Diplomarbeit

Therapeutic options in brainstem cavernous malformations
A retrospective analysis of 26 patients treated at the Department of Neurosurgery in Graz

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AFFIDAVIT

I hereby declare that the present diploma thesis and the work reported herein was originated and composed entirely by myself and without any assistance from third parties. Furthermore, I confirm that no other sources than those indicated in the text have been used in the preparation of this diploma thesis.

Finally, I declare that I have no conflict of interests.

Emanuel Martin Adler eh. Graz, November 16th, 2017

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1.1 LIST OF ABBREVIATIONS

AVM	arteriovenous malformation
BSCM	brainstem cavernous malformations
CM	cavernous malformations
CN	cranial nerve
CT	computed tomography
GOS	Glasgow Outcome Scale
KPS	Karnofsky performance status
mRS	Modified Rankin Scale
PCA	posterior cerebral artery
PICA	posterior inferior cerebellar artery
SI	signal intensity

1.2 ILLUSTRATION DIRECTORY

2 ZUSAMMENFASSUNG

Hintergrund: Hirnstammkavernome sind relativ selten und galten einst als inoperabel, heutzutage sind sie chirurgisch, mit ermutigenden Ergebnissen therapierbar. Es ist bei dieser Erkrankung jedoch noch vieles unklar. Demnach tragen alle Publikationen in diesem Bereich zur weiteren Erforschung dieser Pathologie bei.

Ziele: Ziel dieser retrospektiven Analyse ist es, die Wirksamkeit einer chirurgischen Entfernung der Läsion durch Vergleich des prä- und postoperative neurologische Status zu untersuchen. Des Weiteren wurden Faktoren untersucht, die einen möglichen Einfluss auf das Ergebnis ausüben.

Methoden: Es wurde die Krankengeschichte von 26 PatientInnen der Universitätsklinik für Neurochirurgie in Graz, retrospektiv eruiert. Folgende Parameter wurden analysiert: Basisdemographische Daten, prä- und postoperativer neurologischer Status, in Verwendung der modifizierten Rankin Skala und des Glasgow Outcome Score, Tumor Daten und die chirurgischen Zugangswege. Es wurde eine deskriptive statistische Analyse durchgeführt., um den prä- und postoperativen Status zu vergleichen wurde ein Wilcoxon-Test angewandt. Ein Mann-Whitney-Test wurde verwendet um den Zusammenhang zwischen dem Outcome, und der Größe der Läsion zu überprüfen.

Ergebnisse: Das Alter der PatientInnen reichte von 16 bis 71 Jahren (Mittelwert: 43,1 Jahre, Median 40 Jahre). 11 (42,3%) PatientInnen hatten ein und 15 (57,7%) mehrere Blutungsereignisse. Die Zeit vom Blutungsereignis bis zur Operation betrug im Mittelwert 41 Tag, im Median 28 Tage. Von allen Hirnstammkavernomen waren 14 (53,9%) in der Pons, 6 (23,1%) in der Medulla Oblongata und 6 (23,1%) im Mesencephalon lokalisiert. Die Größe der Läsionen reichte von 0,231 bis 7,9 cm^3. Es wurden 18 (69,2%) Totalresektionen, 1 (3,85%) Subtotalresektion, 4 (15,4%) Partialresektionen durchgeführt, 1 Kavernom war nicht zugänglich, ein (3,85%) Kavernom wurde radiochirurgisch und eines (3,85%) konservativ behandelt. Bezogen auf alle chirurgisch behandelten PatientInnen, traten in 6 Fällen (25%) Komplikationen auf (Liquorfistel bei 4 PatientInnen (16,7%) und Rhinoliquorrhoe bei 2 PatientInnen (8,3%) Rhinoliquorrhoe). Die Resultate des Wilcoxon-Tests zeigten, dass sich der neurologische Status nach der Operation statistisch signifikant ($p=0,006$) verbesserte. Der Mann-Whitney-Test zeigte keinen statistisch signifikanten Zusammenhang ($p=0,698$), jedoch konnte in der graphischen Darstellung eine Korrelation zwischen einer höheren medianen Größe der Läsion und eines schlechteren Outcomes abgelesen werden.

Schlussfolgerung: Die Operation ist die Therapieoption der ersten Wahl, sie sollte in der subakuten Phase erfolgen und als Totalresektion durchgeführt werden.

3 ABSTRACT

Background: Brainstem cavernous malformations are relatively rare and once considered inoperable, nowadays they are surgically treatable, with encouraging results. Nevertheless, there are remaining questions concerning these lesions. Therefore, every report contributes to the exploration of this pathology.

Objective: The aim of this retrospective analysis was to evaluate the efficacy of surgical treatment, based on the pre- and postoperative rates of morbidity and to identify predictors which influence the surgical outcome.

Methods: The medical histories from 26 patients of the Neurosurgical Department of the Medical University of Graz were retrospectively reviewed. We analyzed: patient demographics, pre- and postoperative neurological status using modified Rankin Scale scores and Glasgow Outcome Scale sores, lesion characteristics and surgical approaches. A descriptive statistical analysis was performed. We used a Wilcoxon test to compare the pre- and postoperative scores and a Mann-Whitney Test to investigate the association of the outcome with the size of the lesion.

Results: Ages ranged from 16 to 71 years (mean, 43,1 years; median, 40 years). 11 (42,3%) patients had a single and 15 (57,7%) patients had multiple hemorrhagic events. The time from the last hemorrhagic event to surgery was evaluated with a median of 28 days and a mean of 41 days. 14 (53,9%) cavernomas were located in the pons, 6 (23,1%) in the medulla oblongata and 6 (23,1%) in the midbrain. The size of the lesions ranged from 0,231 to 7,9 cm^3. Total resection was achieved in 18 (69,2%), subtotal in 1 (3,8%), partial in 4 patients (15,4%), in 1 (3,85%) patient the cavernoma was inaccessible, 1 (3,85%) patient was treated radiosurgically and 1 (3,85%) patient was treated conservatively. Complications occurred in 6 cases (25%), which involved liquor fistula in four patients and rhinoliquorrhea in two patients. The Wilcoxon-test showed that the neurological status improved significantly (p=0,006) after resection. The Mann-Whitney Test did not show a statistically significant correlation (p=0,698). However, the graphical illustration showed a correlation of larger size with unfavorable outcome.

Conclusion: Surgical resection is the first choice of treatment, it should be performed in the subacute phase and total resection of the lesion is essential.

4 INTRODUCTION

4.1 ANATOMY OF THE BRAINSTEM

4.1.1 SURFACE SURGICAL ANATOMY OF THE BRAINSTEM

4.1.1.1 Midbrain

The midbrain is bordered by the optic tract cranially and the pontomesencephalic sulcus caudally. The midbrain can be divided into the ventral crura cerebri, the tegmentum in the middle and posteriorly the tectum also called the quadrigeminal plate. The term cerebral peduncles mean the combination of the crura cerebri and the tegmentum. Another way to categorize the midbrain is to divide it by the lateral mesencephalic sulcus into an anterolateral part and a posterior part. The origin of the lateral mesencephalic sulcus is cranially by the medial geniculate body and goes into the direction of the pontomesencephalic sulcus. The interpeduncular fossa is defined as the space between the cerebral peduncles, this fossa contains the posterior perforate substance and is the origin of the oculomotor nerve. The tectum is built by four colliculi, two superior colliculi and two inferior colliculi. The trochlear nerve emerges directly under the inferior colliculus. (1,2)

4.1.1.2 Pons

The pons is bordered by the pontomesencephalic sulcus cranially and the pontomedullary sulcus caudally furthermore, the pons is divided from the middle cerebral peduncle by the origin of the trigeminal nerve. At the midline of the rostral convex pons, the basilar sulcus immerges. The abducens nerve has its origin medially at the pontomedullary sulcus, the supraolivary fossette is the origin of the facial nerve and the vestibulocochlear nerve. The floor of the fourth ventricle, also known as the rhomboid fossa, is built by the dorsal pons and the dorsal portion of the medulla. At the dorsal junction of the pons and the medulla, there is a structure called the striae medullares which divides the rhomboid fossa into two triangles. The borders of the rhomboid fossa are, cranially the apex, located at the sylvian aqueduct, the cerebellar peduncles laterally at the upper triangle, the teniae of the fourth ventricle form the lateral limit of the inferior triangle and the obex forms its inferior and medial limit. There are three vertically sulci at the surface of the rhomboid fossa, in the middle there is the median sulcus and at the left as well as at the right side of it there is one sulcus limitans. The median eminence lies in between the median sulcus and the sulcus limitans. The median eminence contains the facial colliculus, the hypoglossal trigone and

the vagal trigone. Two another important regions of the rhomboid fossa are the locus coeruleus and the vestibular area, both located lateral to the sulcus limitans. (1)

4.1.1.3 Medulla

There are two superior borders of the medulla oblongata, on the ventral side, the pontomedullary sulcus and at the dorsal side the striae medullares. There is no sharp inferior border of the medulla oblongata, but at the level of the pyramidal decussation and the origin of the first cranial nerve, the medulla fuses with the spinal cord. On the ventral side of the medulla oblongata are the paired pyramids, which are divided by the anterior median fissure. The anterolateral sulcus is located at the lateral side of each pyramid, this sulcus divides the pyramid from the lateral located olive and contains the origin of the hypoglossal nerve. The so called retroolivary sulcus lies Dorsolaterally to the olive and contains the origin of the glossopharyngeal nerve and the vagus nerve. The posterior median sulcus divides the dorsal side of the medulla oblongata medially. The gracile fasciculus with its eminence, the gracile tubercle lies at each side of the posterior median sulcus. The cuneate fasciculus with its eminence the cuneate tubercle lies laterally to the gracile fasciculus and they are separated by the posterior intermediate sulcus. The more lateral posterolateral sulcus delineates the cuneate fasciculus.(1,3)

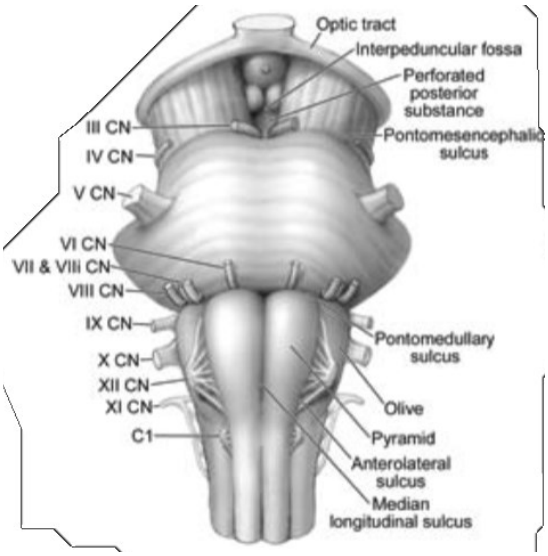

Figure 4.1-1: Schematic illustration of the surface anatomy of the ventral brainstem (G. Giliberto: Brainstem cavernous malformations: anatomical, clinical and surgical considerations. copyright 2010 by Neurosurgical focus)

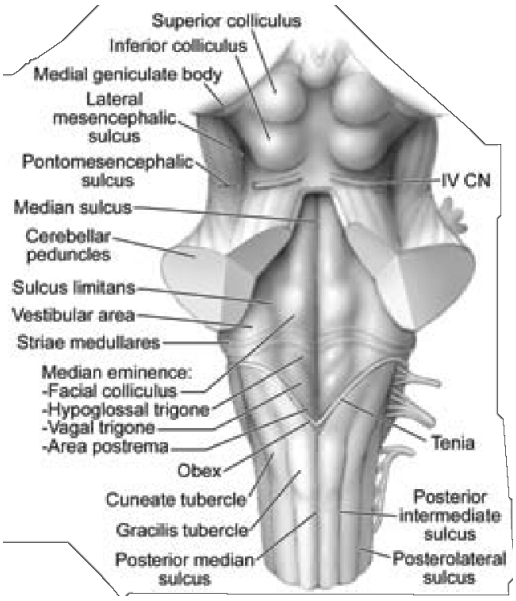

Figure 4.1-2: Schematic illustration of the surface anatomy of the dorsal brainstem (G. Giliberto: Brainstem cavernous malformations: anatomical, clinical and surgical considerations. copyright 2010 by Neurosurgical focus)

4.1.2 INTERNAL AND FUNCTIONAL ANATOMY OF THE BRAINSTEM

4.1.2.1 Midbrain

Crura cerebri

Ventrally, the foremost structures are the crura cerebri. They are the process of the internal capsule of each side. Laterally, they contain projections to the pontine nuclei from the parietal, occipital and temporal lobes. At the center of the crus is the corticospinal tract and medial to that the corticobulbar tract, whereas projections from the frontal cortex to the pons are found medially.(1–3)

Substantia nigra

Dorsal to the crus, there is a dark nucleus complex, the so-called substantia nigra. It marks the border between crus and midbrain tegmentum. The dark color is the result of the high amount of melanin in the substantia nigra cells. Histologically the substantia nigra can be divided into a pars compacta and a pars reticulate. These two parts also have distinct functions. The pars compacta gets the afferent information from the striatum and also from the telencephalic cortex, primarily from the motor and premotor cortex. Accordingly, the fiber tracts are called the strio-nigral fibers and the cortico-nigral fibers. The majority of the efferent fibers grows to the striatum and is called nigrostriatal fibers. These projections from the pars compacta inhibit through dopaminergic neurotransmitter the activity of the striatal neurons whereby they have an essential function for movement initiation. The function of the pars reticulata, containing GABAergic cells, is antagonistic to those of the pars compacta. The substantia nigra also contains efferent projections to the reticular formation and to the thalamus.(1–3)

Red nucleus

The red nucleus is located in the middle of the tegmentum, dorsal to the substantia nigra. The reddish color results from the high amount of iron in the cells of the nucleus.

