations can occur in every location of the head and neck, often they are observed in the area of the mid face and in the oral cavity. Rare manifestations are in the larynx or the cervical soft parts. In cases with diffuse or multifocal manifestation where the nidus or the nidi can no longer be accessed surgically or that are no longer delimitable a safe and specific resection cannot be assured involving all affected areas in the resection borders. So it can be well understood that experts often compare diffuse AVM with malignant head and neck tumors [64].

The difference between AVM and most other vascular anomalies of the head and neck is that AVM have an arterial feeder. Warmth, tension, palpable flow or pulsations are most simple clinical characteristics of AVM. Regarding the most important differential diagnosis of AVM in childhood hemangiomas must be mentioned that may show Doppler-sonographically blood circulation of the high-flow type during the proliferation phase. With this background, each vascular anomaly classified as hemangioma should be differentially diagnosed in the sense of arterio-venous malformation at the latest when no sign of regression can be observed during the second year of life.

Imaging techniques play a major role for the diagnosis of arterio-venous malformations. MRI with Gadolinium-containing contrast agents reveals high-flow lesions mostly by so-called flow voids (Figure 16). A diagnostic angiography can identify in particular afferent arterial feeders of arterio-venous malformations. Additionally, the value of Doppler sonography must be emphasized which should be performed as part of basic examination during the first clinical assessment as well as during follow-up examination of arterio-venous malformations. During the last years, CT angiography has been established as an increasingly valuable tool for the diagnosis of extracranial arterio-venous malformations. The advantage of CT angiography is especially the clearly lower invasiveness in comparison to classic catheter-guided angiography and the better delineation of the lesion from the adjacent tissue. In particular the possibility of three-dimensional reconstruction of CT angiography does not only help to assess the findings for clinical assessment. Generally,

the classic catheter-guided angiography can be replaced by CT angiography for superficial or unifocal AVM because the possibility of delineation from deep tissue as well as the identification of the nidus in these lesions is ensured by CT angiography. In particular for the pediatric patient population the possibly lower irradiation of CT angiography plays a significant role for the decision about adequate imaging. Only when CT angiography leads to the suspicion that a diffuse or multifocal AVM or an involvement of deeper tissue structures is present catheter-guided angiography should be performed afterwards. However, it should be indicated with special questions such as the presence of collateral supply, the further therapeutic course, and in the case of identification of bony involvement of the facial skull.
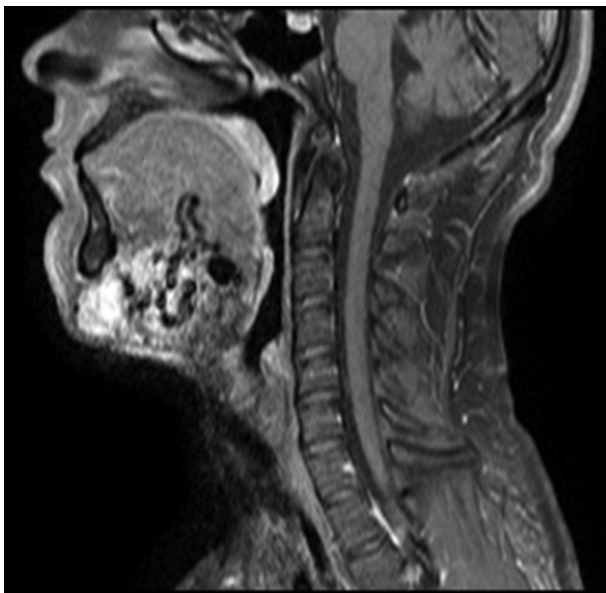

Figure 16: T1 sequence of an MRI with contrast agent of an arterio-venous malformation of the submental region with infiltration of the floor of the mouth and the tongue with evidence of "flow-voids" (→ arrow)

The diagnosis of AVM is made based on the clinic and the imaging; histology is not always required for the diagnosis of arterio-venous malformations. Histologically, often a combination of altered capillaries, arterioles, and venules is observed. An arterialized vein as pathognomonic histological correlation of arterio-venous malformation needs not necessarily be proven in pediatric AVM of the head and neck. The irregular and loose vascular morphologies varying in size in the histology together with the above-mentioned arterialized veins that can only be confirmed in advanced stages represent the typical histological image of AVM (Figure 17).

It is assumed that a missing regression of primitive arterio-venous connections as evolutionary early stage of the normal vascular system is the origin of arterio-venous malformations. Those residual small arterio-venous shunts are subsequently exposed to blood flow and thus grow in volume. This growth leads to hypoxia which is again a further stimulation for the growth of the AVM. This theory for the genesis of intracranial AVM was de-

scribed by Sure and co-workers [65]. The clinical observation that an incomplete therapy basing only on a partial embolization of AVM would lead to a significant progression of the finding at middle- or long-term justifies the assumption that hypoxia could be an important stimulus for an uncontrolled progression of the extracranial arterio-venous malformation as it is already proven for intracranial AVM [66]. This phenomenon is often observed when during a control of the findings the afferent arterial vessels, branches of the trunk of the external carotid artery are erroneously ligated completely or partially. Nearly regularly an uncontrolled progression of the findings is observed afterwards because new feeders from collateral circuits, e.g. the vertebral artery, are activated.
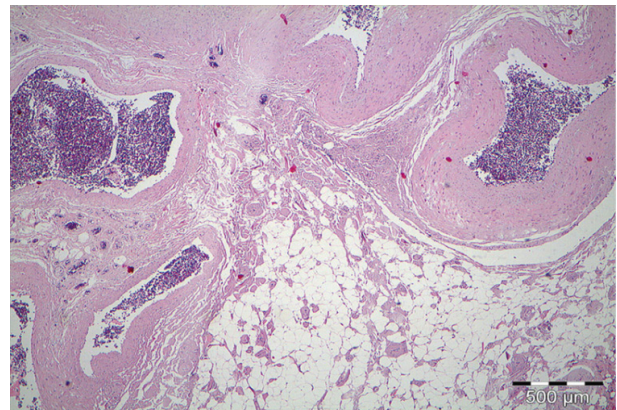

