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TREATMENT OF VENOUS MALFORMATIONS – COMPARISON TO LYMPHATIC MALFORMATIONS

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ABSTRACT

Classification of venous and lymphatic malformations according to the description of the International Society for the Study of Vascular Anomalies is based on clinical and MRI appearance. Although possible limitations exist, it should be carried out for treatment decisions. Treatment modalities include the use of sclerosing agents directly introduced by percutaneous puncture (Ethibloc, Thrombovar, Ethanol in venous malformations or Picibanil in macrocystic lymphatic malformations), laser-induced thermal therapy, surgery, or a combination of different techniques. A promising substance for treatment of venous malformations is an Ethanol mixture with Ethylcellulose at a higher viscosity, which is under evaluation in a multicenter-study.

Keywords: venous malformation, lymphatic malformation, treatment, sclerotherapy, ethanol

Among vascular anomalies there are several entities which need to be differentiated from each other. In the past, the term hemangioma has been used to describe anomalies with heterogeneous radiological findings causing significant confusion in the categorization and treatment of these complex vascular lesions. A variety of classification schemes for vascular lesions have been proposed based on descriptive clinical, histological, embryological, and angiographic features. In 1988, Mulliken (1,2) created a comprehensive classification system emphasizing their clinical behavior and endothelial cell characteristics. Since then, vascular malformations have been classified by the predominant type of vessel involved and include capillary, venous, lymphatic, and arteriovenous types. Whereas systematic classification is not very suitable for research, it is extremely helpful to define the different types for treatment options. The classification given by the International Society for the Study of Vascular Anomalies is now widely accepted and divides the main category of vascular anomalies into tumors and malformations *(Table 1*). This classification was improved upon by Hand and Frieden (3) who subdivided it into simple and combined malformations allowing more practical meaning for treatment (*Table 2*).

In this manuscript, our focus is on venous and lymphatic malformations. Venous malformations can manifest at any location of the body as a solid soft-tissue mass consisting of multiple enlarged venous channels and lakes (*Fig. 1*). They are predominantly located in the skin or subcutaneous tissue, however they also can infiltrate deeply in the soft tissue especially in the head and neck region. Since venous malformations are present at birth, persist and even grow during childhood and at slower rates during adulthood, there is a high need for treatment. Among the basic features found in these common and progressive

TABLE 1
Classification Scheme of Vascular Anomalies from the International Society for the Study of Vascular Anomalies

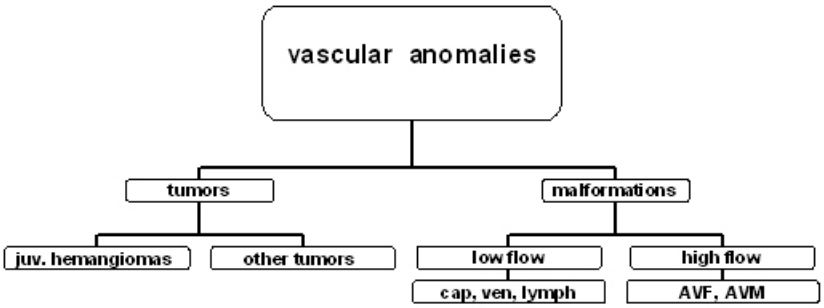

TABLE 2
Classification of Vascular Malformations by Hand and Frieden (2002)

Simple
- Capillary (port-wine stain)
- Venous
- Lymphatic (including "lymphangioma" and "cystic hygroma")

Combined
- Capillary-lymphatic-venous (CLVM-includes most cases of Klippel Trenaunay)
- Capillary-venous (includes many milder cases of Klippel Trenaunay)
- Capillary-venous with arteriovenous shunting and/or fistulae (Parkes-Weber Syndrome)
- Cutis marmorata telangiectatica congenita
- Lymphatic-venous

venous malformations are: venous structures which are fed by capillaries or have variable integration into venous circulation, distribution within the connective tissue of all organs, familiar variants exist with a dominantly inherited type which has been located to chromosome 9p, and endothelial activation by Tie2 which shows close association to lymphatic disorders.

For diagnosis and particularly management, an interdisciplinary approach and cooperation is mandatory. Dependent on location, extension and pre-treatments, different disciplines may need to be involved including maxillo-facial surgery, ENT-surgery, ophthalmology, dermatology, pediatrics and neuroradiology.