Histologically the red nucleus can be divided into a magnocellular part and a parvocellular part. The red nucleus plays an important role in the extrapyramidal motoric system and

exerts its influence on the musculoskeletal system through the rubrospinal tract, which descends to the contralateral spinal cord.(1–3)

Medial lemniscus

The medial lemniscus is located lateral to the red nucleus. It is a fiber tract with its origin in the dorsal column nuclei and in the broadest sense also includes the trigeminal lemniscus with its tactile and proprioceptive information. The medial lemniscus decussates after its origin to the contralateral side and its fibers grow to the ventral posterior lateral nucleus of the thalamus. Functionally, it carries proprioception, vibration and discriminative touch information.(1–3)

Cranial nerve nuclei

In more caudal sections, the decussation of the superior cerebellar peduncle lies centrally and medially, contrary to the more rostrally located red nucleus. Continuing dorsally, CN nuclei are located medially and the spinothalamic tract laterally. The CN nuclei found in the midbrain are the oculomotor nuclear complex and the Edinger-Westphal nucleus rostrally and the trochlear nucleus caudally. The nuclei of CN III, the oculomotor nuclei and Edinger-Westphal nucleus, are found primarily at the level of the superior colliculus and the trochlear nucleus is located caudal to the nuclei of CN III and at the level of the inferior colliculus. The Edinger-Westphal nucleus supplies the parasympathetic innervation to the intraocular muscles for the accommodation reflex, which includes the pupillary constriction and ciliary muscle activation to control lens accomodation allowing for near vision. The CN nuclei III, IV and VI are connected by the medial longitudinal fasciculus. Within its most rostral portion there is the vertical gaze center. The mesencephalic trigeminal nucleus is found at each side of the periaqueductal gray matter.(1–3)

Aqueduct of Sylvius and periaqueductal gray matter

Central and dorsal in location to the CN nuclei is the cerebral aqueduct, connecting the third and fourth ventricles. The cerebral aqueduct is surrounded by the periaqueductal gray matter. This complex of nuclei projects with its fibers to the limbic system and generates anxiety and flight reflexes and also influences the voice formation, by coordinating the CN nuclei. Through its projections to the spinal cord it can inhibit the ascending pain transmission.(1–3)

Corpora quadrigemina

The superior colliculus gets afferent information from the optical tract and projects with its efferent fibers primarily to the oculomotor nuclear complex, to the facial motor nucleus and also into the spine. The primary function of the superior colliculus is to orient the eyes and head to sensory stimuli. The inferior colliculus receives auditory sensory input through a series of relay nuclei that convey this information from bilateral dorsal and ventral cochlear nuclei. (1–3)

4.1.2.2 Pons

The cross-section of the pons can be divided into the ventrally located pars basilaris pontis and the dorsally located tegmentum. The basilar part of the pons contains the corticospinal tract in each hemisection and the pontine nuclei. The tegmentum contains the following CN nuclei: the facial motor nucleus, the abducens nucleus, the chief sensory nucleus, a part of the spinal trigeminal nucleus, the trigeminal motor nucleus, the medial and lateral vestibular nuclei. the cochlear nuclei and the salivary nuclei. It also contains the trapezoid body, as a part of the auditory pathway, the medial lemniscus, the reticulate formation, the medial longitudinal fasciculus, with its function explained above, the posterior longitudinal fasciculus, which projects the majority of the efferent fibers from the brainstem to the hypothalamus and the spinothalamic tract, which conducts the impulses of the anterolateral system, that includes pain, temperature, pressure and tactile sensation. Noteworthy is the course of the fibers of the facial nerve: they surround the abducens nucleus, thus they build the facial colliculus on the bottom of the rhomboid fossa.(2)

4.1.2.3 Medulla

The cross-section of the medulla can be divided into a ventral part and a dorsal tegmentum. The ventral part contains the corticospinal tract and the olivary nucleus, the dorsal part contains the CN nuclei. The positon of the corticospinal tract is most ventrally and directly paramedian. Dorsolaterally to the corticospinal tract is the olivary nucleus. It has a characteristic shape and a hilum which opens into the dorsomedial direction. The gracile nucleus is the most dorsomedial structure and laterally to it, the cuneate nucleus can be found. Both of them are the origin of the medial lemniscus, which grows into the thalamus. A cluster of white matter tracts is found laterally in the medulla. They are the spinothalamic tract, the rubrospinal tract and the anterior spinocerebellar tract. Dorsal to the olivary nucleus is the nucleus ambiguus and lateral to this, the spinal trigeminal

nucleus can be found. Most medially is the hypoglossal nucleus, which is responsible for the formation of the hypoglossal trigone found medially in the caudal rhomboid fossa. Laterally, the next nucleus is the dorsal motor nucleus of the vagus, which is responsible for the formation of the vagal trigone found laterally in the caudal rhomboid fossa. Continuing laterally, the solitary nucleus can be found. Most laterally are the vestibular nuclei, which extend rostrally into the dorsolateral pons and the inferior cerebellar peduncle. The dorsal and ventral cochlear nuclei are adjacent to the inferior cerebellar peduncle.(1,2)

4.1.3 BLOOD SUPPLY OF THE BRAINSTEM

4.1.3.1 Arterial System

On the ventral part of the medulla the two bilaterally located vertebral arteries send direct branches into the medulla, two branches of the vertebral arteries, one from each side, combine to the so called anterior spinal artery, which supplies the whole medial part of the medulla. The PICA, the major branch of the vertebral artery, arises at the lateral side at each vertebral artery, it grows directly inferior to the olives around the medulla to the dorsal side, where it supplies the posterolateral part of the medulla. The two vertebral arteries combine to the so called basilar artery, which lies in the basilar sulcus at the ventral side of the pons. From the basilar artery arises a various amount of so called pontine perforating arteries. These arteries can be divided into medial and lateral ones, depending on the location of the origin on the basilar artery. The medial branches arise directly at the dorsal side of the basilar artery and penetrate the pons perpendicularly, but do not reach the bottom of the fourth ventricle. The lateral branches arise at each side of the basilar artery and supply the V, VI, VII and VIII CN nuclei. At the top of the basilar artery, the superior cerebellar arteries arise at each side of the vessel. The superior cerebellar artery goes through the ambient cistern around the mesencephalon and supplies parts of the midbrain. Finally, the basilar artery divides approximately at the level of the interpeduncular fossa into the two posterior cerebral arteries (PCAs). Several vessels supplying the midbrain have their origin at the PCA. These vessels are: the short circumferential arteries, the quadrigeminal artery, the central posterolateral arteries and the peduncular branches. The short circumferential arteries ascend at the surface of the mesencephalon and supply the tegmentum and the basis pedunculi. The quadrigeminal artery supplies with its branches the basis pedunculi, the tegmentum and the geniculate

complex. The central posterolateral arteries supply the quadrigeminal plate, the dorsal thalamus, the pineal gland and the medial geniculate body. The peduncular branches supply the crura cerebri, the red nucleus and the substantia nigra.(3)

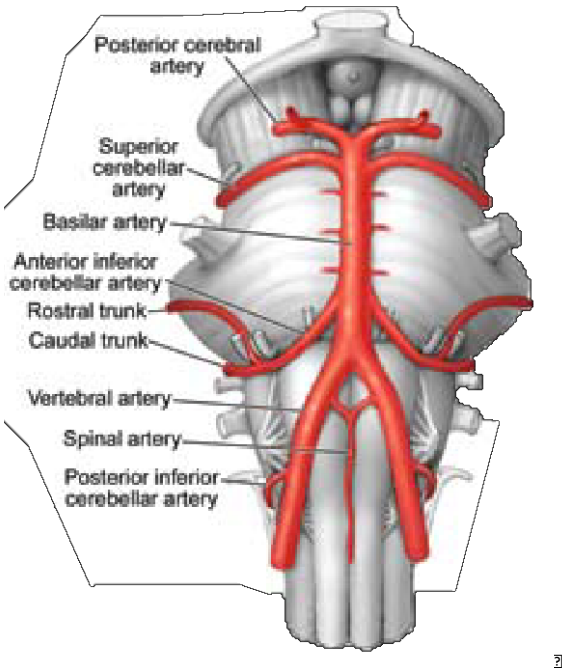

Figure 4.1-3: Schematic illustration of the ventral arterial blood supply (G. Giliberto: Brainstem cavernous malformations: anatomical, clinical and surgical considerations. copyright 2010 by Neurosurgical focus)

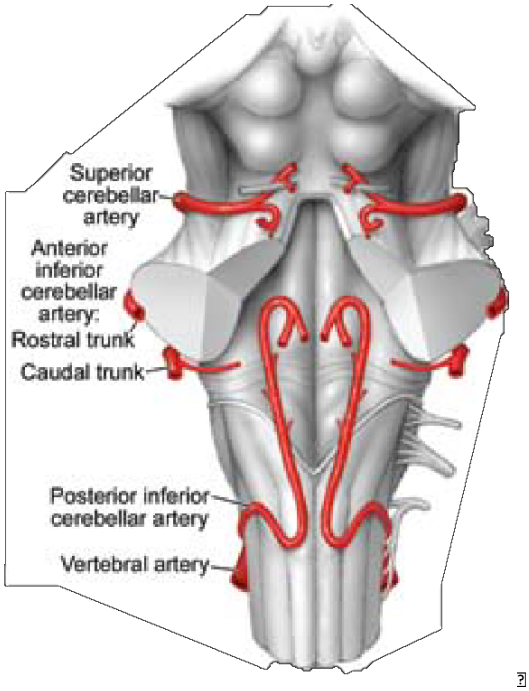

Figure 4.1-4:Schematic illustration of the dorsal arterial blood supply (G. Giliberto: Brainstem cavernous malformations: anatomical, clinical and surgical considerations. copyright 2010 by Neurosurgical focus)

4.1.3.2 Venous System

From each side of the interpeduncular fossa arises a peduncular vein which anastomoses with the contralateral vein, forming the posterior communicating vein, which crosses the interpeduncular fossa. The peduncular vein drains into the basal vein of Rosenthal together with the lateral mesencephalic vein after curving around the cerebral peduncle below the optic tract. The anterior pontomesencephalic vein, running on the ventral midline surface of the pons as a single trunk, is usually a paired vein in its mesencephalic course. The vein of the pontomesencephalic sulcus runs on the homonymous sulcus. On the ventral surface of the pons, the pontine portion of the median anterior pontomesencephalic vein anastomoses with a transverse pontine vein before continuing on the medulla as the median

anterior medullary vein. The vein of the pontomedullary sulcus courses along the pontomedullary sulcus. The important veins on the dorsal side of the brainstem are: the great cerebral vein of Galen in which the basal vein of Rosenthal flows into, the precentral cerebellar vein, also known as the vein of the cerebellomesencephalic fissure, which is an unpaired vein that runs in the caudocranial direction within the quadrigeminal plate cistern and serves as a key landmark for structures of the superior cerebellar vermis and dorsal midbrain, the lateral mesencephalic vein, which is an important and relatively constant longitudinal venous vessel that connects the basal vein at the upper aspect of the midbrain to the petrosal vein at the level of the lower pons, the vein of superior and inferior cerebellar peduncle and the median posterior medullary vein, lying in the posterior median sulcus. (1,3–5)