Figure 17: Histologic specimen of an arterio-venous malformation with confirmed thick-walled (arterialized) venous vessels (→); (H&E x10)

The clinical management of extracranial AVM requires a close and long clinical observation of the course. Conventional surgical measures and the intravascular embolization or a combination of both last-mentioned modalities are nowadays established methods for the treatment. Especially in childhood an individualized treatment strategy must be found considering the optimal time for therapy in the context of curability, control of the findings, and possible iatrogenic consequences. Unifocal AVM can sometimes be well treated with surgical excision, however, multifocal or diffuse AVM are problematic so that despite therapeutic measures such as embolization or surgical excision often recurrences are observed. Based on the above-mentioned facts, an incomplete treatment can probably impair the prognosis of arterio-venous malformations in the long-term course. Incomplete previous treatments by embolization, vascular ligation or unspecific surgical excision can significantly impair a curative approach or even make it impossible (Figure 18).

More so than any other angiomatous alteration, arterio-venous malformations require sound knowledge of the biological behavior. As in particular pediatric patients most frequently have lesions that do not cause significant symptoms, the strategy of watch-and-wait has been favored for many years. With the current knowledge that expanded arterio-venous are significantly more difficult to treat the surgical resection should be recommended

Figure 18: (a) Arterio-venous malformation of the face in a 12-year-old female patient. (b) Status at the age of 41 years with anamnesis of multiple embolisations, resections, and bilateral ligation of the external carotid vein.

when the diagnosis of AVM in children is made and this kind of intervention can be justified. Small AVM in deep tissue layers that can be accessed by superselective embolization should undergo embolization alone when an additional surgical therapy is not justified because of peri- or postoperative morbidity or when already functional problems are present such as ulcerations or bleedings. For those cases a long and narrow postinterventional control is obligatory to early detect recurrences. With the background of the mentioned consequences of incomplete surgical resection, singular symptomatic diffuse AVM are possible candidates for embolization alone for symptom control, of course again with the restriction that hypoxia occurring after embolization may lead to uncontrolled growth stimulation. Often the angiographic documentation shows postinterventionally a successful ablation of the AVM. However it is proven that embolization alone cannot significantly reduce the recurrence rate of arterio-venous malformations [63], which correlates to the previous statements on resulting hypoxia.

In summary, in contrast to a disfiguring surgical intervention, embolization alone can be justified especially in pediatric patients under the condition that narrow clinical controls are performed when functional damage must be expected or ulcerations have already occurred. A surgical treatment must be discussed also in those stages. According to the current knowledge, the treatment with embolization combined with conventional surgical excision removing the arterio-venous nidus can be considered as therapy of choice of extracranial AVM. This combined method helps reducing the risk of intraoperative bleeding and to keep the surgically justifiable limits of resection. According to the experience with intracranial AVM the liquid embolization agent Onyx® (ethylen-vinyl-alcohol copolymer, solved in dimethylsulfoxyd (DMSO)) is recommended also for embolization of extracranial AVM. Onyx® has not only proven to be appropriate for occlusion of small

vessels up to 5 µm in diameter, due to the black coloring of the embolized area the preparation of the AVM is facilitated by a better intraoperative identification. However, Onyx® leads to inflammatory reactions, discolorations of the skin, and induction of necroses. This is why this method is often combined with a conventional surgery soon afterwards.

Especially advanced or diffuse findings present a challenge for the physician who has to decide if the treatment itself leads to a higher morbidity for the patient than the disease. The surgical excision of arterio-venous malformations requires a high technical expertise. The surgeon has to be prepared to cope with potentially massive bleedings. The dissection and the preparation of arterio-venous malformations are difficult. The nearly continuing necessity to perform hemostatic measures requires clearly longer time for preparation of the intervention in comparison to other surgeries (e.g. oncologic interventions). Beside intraoperative safety measures such as the presence of autologous transfusion systems, fibrin glue, and special instruments for vascular ligation (e.g. titanium clips) an operation microscope may be a helpful tool for those interventions. Often the resection of AVM requires a mostly simultaneously performed defect covering by means of local, regional, or pedicled distant flaps. In addition, it must be expected that the wound healing is often impaired in vascular malformations which is especially the case after repeated interventional measures. This is why often postoperative care with intensive wound management are necessary for several weeks.

In summary it can be stated that small and unifocal arterio-venous malformations can often be treated curatively. Advanced or diffuse or multifocal AVM are a major therapeutic challenge. Additional it must be emphasized that an incompletely treated AVM nearly always bears the high risk of recurrence and progression.

Up to now it was not possible to establish a pharmaco-therapeutic approach for the treatment of arterio-venous malformations. The application of medicaments for the therapy of arterio-venous malformations was only reported in single cases with questionable outcome in the context of healing. Propranolol which is a potential therapeutic option for infantile hemangiomas in the proliferation phase is not appropriate for arterio-venous malformations. In single cases, initially a light improvement of the findings can be achieved; however, it is mainly due to the reduction of the blood pressure and the blood flow as general effect of a beta blocker. Further therapeutics that are discussed are Vincristin, which bears a significant risk of induction of a peripheral neuropathy with questionable success, and Marmistat, a matrix-metallo-proteinase inhibitor which was only applied once in a 12-year-old girl suffering from AV malformation in the area of the lower extremities for control of the findings [67].

Notes

Acknowledgement

Competing interests

The authors declare that they have no competing interests.

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