For diagnostic evaluation, a complete history (manifestation at birth, deterioration over years and often recurrence after various treatments) and clinical examination should be implemented with imaging. Imaging of the lesion with MRI for extent and characterization and with different MR-angiography techniques are also helpful for planning the treatment (4,5). Dynamic MR-angiography or digital subtraction angiography is a time-resolved MR-imaging technique using the

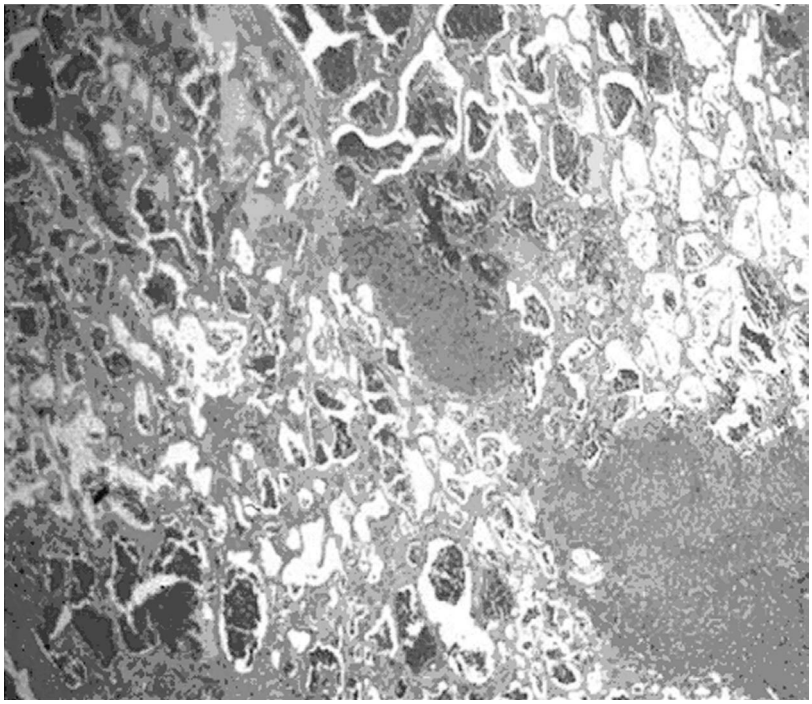

Fig. 1: Histological specimen displaying a venous malformation consisting of differently sized venous vessels and pouches partially thrombosed with central necrosis. Sclerosing therapy is performed by puncture of these vessels with injection of sclerosing agent.

injection of a contrast agent bolus and observing the dynamics of its propagation. This technique is advantageous especially for vascular malformations with strong vascularization because the hemodynamics of the pathologic process can be assessed (6,7). In some patients, opacification of venous pouches and lymphatic cysts can be seen following percutaneous puncture with contrast medium. In most cases, conventional angiography is not necessary.

Although the value of MRI for differential diagnosis of vascular malformations is limited, it delineates very well the extent and especially the extension into deep structures. On T1 images, venous malformations show an intermediate intensity, which is slightly more intense than muscle with a strong enhancement of the venous channels after gadolinium application. Because of the extremely low flow, a signal loss (the so-called flow void) generally does not exist. Black spots within the mass of huge venous malformations correspond to calcifications. On T2- weighted images, the lesions show a high signal which is more homogenous and bright in large venous pouches (*Fig. 2*). Lymphatic malformations have the same or lower signal on T1 as muscle and do not enhance after administration of contrast agents. Their signal intensity on T2 is usually greater than that of fat and septations may be visible especially on T2, leading to a focal inhomogeneous appearance (*Fig. 3)*. Depending on the mixture with other tissue (e.g., fat and septa) and the content of large cysts, signal intensity may vary, e.g., in blood and debris containing cysts, T2 signal may equal that of muscle. *Table 3* summarizes typical MR-signal behavior of venous and lymphatic malformations.

Different treatment modalities are available for vascular malformations depending on the approach by arterial route or by direct