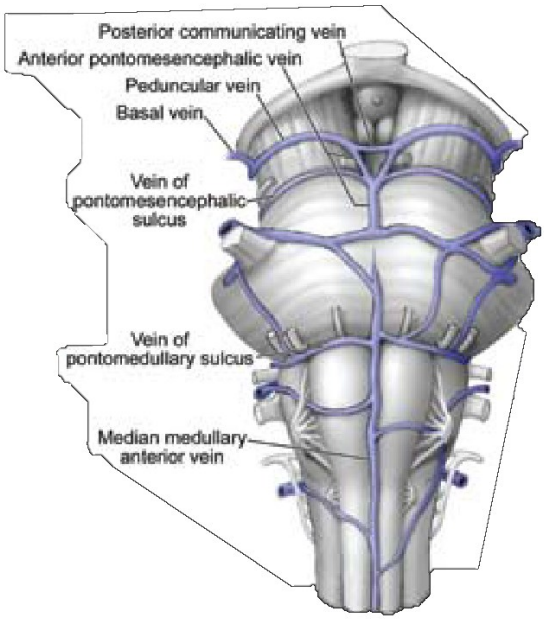

Figure 4.1-5: Schematic illustration of the ventral venous blood supply (G. Giliberto: Brainstem cavernous malformations: anatomical, clinical and surgical considerations. copyright 2010 by Neurosurgical focus)

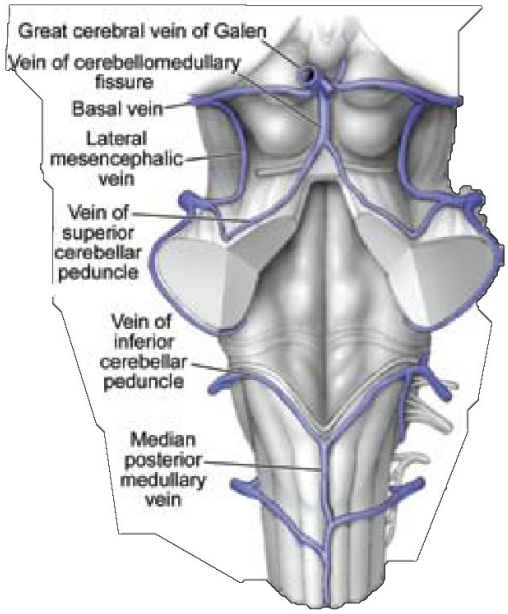

Figure 4.1-6: Schematic illustration of the dorsal venous blood supply (G. Giliberto: Brainstem cavernous malformations: anatomical, clinical and surgical considerations. copyright 2010 by Neurosurgical focus)

4.2 PATHOLOGY OF CAVERNOUS MALFORMATIONS

Definition

Cavernous malformations, also known as cavernous angiomas, cavernous hemangiomas or cavernomas, belong to the family of angiographically occult vascular malformations.(6,7) This group also includes some arteriovenous malformations (AVMs), venous malformations, angiomas and varices.(8)

Cavernous malformations are described as clusters of abnormally enlarged blood vessels or dilated sinusoidal channels lined by a single layer of endothelium.(6,7,9–14) These lesions are characterized by their low bloodflow and absence of arteriovenous shunting.(9) They hemorrhage frequently(9), which is a reason why they increase in size. Campeau et al. emphasize that these repeated self-limited intracavernous hemorrhagic events are the principal reason of the growth of the lesions and that there is no tumoral cellular proliferation involved in this process(15), but other investigations showed that there is a contribution to growth by cellular proliferation(6,16–19). Cavernomas compress and displace surrounding parenchyma rather than infiltrating it(1) but they do cause gliosis in the surrounding tissue(7) and also hemosiderin deposits are found as a result of the repeated bleedings. As a consequence of this compression and changes of the surrounding tissue, cavernomas cause focal neurological deficits, seizures and even death.(9) Cavernomas occur as solitary lesions as well as multiple lesions. Genetic studies showed the association of multiple lesion appearance and an autosomal dominant condition.(9)

Macroscopic structure and different forms

Cavernous malformations have a characteristic mulberry or popcorn like appearance as a consequence of their discrete lobulated structure. They are well circumscribed and vary in diameter from several millimeters to several centimeters.(7,11,20) Generally, cavernomas are described as lesions without an intervening neural tissue between its sinusoid vessels, but there is also a multilobular form, which is characterized by intervening tissue that separates the cavernoma. Such multilobular cavernomas appear with satellite like cavernoma lesions, not necessarily contiguous, which are not directly on the surface of the hematoma cavity, but hidden by a thin layer of apparently intact white matter, producing a shadow beneath this cavity wall, depending on the thickness of this layer.(19,21) Therefore, it can be very challenging to identify every single part of the cavernoma during

the resection. As a consequence, multilobular cavernomas carry a higher risk of residuum and post-surgical re-bleeding.(21)

Furthermore, there are three rare variants of cavernomas. They are distinguished by their form, localization and clinical course. There is a cystic form, which is more common in the posterior fossa and characterized by a cyst with surrounding edema, a dural based malformation with a tendency to have a more aggressive clinical course, and the so-called hemangioma calcificans, common in the temporal lobe and causing seizures.(19)

Histology

The histological appearance of cavernous malformations is characterized by sinusoidal dilated vessels of various sizes, lined by a single layer of endothelium and an amorphous material lacking organized collagen. Histological investigations showed a lower number of tight junctions, which are disposed discontinuously and are poorly formed. This results in sizeable gaps between the endothelial cells. Bertalanffy et al. emphasize that these findings may contribute to the propensity of cavernomas for recurrent microhemorrhage.(22) Bradac et al. describe the same findings, as a loss of endothelial cell junctions and explain the propensity for hemorrhage in these lesions due to this condition and make the link to the histologic findings of associated haemosiderosis and therefore the inflammatory response around the cavernomas.(10) Rigamonti et al. emphasize that vessels with an elastic membrane or mural smooth muscle are rarely found. The collagenous stroma is characterized by the absence of elastin and smooth muscles.(6–8,10,19,20,23–27) It is characteristic for cavernous malformations that there is no intervening brain parenchyma between its sinusoidal vessels. Although Robinson et al. emphasize that lobules from the main lesion of the cavernoma can invade the neighbor tissue. Furthermore, there are cavernomas with a multilobular shape, which is separated by intervening brain tissue, as described by Rigmonti et al. The sinusoidal channels contain blood products in different stages of evolution. Therefore, cavernous malformations with a long clinical history and various microhemorrhagic events carry fibrotic hematomas with hyaline degeneration, calcifications, cysts and cholesterol crystals as a sequel of thrombosis and organization of the hemorrhage. Typical cells within the cavernoma are macrophages, which are normally filled with iron pigment.(7,8,10–14,19,20,24–28) The vessels of cavernomas are compact and the lesion itself is discrete from the surrounding brain. But as a consequence of repeat microhemorrhage, the surrounding parenchyma presents hemosiderin discoloration and

macrophages laden with hemosiderin. Furthermore, a gliomatous reaction in the adjacent white matter can be observed.(7,19,24,26,27)

4.2.1 DEVELOPMENTAL VENOUS ANOMALY

Definition

Developmental venous anomalies are also known as venous malformations, venous angiomas, medullary venous malformations, caput medusae, or simply DVAs. DVAs are composed of radially oriented, dilated medullary veins, similar to a caput medusae. The veins of DVAs are surrounded and separated by normal brain parenchyma, and similar to CMs, DVAs are described as low flow vascular malformations as well. Oliveira et al. go one step further and define DVAs only in relation to the presence of a CM as "a group of abnormal veins located near cavernous malformations".(29)

Nowadays DVAs are classified in two different ways, one is that they are assumed to be congenital benign lesions resulting from failure of normal embryogenesis while the other view is, that they are accepted to represent anatomic variants of normal venous drainage. Despite the different views of the classification, there is consensus that as an isolated finding, DVAs are usually asymptomatic. They are frequently discovered incidentally during medical imaging studies of the brain. Histologically the veins are enlarged and sometimes hyalinized, but otherwise normal and composed of angiogenically mature elements. The multiple veins of a DVA are usually converging in a centrally located dilated trunk, and in this way forming the familiar medusa or spoked wheel pattern known from imaging studies. The DVA drains toward either the superficial system or, rarely, the deep venous system and there is no abnormal arteriovenous shunt placement process.(16,29–31)

Frequency

With an amount of 60%(16,30) developmental venous anomalies are the most common intracranial vascular malformation. They are usually solitary and have a prevalence around 2,5-9%.(30) The coexistence of a CM and a DVA is the most common mixed vascular malformation. The appearance rate of a DVA in association with a cavernous malformation described in the literature ranges significantly from 8-30%(29,31) until 100% as postulated by Abla et al.(32). In the majority of publications, there is consensus about the fact, that only a low number of DVAs are detectable through MRI scans. Abla et al. describe a 27,7% identification rate of DVAs on preoperative MRI scans. However,

Abla et al. postulate, that in all cases of the same study the surgeon (Robert F. Spetzler) identified a venous component of the CM, which was assumed to be a DVA.(29,32) This observation suggests that the prevalence of associated DVAs may be underestimated even when high-field MR imaging is used, because small venous anomalies not visible on preoperative studies may be noticed in the surgical cavity following resection of the CMs. In contrast, Wurm et al. indicate a 93,3% sensitivity in MRI scans for DVAs.(14) Bradley et al. report a one-tenth rate of combined CMs and DVAs verifiable radiographically, but observes a more aggressive clinical course in these mixed lesions.(6) Even a causal relationship of DVAs and the etiology of CMs has been proposed and has been supported by multiple reports of de novo CM development in the presence of a DVA.(6,15) Morisson et al. describe an interesting finding, comparing the incidence of DVA in sporadic versus familial cavernous malformations, where patients with sporadic lesions had a significantly higher incidence of DVAs in relation to their CMs.(31)

Considerations

Several current studies consider the DVA to be the origin of a cavernous malformation. (6,15,16,29,30,33) There are different pathophysiological theories: one is that the abnormal vascular beds of DVAs may induce hemodynamic disturbance (venous hypertension) or may be fragile enough to cause microhemorrhage that in turn might cause reactive angiogenesis with new vessel formation and coalescence. Such a process has been described as hemorrhagic angiogenic proliferation.(16) Cakirer et al. concluding the same way, by describing the theory of CM de novo formation through small petechial hemorrhage or diapedesis outgoing from a DVA with endothelial damage, which stimulates fibroblasts and the occurrence of fragile capillaries prone to recurrent hemorrhage, which leads to the development of a CM. As a cause of this endothelial damage and venous stenosis, which as described above is assumed to be one reason for an initial hemorrhage of a DVA, he proposes cranial radiotherapy or immunosuppressive treatment among others.(30) Campeau et al. agree with this theory by describing measurement results, which show elevated pressure within DVAs and suggest that this may be a key factor in subsequent hemorrhage with the sequel of the development of CMs.(15) Cakirer et al. admit, that there are still unanswered questions about the mechanism for initial hemorrhage in association with DVAs, but propose that high pressure due to venous restrictive disease might be the cause of hemorrhage from a DVA with subsequent formation of CMs.(30) Another theory suggests that DVA-related venous

outflow restriction and venous overload may open preexisting arteriovenous connections, resulting in tiny arteriovenous fistulas that can enlarge over time.(16) However, Garcia et al. claim that CMs do not have arteriovenous shunting.(9) Another theory suggests, that chronically increased intraluminal pressure and resultant reduced tissue perfusion leading to tissue hypoxia may stimulate a local increase in angiogenic factors inducing the formation of CMs.(16) Ekovic et al. claim that gross connections between a CM and its associated DVA is at odds with their observations during routine excision of CMs, but confirm the influence of venous hypertension and the likelihood of CM hemorrhage, though they have problems to make the link between changes in venous pressure and the transmission to the CM.(33)

Perrini et al. cite a communication between the venous circulation and CMs, which was measured intraoperatively by comparing the cortical blood flow and intravascular blood pressure in patients with CMs. They therefore explain the likelihood of CM hemorrhage caused by venous hypertension.(16) Both Campeau et al. as well as of Cakirer et al. describe a case, where initially a DVA was found, and the patients presented years after this incidental finding with new neurological deficits whereat MRI scans had been performed which showed the occurrence of a new developed CM.(15,30) This theory of DVAs being a potential origin of CMs is encouraged by articles reviewing that the coexistence of CMs and DVAs is more common in the adult than the child.(15)

Surgical treatment

With few exceptions, there is consensus about the treatment of DVAs associated with CMs. DVAs as incidental solitary findings do not require treatment.(30) Knowing that a DVA is integrated in the venous drainage of normal brain parenchyma, the removal of DVAs is likely to be followed by brain swelling and venous infarction.(16) Therefore the majority generally agrees to preserve a DVA.(16,25,29–32,34) Some authors describe that they even modify the approach when a DVA is visible in preoperative MRI scans in order to protect it.(29) But, considering the influence of DVAs on the genesis of CMs, some advocate the surgical division of the main trunk of a DVA to prevent recurrence.(16) Wurm et al. describe nine cases in which the DVA was divided without intraoperative brain swelling and an uneventful postoperative course.(14) In the study of 2010 Oliveira et al. state that the involvement of DVAs in the genesis of CMs may play an important role in the recurrence of CMs after surgical intervention.(29) Perrini et al. summarize the current status of knowledge as follows, “it cannot be excluded that by treating the CM we are

treating the result of the so-called “hemorrhagic angiogenic proliferation” and not the disease itself, which may indeed be the DVA”.(16)

4.3 ETIOLOGY OF CAVERNOUS MALFORMATIONS

Regarding the question of the origin of CMs there are two major theories: one is that CMs are congenital vascular malformations. This class also includes the genetic origin of CMs. The other theory is that CMs are de novo lesions due to a preexistent DVA or the result of previous cranial radiotherapy or immunosuppressive treatment.(30) The pathophysiology behind the angiogenetic proliferation theory is, that alteration in blood flow with hemodynamic turbulence, progressive obstruction and venous hypertension of DVAs as well as diapedesis of blood cells through leaky capillaries stimulates angiogenetic factors and may cause a reactive angiogenesis with new vessel formation and coalescence which is known as the “hemorrhagic angiogenetic proliferation theory”, which results in the development of CMs.(6,14,16,30,33)

Morrison et al. support this theory by reporting a case of a patient with a large solitary DVA. Two years later, a subsequent MRI scan showed the typical appearance of a solitary CM in the same location.(31) Bruneau et al. describe a similar case, where a patient was investigated for headache by MRI without any findings and presenting three years later with a mesencephalic cavernoma.(35) Cakirer et al. emphasize that de novo formation of CMs has been documented in only a few non-familial cases but this sporadic de novo formation usually requires the presence of a DVA.(30) There is also the discussion about an involvement of a neoplastic process in the genesis of CMs. This theory is supported by reports of new lesions appearing under hormonal influence during pregnancy, apparent seeding of a lesion along a biopsy track, the presence of lesions of endothelial cells expressing proliferating cell nuclear antigen and the occurrence of CMs in areas previously irradiated.(17) Ferroli et al. also emphasize a mitotic activity of the endothelium of CMs.(18)

What supports the theory that CMs are congenital vascular malformations is, that the lesions have a general trend to decrease in size, reflecting a low hemorrhage rate at any given point in time. But this theory has its limitations in explaining the de novo appearance of CMs and increases in lesion size without obvious hemorrhage.(17) Another hypothesis is that familial CMs represent a forme fruste of a neurocutaneous disorder in which the cutaneous and ocular manifestations of the disease have incomplete expression or are not presently well recognized.(17)

4.3.1 GENETICS

In the familial form of cavernous malformations, characterized by multiple lesions, three gene loci with autosomal dominant character (and therefore equal distribution of males and females) could be identified causing cavernous malformations.(9,10,13,20,22,31) These genes are called CCM1, localized on the long arm of chromosome 7q11-22, CCM2, identified at the locus 7p15-13 and CCM3, localized at 3p25.2-27. The most common locus for causing this disease has been identified as CCM1. Bertalanffy et al. cite in the study of 2002 a distribution of 40% to CCM1, 20% to CCM2 and 40% to CCM3 in familial cases.(19) All of these three genes are involved in the central nervous system interendothelial cell junction integrity.(10)

When it comes to the question about the clinical course of familial versus sporadic cavernomas two different opinions have to be mentioned: the first is that cavernomas with familial background have bleeding rates of 1.1% per lesion-year and therefore a higher risk for hemorrhage and a higher proportion of developing clinical symptoms.(13,20) On the other side, Moriarity et al. declare that no significant statistical difference in the annual hemorrhage rate between familial and sporadic patients was found.(7) The frequency of the familial form is assumed to make an amount of 30 to 50% of all CM cases.(7) In contrast Bradac et al. report a 20% rate of the familial form.(10) Variation in the percentage of familial cases can be explained by a combination of varying degrees of aggressiveness in screening asymptomatic relatives as well as possible geographic bias and the presence or absence of extended, affected families in the region of study. The higher rate of multiplicity in familial cases is assumed to be about 84% compared to 10 – 15% in sporadic cases. Therefore, Zabramski et al. suggest to consider a familial disease by finding multiple lesions in a patient. (7,20) In Hispanics, a significant higher frequency of the CCM1 mutation has been observed.(8,29,31) However, the current knowledge about the genetic and cellular mechanisms of the pathogenesis of CMs as well as the role of de novo mutations, which stays unclear up to now, demands further research, to improve genetic counselling, but also to define specific targets for future therapeutic interventions.(22)

4.4 EPIDEMIOLOGY OF CAVERNOUS MALFORMATIONS

Methods to investigate the prevalence

Before the availability of MRI-scans, the only useful method to assess information about the prevalence of CMs was the autopsy. But since the rise of MRI, which became the main diagnostic tool for cavernous malformations and large MRI-based retrospective studies, non invasive pre mortem study on the prevalence of CMs are possible.(19)

General prevalence of cavernous malformations

In several recently published autopsy-based and MRI-based studies, the prevalence of CMs ranges approximately from 0,34% and 0,9%.(7,11,19,20,35–37)

Prevalence of cavernous malformations referred to vascular malformations

CMs affecting the central nervous system represent approximately 5% to 20% of all central nervous system vascular malformations.(7,11,12,19,34,35,37)

Sex distribution

The majority of studies based on large case material agree that there is no difference on the sex distribution of cavernomas.(6,19)

Distribution of the cavernous malformations referred to supra- and infratentorial

The distribution of cavernomas seem to be depending on the general distribution of the mass of the neuronal tissue. The current studies show about 73% of the cavernomas located supratentorial and 27% located infratentorial.(6,12,19,35,36)

Size

The size is reported to vary between less than 1 mm to up to more than 10 cm in diameter. The mean cavernoma size in several larger series is approximately 15 mm to 19 mm in diameter.(19)

Prevalence and distribution of cavernous malformations in the brainstem

The prevalence of CMs within the brainstem is relatively rare, and varies from 4% to 35% of all CMs located in the central nervous system, according current studies, but the majority of the publications claim a prevalence of approximately 20% for BSCMs. The majority of the BSCMs seem to occur in the pons (approximately 57%), followed by the

midbrain with an amount of 14%, the pontomedullary junction with 12% and the medulla oblongata with 5%.(9–12,18,19,32–35,38)

Prevalence of multiplicity

The current publications show an amount between 10% and 21% of multiple cavernomas. The frequency of cases with multiple lesions varies widely between sporadic and hereditary (familial) forms. Up to 93% of patients with a hereditary form have multiple lesions.(6,19)

4.5 PRESENTATION/NATURAL HISTORY

4.5.1 PRESENTATION

Usually the symptoms are produced by intralesional or perilesional hemorrhage. But cavernomas may also cause symptoms by obstructing cerebrospinal fluid pathways. The presentation of cavernous malformations depends on the location of the lesion. Therefore, supratentorial lesions present most commonly with seizures. The origin of the seizures is most apparently, the epileptogenic potential of blood breakdown products within the perilesional area. On the other hand, patients with infratentorial lesions tend to present more likely with focal deficits compared to of patients with supratentorial lesions, which is reflecting the high density of eloquent regions in the surrounding tissue of brainstem lesions. Neurological deficits may be transient, progressive, recurrent, or fixed.(6,19)

General symptoms and typical presentation

The onset of signs and symptoms caused by cavernous malformations is generally abrupt. There are two possible ways in which cavernomas cause symptoms: either by local compression of surrounding eloquent neural tissue, caused by intralesional hemorrhage or proliferative growth of the lesion itself or by gross extralesional hemorrhage. The clinical presentation of cavernous malformations can vary widely. In general, their presentation is grouped into four categories including headache, seizure, focal neurological deficit and compression through gross hemorrhage. Wang et al. state that compared to brainstem hemorrhages from hypertension, AVM or tumors, hemorrhage from cavernomas is rarely fatal. They further claim, that with conservative treatment, the neurologic deficits usually improve. The gender distribution based on symptoms indicate a tendency for male patients towardsseizures while female patients seem more likely to present with hemorrhage or neurological deficit.(7,20,27,32,37)

Seizures

Compared with AVMs (20%-40%) and gliomas (10%-30%), cavernous malformations (25%-70%) tend to present more often with seizures. Naturally the incidence of seizures depends on the localization of the CM. Therefore, CMs located in the temporal lobe cause seizures more frequently and additionally appear to be most likely to result in intractable epilepsy. On the other hand, lesions located in the frontal lobe seem to have a lower incidence in seizures. Furthermore, CMs located supratentorially tend to present significantly more often with seizures than those located infratentorially.(7,19) Up to now there is no consensus about the pathophysiological origins of seizures produced by CMs. There are three different theories under debate. One theory centers around the deposition of hemoglobin breakdown products, which leads to pathological amounts of iron salts in the cells, and these salts are proven epileptogenic agents. The second theory is about the overload of lactate in the hemorrhage adjacent astrocytes. These results of a high uptake of glutamate by these astrocytes, which leads to increased anaerobic glycolysis with its metabolite lactate. And this high amount of lactate, which overcharges the normal utilization, is under suspicion to be responsible for the generation of seizures. The third theory has his origins in the findings of abnormally high amounts of serine, glycine and ethanolamine in the adjacent brain tissue of cavernous angiomas, which is believed to be responsible to cause excessive activation of excitatory neurotransmission. The vascular malformation itself may not be able to generate seizures.(19)

Rare symptoms in cavernous malformations

Cavernomas are able to present with a wide spectrum of symptoms, which results from the heterogeneity in size, the different locations in which they can occur and propensity of bleeding. The clinical symptoms can change over time and present with repeated exacerbation of complaints and alternating periods of remission. Beside the common symptoms, cavernous malformations can also present with rarer symptoms such as hydrocephalus, cranial neuropathies such as trigeminal neuralgia, papilledema, hypothalamic disturbances or even with simulation of multiple sclerosis due to the fluctuating progressive neurological deficits.(19,20)

Presentation of supratentorial cavernomas

Supratentorial cavernomas are significantly more likely to be associated with seizures, also common for supratentorial lesions are visual problems, sensorimotor deficits or speech disturbances.(24,37)

Presentation of infratentorial cavernomas

In contrast to supratentorial lesions, BSCMs are less likely to manifest with seizures.

BSCMs are usually associated with symptoms related to mass effect such as cranial neuropathy, hemiparesis, or hydrocephalus. Presenting signs and symptoms tend to correlate with expected deficits based on the location of the lesion within the brainstem. Therefore, common signs and symptoms for the midbrain are palsy of the cranial nerve III, red nucleus tremor, involuntary laughing, increased intracranial pressure and paroxysmal coma. Lesions of the pons tend to be associated with a higher rate of complaints referable to cranial nerve V, VI, VII such as trigeminal numbness, abducens palsy or facial paresis. Furthermore, high fever is a possible symptom for pontine lesions.