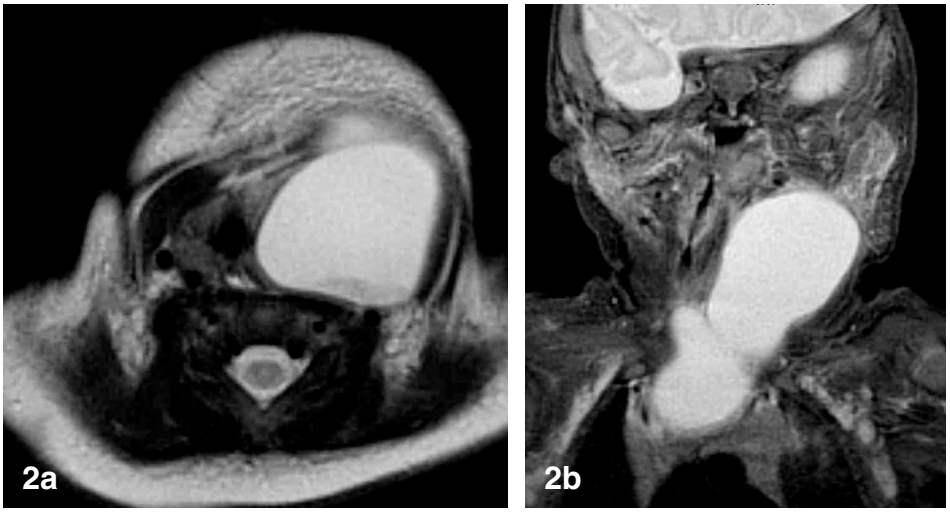

Fig. 2: Large cystic lymphatic malformation in a 3 week old newborn. Coronal (a) and transverse (b) T2 slices display the space-occupying lesion with compression of cervical soft tissue and deviation and narrowing of the trachea leading to stridor. The tumor was immediately extirpated surgically. Note the characteristic sedimentation (hypointense) at the bottom of the cyst in the transverse slice (b).

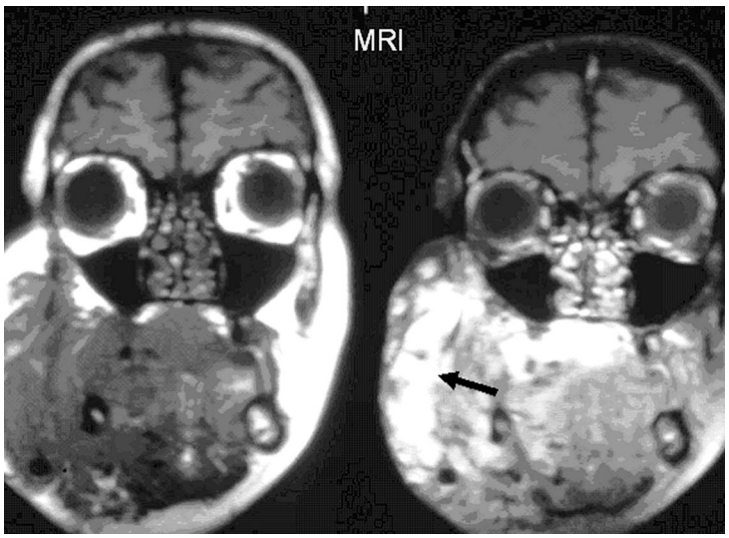

Fig. 3: MRI with T1- (left) and contrast enhanced fat suppressed T1-weighted image (right) showing a large subcutaneous mass of the right cheek consisting of partially open venous pouches (arrow).

percutaneous puncture. In venous malformations as well as in larger lymphatic cysts, mainly sclerosing agents are used or embolic material such as Ethibloc. Other options are surgery or laser-induced thermal therapy (LITT) or a combination of several techniques.

Although there has not yet been a prospective, randomized study comparing the different substances for sclerosing effectiveness, recurrence rate and risk of local or systemic side effects, ethanol as well as Ethibloc have been widely used for years

TABLE 3
Typical MR-Signal Behavior of Venous and Lymphatic Malformations

	T2	T1	Contrast Agent
Venous malformation	High signal	Slightly higher than muscle	Strong enhancement
Lymphatic malformation	Higher than fat	Equal or lower than muscle	No enhancement

TABLE 4
Treatment with Ethibloc

Authors	Injected rates	Success rates	Complication rates[1]					
			N	F	S	Ne	Syst	B
Baud	30% of MV	80.0%	0	50%	30%	0	10%	0
Breviere	ND	88.8%	0	11%	0%	0	0%	0
Dubois	6 ml	76.0%	5.2%	0	39.5%	0	2.6%	0
Gelbert	1/3 of MV	100%	0	0	44%	0	0	0

[1]N=Necrosis; F=Fistula; S=Surgical excision; Ne=Nerve damage; Syst=Systemic manifestations; B=Bleeding; ND=Not done.

(8-19). Both agents have proved to be highly sclerosing solutions. Also, data are not available regarding Trombovar (Sodium Tetradecyl Sulfate), a third commonly used sclerosing liquid. In a meta-analysis by Sannier (20, *Table 4*), therapeutic efficacy of Ethibloc is comparable to Ethylcellulose-Ethanol but the injected volumes of Ethibloc were larger.