BSCMs of the medulla usually manifest with symptoms reflecting lower cranial neuropathy such as intractable hiccup, vocal cord paralysis and dysphagia. Furthermore, seizures are often present in patients with medullary cavernomas. In all three locations hemiparesis and ataxia are the most common presentations. Lesions located in the cerebellum tend to present with vertigo, ataxia, dysarthria and dysgraphia, respectively. Spinal cavernomas usually cause sensorimotor paresis accompanied by pain or bladder dysfunction.

BSCMs are very likely to rebleed and because of their eloquent location they appear to do that more often than supratentorial CMs. Because of this fact and the different clinical presentation some authors suggest that BSCMs should be considered as distinct entities for supratentorial lesions.(12,24,27,32,33,37)

Age of Presentation

CMs are usually detected clinically in the third to fifth decade.(7) In addition, male patients may comprise the majority of patients presenting before the age of 30 years.(7)

4.5.2 NATURAL HISTORY

4.5.2.1 Hemorrhage Rate

General notes on hemorrhage

Evidence of prior hemorrhage is a nearly constant feature of cavernous malformations. These lesions are thought to grow and produce symptoms by recurrent episodes of hemorrhage. The bleeding habits can be divided into three different types of hemorrhage or basic patterns of cavernoma bleeding. First of all, the “slow ooze” type which is thought to be the origin of the hemosiderin ring frequently seen in the adjacent neuronal tissue. The second type is the so called “intralesional hemorrhage or thrombosis”. This bleeding pattern seems to play the major role in lesion expansion and its dynamic nature due to the rupture of caverns within the cavernoma, formation of new cysts and possible reactive angiogenesis. The third type is called “gross hemorrhage” which is characterized by extralesional bleeding and therefore this kind of bleeding type is thought to be responsible for causing acute symptoms by the destruction of the surrounding tissue.

about it is estimated that the extralesional type of hemorrhage is relatively rare compared to the other bleeding types. However, it is more dangerous and becomes more frequent after a previous extralesional bleeding. In contrast, there is evidence that the rate of intralesional hemorrhage does not increase after a previous intralesional bleeding. Interestingly, significant intracavernous hemorrhage my even destroy the lesion. Nevertheless, precise radiological differentiation between these bleeding patterns remains difficult in the majority of the cases. Considering the reason for hemorrhages there is some evidence that the intraluminal pressure of a DVA communicating with the CM is identical to dural sinus pressure. Therefore, it is plausible that general changes in cerebral venous hemodynamics may be transmitted to a DVA. However, the way in which changes in DVA hemodynamics might increase the chance of hemorrhage from a CM is unclear. The symptoms generated by hemorrhage usually present in an acute or subacute pattern over hours or days. Loss of consciousness or even death due to a hemorrhage has been described but is very rare.(12,19,20,22,33,39)

Hemorrhage rate based on the theory of congenital existence of cavernomas

First of all, it must be stated that different authors use different definitions of hemorrhage or bleeding. Therefore, it is not utterly valid to compare the values stated in these studies. Based on hemorrhage rates the literature is divided into two different methods of

information gathering. One method gives information about the hemorrhage rate assuming that all lesions have been present since birth. This method, using the congenital theory, explains the extremely low annual hemorrhage rate. Therefore, the average hemorrhagic rate ranges from 0,1% to 2,3% per lesion per year and from 3,8% to 6,6% per patient per year. Rebleeding rates range between 26,0% and 34,7% per patient per year.
Calculating the retrospective hemorrhage rate is difficult and not very valid because of two reasons. The first reason is that patients sent to hospitals specialized in cavernoma treatment tend to have suffered a bleeding and may be considered more aggressive. The second reason is that there is hard evidence that not all CMs are present since birth and that de novo lesions can develop.(6,18,28,32–34,38–40)

Hemorrhage rate based on prospective/follow up studies

A more precise strategy to calculate the hemorrhage rate of CMs is to use a prospective study, by taking the quotient of total number of hemorrhages experienced by an individual patient and the number of years the patient is followed up. But it is important to consider, if the hemorrhage rate is calculated per patient per year, that patients with multiple lesions my present with higher hemorrhage rates. Therefore, to avoid distortions of the real hemorrhage rate, calculating the hemorrhage rate per lesion per year seems to be the correct method. The hemorrhage rate per patient per year ranges from 0,7% to 6,5% in prospective studies, but the most commonly cited rate is 3,1% per patient per year., The most cited value for the hemorrhage rate per lesion per year is 0,7%. The two values 3,1% per patient per year and 0,7% per lesion per year hemorrhage rate are the most valid statements, because they were elicited using the most stringent and clinically relevant definition of hemorrhage, which was defined as extralesional hemorrhage and new symptoms.(6,7,24,33,39,41)

4.5.2.2 Influencing Factors in Hemorrhagic Rates

Location

The location is considered to be an influencing factor for the hemorrhage rate or particularly for the event rate, not only because there is some evidence that the hemorrhage rate in some particular locations at least seem to be more likely than in others but also because of the logical consideration that subtle, morphological changes in a CM would be detected more frequently in eloquent locations. Nevertheless, there is the theory that some structural distinctions in the central neural tissue predispose to lesion activity and that

differences in the deep venous drainage system promote changes in CMs located in such areas more frequently. But if there are specific factors, which cause a present CM to rupture, they are unknown yet.(6,19) The disagreement based on location as an influencing factor for hemorrhage may have its origin in the method of how a hemorrhage is defined in each study. Some use the strict definition of extralesional blood and new symptoms, while others use a combination of changes in lesion size with new symptoms and other again rely on radiographic evidence alone.(6)

Some authors state an influencing effect on hemorrhage by the location, not only because of a higher sensitivity of the neuronal tissue in the specific location but because of a higher rate of bleedings. Therefore, an infratentorial CM, all deep-seated lesions including diencephalic cavernous malformations and especially those located in the brainstem seem to have a significantly higher rate of hemorrhage.

There is evidence that the hemorrhage rate of brainstem cavernomas is up to 30 times higher than at other locations within the brain.(42) Other authors claim a two times higher rate compared with those located supratentorially.

According to Bertalanffy et al. and Kivelev et al. the rehemorrhage rate, regarded separately, with 17% is higher in patients harboring a BSCM compared with patients harboring a supratentorially located cavernoma with a rehemorrhage rate of 6%.(19,33,37,41–43)

On the other side, there are several publications in which the phenomenon of a higher hemorrhagic event rate is exclusively attributed to the higher eloquence of some locations and therefore a clinically more aggressive appearance, but according to that, the actual annual hemorrhage rate is generally not affected by the lesion location. Moriarity et al. declare that they couldn't find a significant difference in the likelihood of presenting with hemorrhage, neither between supratentorial and infratentorial lesions, nor between superficial and deep lesions.(6,7,25,35,42,43)

Size

The bias here is, that most of the time just the CMs which present with symptoms are under a physicians' observation, therefore the clinically silent CMs regardless of their size cannot be included in these considerations, except those which are found incidentally. However, in contrast to the location, it is widely accepted that size does not influence the hemorrhage rate. Furthermore, Clatterbuck et al. cite, that in their series despite the size of the CMs increased in 35%, the clinically relevant hemorrhage rate over the same time

period decreased.(17) MRI based prospective studies show the dynamical behavior of CMs.

In the study of Clatterbuck et al., only 10% of the observed lesions were stable in volume over the follow-up period, 35% increased and 55% decreased in size. Keeping in mind the decreasing rate of hemorrhagic events, two different mechanisms for size changes are assumed:Decrease in size is presumed to happen due tohemorrhage and resolution while increase in size may be caused by growth and proliferation.(6,17,41)

Age

Age does not influence the hemorrhage rate significantly, but in several studies a trend for an increased risk of hemorrhagic events for patients younger than 40 years old was observed.(6,43)

Sex

The theoretical background for the theory of gender being an influencing factor for the hemorrhage rate is based on investigations which detected estrogen receptors in CMs in female patients and on an observed hormonal responsiveness of CMs. These findings are supported by case reports. Bradley et al. published a case of a 26-year-old woman who suffered 4 hemorrhages from a thalamic CM, each occurring 3 weeks after starting a hormonal therapy and never recurring once hormonal treatment ceased. Other case reports describe bleeding episodes in female patients occurring during pregnancy.(6,19)

In several studies a significantly higher propensity of hemorrhage in female patients was observed. In addition to that, in the study Moriarity et al. female sex was actually the most significant factor for increased hemorrhage rates, with an annual bleeding rate of 4.2% per patient-year for females as opposed to 0.9% per patient-year for males. Chen et al. published a hemorrhage rate for female and male patients of 5,7% and 4,1%, respectively.(6,7,24,39,41)

Some authors also found out that female patients tend to rebleed more frequently than male patients.(6,27) Nevertheless, some authors did not find a significant difference between males and females based on the hemorrhage rate. Hauck et al. even found a tendency of an increased risk of hemorrhagic events among male patients, even though that findings were not statistically significant.(13,28,42,43)

Rehemorrhage rate

The majority of studies claim the association of previous hemorrhages with an increased rehemorrhage rate citing annual rebleed rates ranging from 3.8% to 35%. Abla et al publishing the high value of 35% rehemorrhage rate per year, mention that this value was calculated using patients who were referred to a high-volume BSCM center after multiple hemorrhages and that 35% is not representative for all BSCM patients, suggesting a 15% rehemorrhage rate for BSCM patients after a single hemorrhage. Wang et al. even stated a rebleeding rate for BSCMs of 60%.(6,19,27,28,32–34,38,40,41)

Hauck et al. published ,additionally to the higher risk of a second hemorrhage based on an initial event, that after a first recurrent event the risk for a second recurrent event was as high as8,6% per month.(43)

Some authors even found evidence, that patients harboring a brainstem cavernoma that has already bled are more likely to experience repeated hemorrhage than patients harboring the malformation in other locations.(19)

For the special case of a BSCM, Wang et al. postulate that after a bleeding the annual rebleeding rate increases regardless of the location within the brainstem.(27) Nevertheless, in the study of Moriarity et al. a prior hemorrhage was found not to be a risk factor for subsequent hemorrhage.(7)

Familial form

In the familial form of CMs a hemorrhage rate of 6,5% per patient-year is found in the literature. This is roughly up to twice as high as in CMs of the non-familial form.(7)

4.5.2.3 Brainstem Cavernous Malformations

Regarding the hemorrhage rate of BSCMs there are two different opinions: one is that BSCMs do have a higher hemorrhage rate while the other is that just because of the eloquence of the location it seems like there is a higher risk of bleeding in BSCMs because a subtler hemorrhage will become more likely clinically conspicuous. In the literature, the current values of a BSCM event rate ranges between 1% to 10% per year in patients without previous events and between 2% to 60% in patients with previous events. The main reason for the wide range of the suggested event rates is that different authors use different definitions of an event as previously explained. Some authors consider only a proven hemorrhage as an event, whereas others only consider acute neurological deterioration.(9,43)

The three parts of the brainstem seem to have a different predisposition for the likelihood of multiple hemorrhagic events. In the study of Samii et al. the distribution was as followed: the highest rate of rebleeding with 75% occurred in pontomesencephalic cavernomas followed by pontine cavernomas with 42,9% and at last in lesions within the medulla oblongata with 25%, the same distribution was found in our investigation. Also, a correlation between multiple hemorrhages and an increased rate of morbidity was found. In patients in whom multiple brainstem hemorrhages had occurred, a greater number of cranial nerve deficits was present compared to those in whom only one hemorrhagic event had occurred.(12)

Despite the disagreement on the higher hemorrhage rate in BSCMs, there is consensus about the more aggressive course of these lesions due to the high density of eloquent areas within the brainstem. In the study of Bertalanffy et al. a possible fatal course of a BSCM hemorrhage is quoted with a risk of up to 20%. Furthermore, owing to the higher sensitivity of the brainstem to any pathological growth or event compared with less eloquent supratentorial locations, BSCMs are more likely to become symptomatic. Another noteworthy finding in BSCMs, which is especially important for the surgical treatment and for the planning of the approach is, that because of the horizontal and longitudinal run of the fibers within the brainstem and the compact structure, BSCMs rarely hemorrhage into either subarachnoid space or the fourth ventricle.(20,27,32,33,42,43)

4.5.2.4 History of Cavernomas after Surgical or Conservative Treatment

Some investigators have observed a very benign natural history of CMs and favor a conservative approach. In the study of Chen et al. which compared a surgical group comprising of 57 patients and a conservative treated group containing 17 patients, they found no significant difference in the initial and final neurological states between these two groups. They calculated the hemorrhagic rate of the operated versus the conservatively treated patients with 5,2% versus 3,3% with a mean follow-up of 44 months. They also claimed that they found evidence that BSCMs might become quiet after the onset of bleeding, especially deep-seated BSCMs. Ferroli et al. stated that how investigators found a benign course of CMs may have grounded their findings on a misleading comparison between the benign course observed in their highly selected subgroup of patients and the mortality/morbidity rate observed in highly selected subgroups of critical patients operated on in tertiary referral centers after clinical deterioration.(18,39)

4.5.2.5 Change in Size

In the study of Clatterbuck et al. the natural behavior of changes in size on CMs was investigated based on MRI. The results show after an interval of 26 months, that only 10% of the lesions were stable in volume, 35% increased and 55% decreased in size. After a second-time period of 18 months, 22% of lesions were stable in volume, 43% increased in volume and 35% decreased in volume. Interestingly they found no correlation between the growth of CMs and a change in the hemorrhage rate, explaining this finding with the theory that changes in size may also be related to another process than hemorrhage. Furthermore, Robinson et al. observed in a study with serial magnetic resonance images in 31 of 35 patients a tendency of the hemosiderin ring to widen and become more distinct with time.(17,24)

4.6 EVALUATION/IMAGING

4.6.1 LIMITATIONS OF IMAGING METHODS

Using only imaging methods for the evaluation of the natural history and the course of cavernous malformations may lead to the loss of important information about the lesion and the miss of a clinically important event, in fact, to false interpretations because a cavernoma bleeding may not always be identifiable on neuroimaging as an identifiable gross hemorrhage. Therefore, several authors propose to use event rates instead of pure radiologically defined changes in cavernomas. The term “event rate” refers to neurological deterioration that is experienced by the patient as a subjective worsening and is confirmed by objective worsening of the neurological status, independently of the neuroradiological finding.(19)

4.6.2 COMPUTED TOMOGRAPHY

In the age of magnetic resonance imaging, computed tomography (CT) still has its value and indications. Two clinically significant benefits of CT in the case of cavernous malformations should be mentioned here: the first is that a CT scan is still the number one diagnostic tool when it comes to acute clinical symptoms suggesting an intracranial hemorrhage. The second benefit of CT scans is the unmatched quality of illustrating the bony anatomy of the skull base which is provided best by thinslice CT scans taken with special bone algorithms. Further advantages of CT scans are cheap, fast and a common toll in barley every hospital nowadays. This is important for planning the surgical approach.(19) On the other hand, there are several reports about the poor ability of CT scans in detecting CMs. In the study of Cakirer, a correct detection of CMs was only possible in 30% to 50% of the cases, in the study of Rigamonti et al. only 14 of 27 lesions were correctly identified in CT scans while Robinson et al. found a specifity of only 38% for CT scans based on CMs. Rigamonti et al. conclude that computerized tomography may occasionally miss even relatively large lesions and is not sensitive enough to detect small lesions.(24,26,30)

4.6.3 MAGNETIC RESONANCE IMAGING

4.6.3.1 General notes

The most sensitive and therefore most important imaging method is the magnetic resonance imaging. It excels in the visualization of the anatomical as well as the

pathological findings, such as the extent of a cavernoma lesion and hemorrhage. In MRI scans, cavernous malformations typically appear as “popcorn” or “mulberry” lesions due to the presence of a surrounding gliotic or hemosiderin rim and possible distortion of the adjacent brain structures. Hemosiderin-laden macrophages, the presence of multiple lesions, a reticulated core of increased and decreased SI, a prominent surrounding rim of decreased SI, and a pertinent family history strongly support the diagnosis of cavernous malformation. Zabramski et al. propose a classification of cavernous malformations which divides them into four types based on the radio-pathological appearances of CMs.

Type I lesions (19/59, 32.2%) appear on T1with a hypointense and on T2 with a hypo- or hyperintense core with pathological features and indications of a subacute hemorrhage. Type II (26/59, 44.1%) corresponds to the originally described reticulated core of mixed signal intensity on T1 and T2, with a surrounding hemosiderin ring and with pathological features of the lesion like thrombosis of varying age. Type III lesions (8/59, 13.6%) appear hypointense on most signal sequences, probably indicating chronic hemorrhage while Type IV lesions (6/59, 10.2%) are poorly visualized, except on gradient echo sequences. On these images, the lesions appear as punctate areas of hypointensity that are similar in appearance to a capillary telangiectasia; however, capillary telangiectasias exhibit contrast enhancement while Type IV CMs generally do not.

Using a high field MRI with 1,5 or 3,0 Tesla is recommended. Rigamonti et al. describe a case in which a patient underwent both, low-field (0.35 Tesla) and high-field (1.5 Tesla) imaging. Two lesions were not visualized with the low field MRI scan.(7,8,14,17,19,21,22,24–26,28,44)

T2*-weighted gradient echo imaging is considered the best MRI sequence for assessing cavernous malformations, especially for the diagnosis of small and multiple cavernomas. Hemorrhage and/or calcifications lead to susceptibility effects and T2*-weighted gradient echo sequence is the most sensitive tool to visualize these effects. T2-weighted images are necessary to recognize the typical “popcorn” appearance of CMs and therefore increase the MRI specificity for this purpose. However, the exact size of lesions can be difficult to determine on T2-weighted sequences due to hemosiderin bloom artifact, so the thickness of the CM rim is usually best determined on T1-weighted sequences. In the study of Rigamonti et al. T1-weighted MRI studies were shown to be less sensitive than the T2-weighted images and detected only 23 of 27 lesions.(14,25–27,29,44)

Bertalanffy et al. cited the work of Vanefsky et al. in which the reflection of the histopathological features of cavernomas in characteristic MRI patterns was shown.

Another application of MRI besides the diagnostical part is the postoperative follow-up imaging. This is recommended in all surgical cases in order to confirm the completeness of cavernoma resection and later to assess a possible de novo formation. A more recent utilization of MRI is the diffusion tensor imaging-based fiber tracking which was used in the study of Chen et al. to locate the corticospinal tract as a tool for approach planning and intraoperative navigation.(19,39)

4.6.3.2 Pros

Beside the accuracy in establishing the diagnosis of a cavernoma, MRI is unsurpassed in defining the exact size of a CM and its location as well as the assessment of the condition of the neighbouring neural tissue. But it is also the most important tool do define other features such as multiplicity and associated hydrocephalus and the presence of intra- or extralesional bleeding.

Again, at this point it should be mentioned that MRI is not only a diagnostic tool but has also high value in postoperative follow-up investigations to confirm the completeness of cavernoma resection and later to assess a possible de novo formation. T2-weighted gradient echo imaging is considered the best MRI sequence for evaluating cavernous malformations, in the study of Clatterbuck et al. in which 10 patients were investigated for CMs, computerized tomography was able to detect only 14 lesions, whereas T1-weighted MRI scans revealed 23 lesions and the T2-weighted gradient echo sequence detected 27 lesions. And therefore, since the era of MRI and especially the T2-weighted gradient echo sequences, the detection rate of deep-seated cavernomas has rapidly increased. Furthermore, with no other diagnostic tool the relationship between a cavernous malformation and its adjacent brain parenchyma can be demonstrated as exact was with MRI scans. This for example is essential for planning and designing the surgical approaches.(11,17,19,27,29)

4.6.3.3 Cons

It has to be mentioned that MRI does not have a specificity of 100%. Due to the morphologic structure of cavernomas several other lesions with distinct entities can have a similar appearance on MRI and can also cause a similar clinical course like cavernomas. Lesions which can appear similar in MRI and clinical pattern include hemorrhagic neoplasms such as bain metastases, meningiomas, low-grade or even high-grade gliomas,

inflammatory lesions such as cysticercosis or chronic granuloma and rare intracranial lesions such as lipomas.

Another disadvantage of MRI is that it also does not have a sensitivity and specificity of 100% when it comes to postoperative investigations. Some residual cavernomas can be missed or being confused with hemosiderin staining. This hemosiderin staining also known as ferromagnetic blooming is another disadvantage of MRI scans. In T2-weighted sequences MRI can provide an incorrect sense of proximity of the lesion to the pial surface. If a cavernoma does reach the pial surface or not is highly important for surgical planning. A characteristic mechanism of MRI in the time-of-flight and phase-contrast angiography has to be pointed out and leads to another disadvantage, both sequences rely on the presence of moving blood and are best in detecting vessels in the sensitized direction. In the case of cavernous malformations, when the vessels are organized in a multidirectional and complex manner, these techniques are much less effective.(19,35,45)

4.6.3.4 Ferromagnetic Blooming

The origin of the ferromagnetic blooming effect are residual macrophages laden with hemosiderin. This hemosiderin deposition in and around a cavernous malformation is most likely related to repeated subclinical hemorrhages or to slow lysis of red blood cells. This indelible tissue signature of hemosiderin deposition in T2-weighted MRI sequences is particularly valuable in the specificity for cavernomas. The blooming effect is characterized as an area of mixed signal intensity with a reticulated appearance, although residual hemosiderin-laden macrophages are clearly not unique to cavernous malformations. Therefore, based on the appearance of a hemosiderin ring, Vanefsky et al. published a sensitivity of 86% and a specificity of 50% in detecting a CM when the lesion is a CM. But due to the hemosiderin bloom artifact, the exact size of the lesion can be difficult to determine. Additionally, the T2-weighted images can provide a false sense of proximity of the cavernoma to the surface, this can be particularly dangerous when a lesion that is supposed to come to the surface of the floor of the fourth ventricle is actually deeper than expected. Both above mentioned effects of the blooming artifact are disadvantages regarding surgical planning. Therefore, T1-weighted sequence provide the best images for determining the size of a CM and for planning the surgery.(18,23,25,26,34,41)

4.6.4 ANGIOGRAPHY

Several studies have shown that cavernomas produce no or little pathological changes on angiography. Therefore, today digital subtraction angiography is considered a rather unnecessary diagnostic tool. Indeed, to establish the diagnosis of a cavernoma, angiography may be of little practical value. Angiograms generally fail to reveal cavernous malformations because they lack arterial feeders, although in some lesions a capillary blush or an early filling of veins may be present. However, DVAs can be detected during the venous phase of angiography, sometimes with the appearance of classical caput medusae, representing tiny tributaries draining into the large collector vein. In the study of Ferroli et al. angiography failed in revealing the cavernous malformation, but in four cases a DVA was visualized and considered to be a possible indirect sign of the presence of a CM. But even if angiography is not a primarily diagnostic tool for CMs, there are two indications where angiographies deliver valuable information in the case of a CM. One is, that angiography is the gold standard in excluding coincidental vascular malformations such as a mixed lesion with arteriovenous shunts, venous angioma or capillary telangiectasia. Furthermore, it is a helpful tool in designing the surgical approach, because it shows exactly the venous drainage pattern at the surface of the brain.(7,18,19,27,30,34,46,47)

4.7 TREATMENT/MANAGEMENT

4.7.1 SURGICAL EXCISION

The general indications for a surgical excision of a CM are young age, neurological symptoms, mass effect of a lesion, hemorrhagic behavior, accessible location and low operative risk with regards to the natural history of the disease.

The main goal of surgery is the radical and complete removal of the whole lesion especially in BSCMs. The possibility of achieving this goal depends also on the location of the lesion. CMs in the cerebral and cerebellar hemispheres can often be resected safely and in most cases en bloc. It can be difficult to achieve complete resection of lesions centered in the ventral and ventrolateral midbrain, this subgroup displays the highest percentage of incomplete resections with subsequent persistent risk of rebleeding at follow-up. To achieve a total removal of the lesion timing of surgery as well as the correct surgical technique is essential. In cases of well-organized hematoma within the CM, the hematoma should be aspirated prior to resection of CM. The evacuation of the hematoma provides enough room for the safe excision of CM avoiding any unnecessary retraction of the adjacent tissue. Partial removal is associated with a persistent higher risk of recurrent hemorrhage from the residual lesion.