In a study, first published by Tiret (21) and republished with clinical aspects (20,22, *Table 5*) a modified absolute Ethanol with higher viscosity due to combination with Ethylcellulose was clinically tested and compared to the results of several studies in the literature. The main advantages of this gelified liquid were its high sclerosing property with a smaller amount of substance, and the low risk of systemic side effects due to the local distribution with no diffusion far from the target.

OK-432 (Picibanil®) may be an interesting relatively new therapy for macrocystic lymphatic malformations. Smith and coworkers published 2 completely occluded macrocystic lymphatic malformations, whereas 3 microcystic lymphatic malformations and one venous malformation showed no response (23). Similar results were found by Bloching et al.and Knipping et al. in patients with cervical cystic lesions (24,25).

In our own ongoing multicenter study, we are testing ethanol mixed with etyhlcellulose at a higher viscosity in the treatment of venous malformations. In vitro testing showed that the mixture promptly precipitated when injected into sodium solution or whole blood. Further, it proved to have no

TABLE 5
Treatment with Alcohol

Authors	Average procedures	Injected volumes	Blood alcohol level	Success rates	Complication rates[1] N	F	S	Ne	Syst	B
Berenguer	2.5	1 ml/kg	ND	75%	13%	0	0	7.5%	0	28%
Berthelsen	3	ND	5 mmol/l	ND	20%	40%	0	0	0	0
Lee, Kim	3.26	ND	ND	ND	6.6%	0	0	16.6%	20%	0
Lee, Bergan	3.2	1 ml/kg	ND	95%	40%	0	0	1.3%	0	0
Lee, Do	4/58	ND	ND	ND	58.6%	0	0	2.3%	0	0
Pappas	2.5	9 ml	ND	92%	50%	0	50%	0	0	10%
Shireman	2.5	9 ml	ND	92%	50%	0	0	0	0	16.6%
Suh	1.29	6 ml	ND	ND	0	0	0	0	0	0
Svendsen	ND	ND	21.7 mmol/l	97%	9.7%	0	25.8%	3.2%	00	
Yakes	ND	ND	ND	ND	11.1%	0	0	0	11.1%	0

[1]N=Necrosis; F=Fistula; S=Surgical excision; Ne=Nerve damage; Syst=Systemic manifestations; B=Bleeding; ND=Not done.

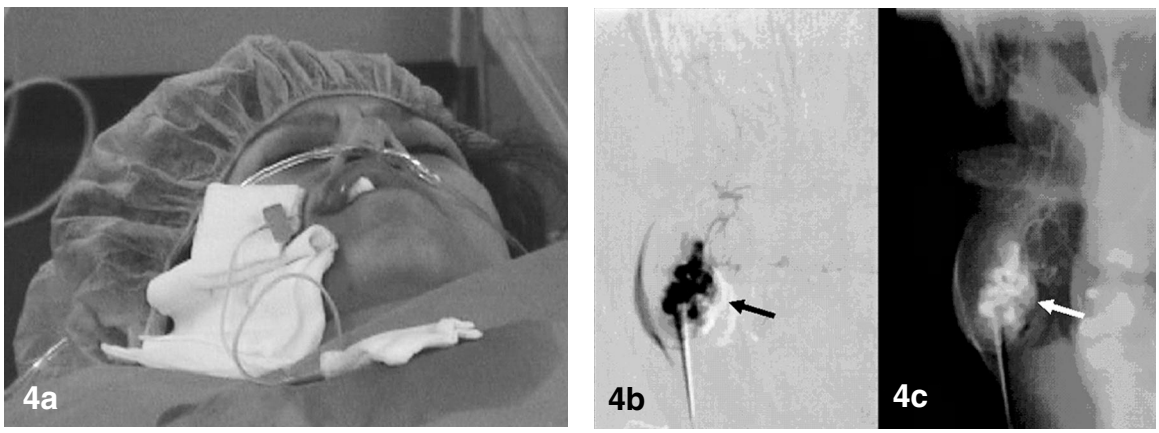

Fig. 4: Direct puncture of venous malformation at the angle of the right upper lip. Procedure performed on the angio suite table showing the butterfly needle and connection cable (a). Substructed (b) and non substructed (c) angiographic picture after injection of contrast medium showing the extension of the venous malformation (arrow).

gluing effect prohibiting a gluing of puncture devices or catheters when used in venous malformations in human. However, animal testing demonstrated that the material is not suitable for arterial injection because it escapes from the capillary bed in humans.