Brainstem CMs are usually removed through an incision smaller than the lesion itself. This makes internal decompression and piecemeal removal necessary. En bloc resection is usually neither safe nor feasible in this location. However, this implicates a higher risk for partial removal. Besides the rule of complete exstirpation, every attempt must be made to preserve any associated DVA to avoida venous infarct with potentially disastrous clinical sequelae, especially in BSCMs.

Not every DVA is visible on MRI scans, therefore a DVA should be suspected even when the preoperative MRI does not show one. Another major goal of CM surgery is to avoid the recurrence of seizures. Today there is still no consensus about whether to remove the hemosiderin-loaded gliotic rim which surrounds the malformation itself or to preserve it. The idea of removing this rim derives from the theory that this pathologically changed tissue is believed to be the origin of seizures. However, some studies in which surgical treatment was intentionally limited to lesionectomy and the hemosiderin rim was preserved, even in patients with intractable seizures, show that the persistence of the hemosiderin ring does not seem to habe an adverse effect on the outcome regarding seizures compared to those with removal of the hemosiderin ring. Furthermore, there

remains the possibility that the visualized CM may not necessarily be responsible for the seizure disorder, therefore some authors recommend sufficient preoperative electroencephalographic evaluation to confirm the epileptigenic region. The removal of the hemosiderin rim, which is a possible option for supratentorial lesions, should be avoided in the brainstem. Although during the operation on a BSCM a xanthochromic discoloration on the surface of the brainstem is a good landmark for cavernoma localization, it should be considered as functioning tissue and preserved as much as possible. And finally, the goal of surgery and total removal of the lesion is to prevent future hemorrhage and an improvement in neurological deficits.(1,9,18,19,32,41,44)

4.7.1.1 Goals of surgery

The most important aim of a surgical intervention is a complete resection of the cavernous malformation, because only in the case of total removal, the prevention of renewed hemorrhage is given. Several studies show a significantly higher rebleeding risk of up to 43% in cases of remnants after surgery.(21,22,32) Therefore, incomplete resection carries a greater risk than the natural history after the first bleeding episode. Most authors describe the appearance of remnants in cases of multi-lobular cavernomas, with a mullberry structure made up of several nodules, some of them hidden by a thin layer of with matter. So even if the surgical cavity appears clean, as in the case of a multi-lobulated cavernoma, a postoperative MRI within 72 hours, should be performed to detect a residuum. But in the case of an early postoperative MRI, it should be considered that a residual lesion may be masked by surgical products. Nevertheless, this circumstance should not urge the surgeon to an unnecessarily aggressive removal putting the patient at risk for additional surgery related morbidity. Another major aim of the surgical intervention is to produce as little disruption of normal structures and the surrounding parenchyma as possible, especially in eloquent locations like the brainstem. This implies designing a special and individually tailored approach for each patient. Moreover, the preservation of a DVA, especially in BSCMs is imperative because of the risk of venous infarction. And finally, surgery is intended to not only improve neurological deficits but also to improve the patient's quality of life. (11,19,21,22,25,32,35,39,46)

4.7.1.2 Surgical technique

There are three generally accepted rules for the surgical removal of CMs. These involve the complete removal of the lesion, the avoidance of any injury to associated venous

malformations (such as DVAs) and the preservation of the surrounding hemosiderin-loaded gliotic parenchyma. In addition to these rules there are some important points about the microsurgical technique which are worth mentioning: Meticulous and selective coagulation and cutting of anomalous vessels surrounding cavernomas is imperative to avoid thermal injury to adjacent tissue. The exact knowledge of the anatomy of the brainstem and the mastery of the precise usage of microinstruments such as bipolar forceps, microscissors, suction devices, dissectors and brain retractors is essential. Supratentorial and cerebellar CMs can be removed en bloc, but in BSCMs piecemeal removal should be performed, because of the high density of eloquent structures surrounding the cavernoma and the oftentimes onlynarrow opening. Thus, the CM is resected from the inside, entering the capsule and working internally to draw the margins inward. After removal, the cavity is thoroughly inspected for bleeding and lesion remnants.(14,25,27,29,32,38,41) As stated above considering the hemosiderin ring surrounding the cavernoma the majority of authors recommend to preserve this layer at the region of the brainstem because of the risk of damaging healthy brain tissue. Very few authors instead recommend to peel the hemosiderin-loaded brain parenchyma away, arguing to do this so because of the risk of the epileptogenic potential of iron in the cortex.(14,25,27,29,32,38,41)

Although DVAs may be the potential origin of CMs and preserving them means leaving a risk of recurrent CM development, there is consensus that DVAs should be preserved if possible. Up to now, there is no diagnostic tool capable of predicting whether removal of a DVA will be tolerated by the surrounding brain or whether swelling and infarction will evolve.(14,27,29,32,38,41)

In deep seated lesions the surgeon has to work through an opening in the size of just a few millimeters to remove a CM with a lesion size of up to several centimeters. Therefore, the surrounding normal brainstem parenchyma should be manipulated as little as possible. Therefore, retractorless surgery becomes increasingly popular to avoid any unnecessary manipulation of the surrounding neuronal tissue. Instead, dynamix retraction is achieved using the two instruments in hand. To compensate for the small opening in the brain the bony opening is maximized to improve the visibility while limiting the need to see around corners.(29,32) It should be mentioned that the surgixal manipulation itself frequently causes symptoms that mimic a prior bleed, but these symptoms often resolve.

4.7.1.3 Patient selection and indications for surgery

Even nowadays there is a controversy about the criteria of patient selection for surgery. Therefore, the general outcome of the procedure of a CM surgery also depends on the choice which patient will be operated. This again depends on the judgement of the neurosurgeon, who relies on his experience and surgical skill. Porter et al. describe four factors to be considered for making the choice in favor of surgery: an exophytic lesion close to the ventricular or pial surface by less than 2 cm. Single large extralesional hemorrhage with significant neurologic deficit. Repeated hemorrhages resulting in progressive worsening of a neurological deficit. Significant mass effect produced by a large intra-lesional hemorrhage.(40)

Additionally, to the recommendation of Porter several other suggestions are found in the literature. Bertalanffy et al. recommend surgery for all symptomatic patients where neuroimaging demonstrates the presence of a readily accessible CM, for deep seated lesions causing massive hemorrhage, repetitive minor bleeding, or significant long-standing and progressive neurological disabilities. The best prognosis with a negligible risk of surgical complications and therefore highly recommended for microsurgical exstirpation are patients presenting with seizures or neurological deficits caused by easily accessible cavernomas of the hemispheres. Not recommended for surgery by Bertalanffy et al. are clinically silent cavernomas located in eloquent regions of the brain, particularly when approaching these lesions would require traversing healthy and functionally important neural structures, intrinsic brainstem lesions that do not reach the ventricular or pial surface of the brainstem, because this is believed to result in unacceptable neurological consequences and incidentally found BSCMs.(19,46)

Hauck et al. emphasize that the procedure of surgical exstirpation of a CM which is accompanied by a probable morbidity greater than 10%, provides little benefit in asymptomatic patients and the absence of previous events. In the same article Hauck et al. encourage to consider surgery after a first event.(43)

Bradac et al. also advocate the surgical treatment after a first symptomatic hemorrhage(10) while Bruneau et al. add cavernomas which are responsible for a progressive neurological deterioration due to mass effect as indication for surgery. However, they refuse to operate on patients even after multiple episodes of bleeding if the neurological state of the patient recovers, because they consider the risk of postoperative worsening equal to the risk of neurological impairment due to rebleeding.(35)

4.7.1.4 Timing of surgery

Regarding the right timing of surgical intervention, there are several factors to consider to choose the optimal time. The following factors play an important role: the presence or absence of hemorrhage, the presence or absence of intractable seizures, the acuteness and the mass effect of hemorrhage and the patient's clinical condition.

A very important factor is the time to the last hemorrhage, because it allows a partial liquefaction of the hematoma which provides a natural buffer that diminishes surgery-related trauma, by creating working space around the CM that can minimize brain transgression or allow access to deep-seated CMs that might otherwise have been unreachable.(1) However, not too much time should pass to avoid fibrosis, glial scarring and calcifications of the hematoma and thus adherence of the CM to the surrounding parenchyma, which compromises the well-demarcated dissection plane, makes the surgical resection more difficult and increases the likelihood of mechanical trauma from surgical manipulation.(1,9,19,35)

There are different recommendations found in the literature about the right timing for surgical exstirpation of CMs. The majority of recommendations ranges between 1 to 6 weeks. Bruneau et al. recommend surgery during the subacute stage after the hemorrhage and deterioration and in cases of multiple bleedings, they base the delay on the last bleeding event. In their study they reached a mean time of 22 days to surgery.(35) Cenzato et al. suggest an interval for surgery within 1 to 3 weeks after the last bleeding episode and after stabilization of the neurological condition.(21) Chen et al. publish a delay of 2 to 6 weeks from hemorrhage to surgery in 38.2%, a delay of 7 to 13 days in 27.3% and a longer delay, not more precisely specified, in 34.5% of their patients.(39) Giliberto et al. recommend delaying surgery after a symptomatic hemorrhage if possible for 2 to 3 weeks.(1,21,35,39)

Clinical observations show that operating within 3 weeks after bleeding is accompanied with better neurological results in the early postoperative period.(35) These results are explained by the fact that in this early stage the hematoma is not organized and no reactive gliosis is developed. Furthermore, the hematoma provides the direction for the surgical approach while removal of the fresh clot after extralesional hemorrhage or removal of a larger cavernoma after intralesional hemorrhage alleviates the mass effect on the brainstem nuclei and tracts and thus improves the neurological condition.(1)

4.7.1.5 Choice of the surgical approach to the brainstem

In this chapter, the widespread two-point method suggested by Brown et al. will be described as well as all the approaches used in the current study will be introduced.(20)

4.7.1.5.1 Two-point method (as suggested by Brown et al.)

The two-point method was described by Brown et al. to establish the best access route to a cavernous malformation. For the application of the two-point method, one point is placed in the center of the cavernous malformation, and a second is placed at the point where the lesion reaches or is closest to the pial surface or where the safest entry point is determined. In case of a DVA lying between the access trajectory and the cavernoma, the entire approach has to be modified to avoid injury to the DVA. However, according to most authors, the value of this technique is an objective means to guide the selection of the surgical approach. Therefore, the right approach has to be selected on a case-by-case basis considering the anatomic location of the lesion.(19,22,32)

4.7.1.5.2 Median suboccipital approach

Indication

Because of the general distribution of lesion location (see below), the median suboccipital approach, which provides perfect access to the rhomboid fossa, is one of the most frequently used approaches. Indications for using this approach are therefore lesions which cross the surface of the floor of the fourth ventricle or protrude into the ventricle. Furthermore, it can be used for posterior medullary lesions.(48)

Contraindication

The contraindications are based on the extent of the lesion, for example, if the lesion reaches into the rostral direction to the tentorium(this would require a combined supracerebellar and supratentorial approach)or if the lesion extends to the middle fossa, (here, a combined middle and posterior fossa approach is recommended in the literature).(48)

Procedure

The best patient position for a median suboccipital approach is the prone position according to the literature. (Figure 4.7-1) Important for lesions in the midline is, to flex the head as much as possible to widen the space between the foramen magnum and the first cervical vertebra. This ought to facilitate the bony opening.

Figure 4.7-1: Prone position (Jindal, Rahul. Core Techniques In Operative Neurosurgery. copyright 2011 by Saunders)

The landmark for the skin incision is the inion. Orientated on the inion, a linear midline incision is made from 4 cm cranially to the inion, down to the spinous process of the second vertebra. During preparation in the region of the arch of the first vertebra, the surgeon has to be attentive of the vertebral artery located laterally.