To date, 61 patients aged 4-38 years have been treated with the substance showing no systemic effects but high sclerosing efficacy. This preliminary experience confirms that the substance is easy to handle, safe in application with a low rate of systemic side effects,

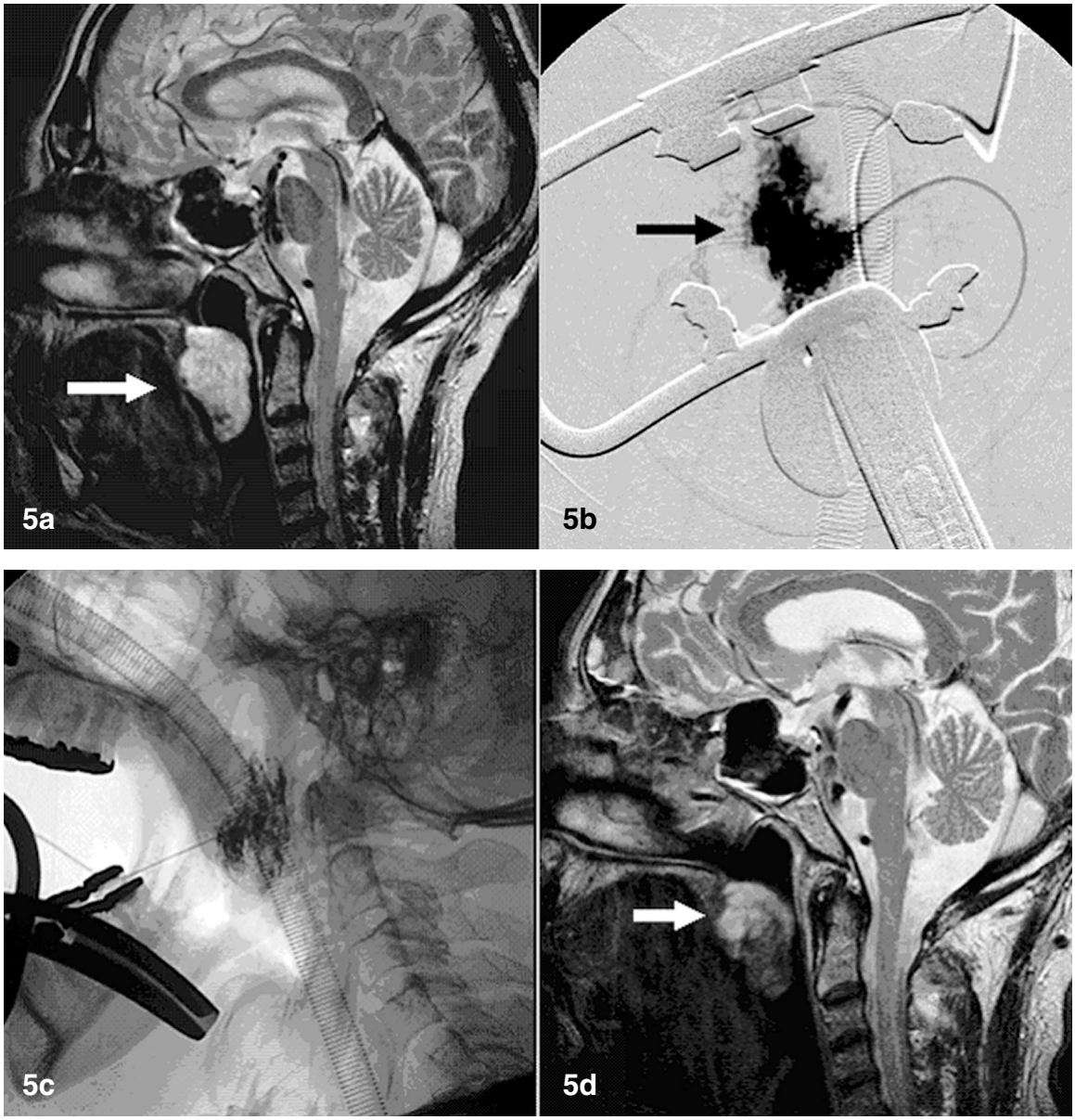

Fig. 5: Pharyngeal venous malformation demonstrated by sagittal T2-weighted image before (arrow in a) and after the first treatment (d). Opacification of the lesion after injection of contrast medium (b - before and c - after first sclerosing treatment).

and with a high efficiency due to specific target injection. Most of the procedures can be performed with local anaesthesia, or if necessary, general anaesthesia in smaller children. Although the venous malformations have low or no flow after puncture of the venous pouches, we routinely inject contrast medium to analyze any connection to draining veins, e.g., into the external jugular system in case of a facial malformation (*Figs. 4,5)*. In summary, based on our limited knowledge, small to medium sized venous

malformations may be treated by sclerosing alone but larger lesions still require surgery after reduction of their volume by ethanol-ethylcellulose.

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