The burr holes for the craniotomy are recommended to be placed close to the transverse sinus. The surgeon has to take care of performing the craniotomy carefully to preserve the underlying dura. If necessary, a laminectomy of the atlas allows a wider dural opening, which can be necessary for lesions in the fourth ventricle.(48)

Bertalanffy et al. describe the technique of a C1 and even a C2 laminectomy to expose the lower brainstem as a unnecessary surgical step. (19) Furthermore, there are two optional approaches to expose the floor of the fourth ventricle. One is the technique of splitting the posterior inferior vermis, which can be accompanied by postoperative truncal ataxia. Therefore, the majority of authors prefer the intertonsillar or the transcerebellomedullary fissure approach, respectively. In the case of using the intertonsillar approach, Bertalanffy et al. recommend the sitting position. (19,41)

4.7.1.5.3 Suboccipital retrosigmoid approach

Indication

The general indications for a retrosigmoid approach are lesions of the anterolateral pons, rostral pontomedullary lesions, BSCMs of the cerebellopontine angle or the middle cerebellar peduncle and the pretroclival region. This approach is a safe and effective alternative to more radical cranial base approaches to the cerebellopontine angle and to the petroclival region. However, the cerebellum may need to be mobilized to provide a sufficiently lateral trajectory into the pons through the middle cerebellar peduncles. (32,41,48)

Contraindication

Because of the limited ventral exposure achieved through the retrosigmoid approach, lesions extending too far into the ventral direction are not suitable for this approach. The extended retrosigmoid approach provides an appropriate alternative. (41) An insufficient contralateral transverse and sigmoid sinus constitutes a contraindication for using the retrosigmoid approach because of the risk for potential venous injury.(48)

Procedure

The general patient position is recommended to be the supine position. (Figure 4.7-2) For facilitating the trajectory, the head is rotated toward the contralateral side and the neck is extended.At the end of the positioning the zygomatic bone should be the highest point in the operative field, this indicates the appropriate position of the patient's head. An alternative position technique is recommended to be the park bench position or a modified prone position.(48,49)

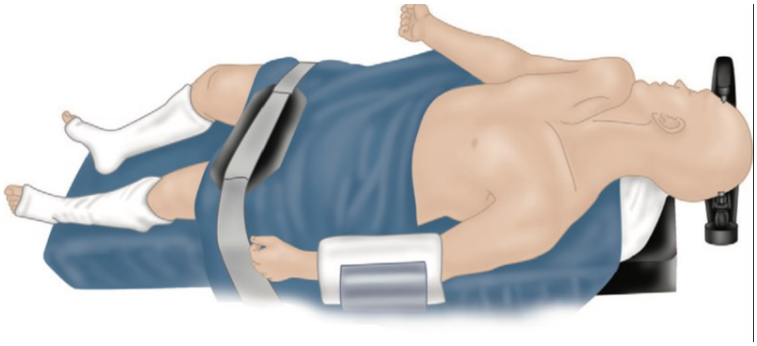

Figure 4.7-2: Supine position (Jindal, Rahul. Core Techniques In Operative Neurosurgery. copyright 2011 by Saunders)

A c-shaped skin incision from the mastoid tip around the ear is made. Afterwards a soft tissue dissection, from the asterion down to the mastoid process and posterior to the sigmoid sinus for bone exposure is performed.

Then a burr hole is placed at the angle between the sigmoid sinus and the transverse sinus. A craniotomy along the border of the edge of the sinuses is performed, avoiding an opening of the mastoid.(49) The extended retrosigmoid approach has the benefit of a better ventral exposure compared to the traditional retrosigmoid approach. Areas like the ventral brainstem near the tentorium become more accessible. This benefit derives from a limited posterior mastoidectomy, skeletonization of the sigmoid and transverse sinuses and anterior mobilization of the sinus with dural flap. The disadvantages of this approach are an increased risk of venous sinus thrombosis and cerebrospinal fluid fistula. (41,48,49)

4.7.1.5.4 Pterional approach

Indication

The pterional approach is appropriate for tumors of the anterior and middle cranial fossa and in the case of BSCMs especially suitable for lesions in the ventral to ventrolateral mesencephalon or pontomesencephalis region.(48,49)

Contraindication

If the cavernoma extends too far rostral based on the meynert axis, this approach does not deliver a sufficient trajectory. Another important fact concerning this approach is the vascular situation, it is difficult to manipulate at the ventral pons from this trajectory because of the basilar artery and the rami ad pontem.(32,48,49)

Procedure

The patient is usually positioned in supine position. (Figure 4.7-1) For facilitating the trajectory, the head is rotated toward the contralateral side and the neck is extended, which results in a self-retraction of the frontal lobe off the anterior cranial fossa floor. At the end of the positioning the zygomatic bone should be the highest point in the operative field which indicates the appropriate position of the patient's head. The incision for a pterional craniotomy is curvilinear and starts from the leading hairline near the midline and continues behind the hairline up to 1 centimeter above the external acoustic meatus.

For the muscle preparation, an incision of the temporal muscle along the linea temporalis and the frontal process of the zygomatic bone is performed. The muscle is then mobilized with a temporobasally directed stem. By shoving the skin and muscle together off the bone, the facial nerve can be protected. The burr holes can be placed at different strategic points, the technique explained here is recommended by Jandial et al. It comprises five burr holes, the first is placed at the keyhole, the second is placed above the root of the zygoma, the third is placed inferior to the linea temporalis, approximately 1 centimeter above the temporal squamosa, in line with the zygomatic root, the fourth is placed anterior to the coronal suture and the fifth is placed in the anterior frontal bone above the orbit and frontal sinus, as shown in Figure 4.7-3.

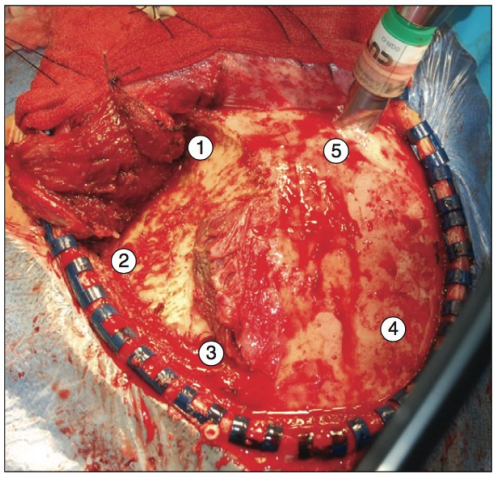

Figure 4.7-3: Burr hole position (Jindal, Rahul. Core Techniques In Operative Neurosurgery. copyright 2011 by Saunders)

The craniotomy is done by connecting the burr holes with the saw, the recommended tool is the Gigli saw. It is recommended because it produces thin and beveled cuts, which can result in a superior cosmetic appearance. Subsequently the subtemporal exposure and drilling of frontal and sphenoid bones are performed. An important step is the removal of the lesser wing of the sphenoid, by using a drill. By cutting the dura, special care has to be taken to dissect any bridging veins deriving from the Sylvian fissure beneath it. The dura incision is done in a semicircular shape and the resulting dura flap should be reflected anteriorly. After that, the Sylvian dissection is performed. Next, the anterior clinoid should be visualized. It can be removed by drilling if necessary but special care has to be taken to not injure the optic nerve which lies in direct vicinity.(32,48,49)

4.7.1.5.5 Subtemporal approach

Indication

This approach is appropriate for lesions of the middle and posterior fossa.

It is well suited for anterolateral CMs as well as for more caudally located pontomesencephalic CMs. (32,41,48,49)

Contraindication

The subtemporal approach is rarely used for the dominant hemisphere. The primary limitation or risk of this approach is the potential for venous injury, especially the vein of Labbé. Therefore, preoperative imaging studies should be performed to investigate the location of the vein of Labbé and if it crosses the surgical trajectory.(32,48,49)

Procedure

The general patient position is recommended to be the supine position (Figure 4.7-2). For facilitating the trajectory, the head is rotated toward the contralateral side and the neck is extended, which results in a self-retraction of the temporal lobe. At the end of the positioning the zygomatic bone should be the highest point in the operative field, this indicates the appropriate position of the patient's head. An alternative patient position recommended by Hölper et al. is the park bench position. The incision is horseshoe like, starts from the zygomatic root and ends at the asterion. The preservation of the superficial temporal artery is recommended. The burr holes for the craniotomy are placed at the squamosal temporal bone at the zygomatic root, at the superior temporal line, at the asterion flush with the middle fossa and superiorly and behind the insertion of the vein of Labbé into the transverse sinus. Hölper et al. claim that a singular burr hole at the zygomatic process is enough. Subsequently the craniotomy is performed into the temporobasal direction. The dura is incised in a U-shaped form with the base inferiorly. Special care has to be taken of the vein of Labbé. At this point, further dissection proceeds according to the targeted lesion. The advantages of this approach are less cerebellar retraction and a potentially decreased risk of injury to cranial nerves. On the other hand, the limitations of this approach are the temporal lobe retraction, related edema and an increased risk of injury to the vein of Labbé with subsequent venous infarction. (32,41,48,49)

4.7.1.5.6 Supracerebellar infratentorial approach

Indication

This approach is one of the most commonly used and recommended approaches for BSCMs. It provides excellent exposure for lesions of the pineal region, the posterior third ventricle, the quadrigeminal plate, the pontomesencephalic junction and to laterally situated lesions of the midbrain and cerebral peduncle. (22,32,48,49)

Contraindication

One contraindication for this approach are lesions which extend too far caudal into the pons or the fourth ventricle, because the view produced by this approach may not be able to deliver a sufficient trajectory. Another contraindication is a too steeply angled tentorium. (41,48,49)

Procedure

The patient position recommended by Jandial et al. is the sitting position (Figure 4.7-4), because of the fact that the cerebellum tends to fall away from the tentorium and therefore produces an excellent trajectory. In case of a persistent foramen ovale, the sitting position should not be used because of the higher risk of air embolism. An alternative approach recommended by Hölper et al. is the concord position. The side effect of this position is the increased infratentorial pressure.(48,49)

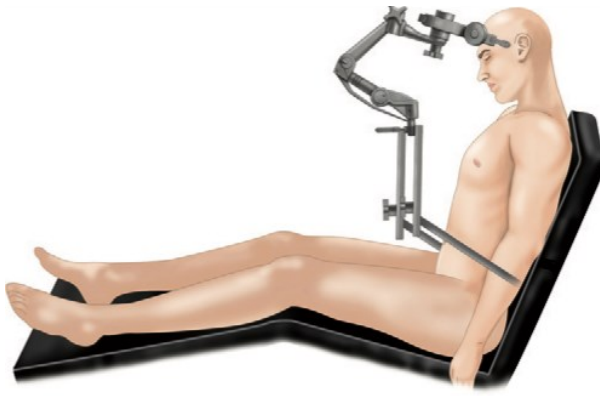

Figure 4.7-4: Sitting position (Jindal, Rahul. Core Techniques In Operative Neurosurgery. copyright 2011 by Saunders)

The skin incision should be performed in a slightly S-shaped form or alternatively a straight one and is made from above the inion down to approximately C2 (maximum to

C4). Subsequently the suboccipital exposure is performed with dissection of the suboccipital musculature. Burr holes are placed on each side of the superior sagittal sinus right above the torcular Herophili, and superior and inferior to each transverse sinus a few centimeters distal to the torcular Herophili. A craniotome is used to connect the burr holes to create a bone flap. An alternative technique of burr hole positioning is directly beneath the transverse sinus and as far laterally as possible. In this technique, the craniotomy includes the margin of the foramen magnum to create the bone flap.(48,49)

A semilunar or cruciate dural incision is made based on the transverse sinuses and torcular Herophili.(48) Subsequently the arachnoid adhesions and bridging veins between the vermis and tentorium are divided close to the cerebellar surface. In the process of continuing the dissection the cerebellum falls with gravity and the view of the normal anatomy of the posterior mesencephalon should be achieved.(32,41,48,49)

4.7.1.5.7 Interhemispheric transcallosal transchoroidal approach

Indication

The general indications for the transcallosal approach are lesions in the third ventricle or supra pineal tumors, but by going through the bottom of the third ventricle, rostrally located lesions of the mesencephalon based on the axis of Meynert are accessible as well.(48,49)

Procedure

A supine patient position is recommended and the head should be slightly flexed. The appropriate location of the craniotomy, based on the midline, the coronal suture and the extent of the craniotomy, depends on the location and extent of the targeted lesion. The burr holes are placed at the projection of the superior sagittal sinus. Before performing the craniotomy, a detachment of the dura away from the venous sinus is recommended. After accomplished craniotomy the dura is incised in a U-shaped form based at the superior sagittal sinus. Then the preparation goes on between the hemispheres until the callosomarginal artery is reached, beneath this artery the pericallosal artery follows. Then the gyrus cingula is prepared and followed by the corpus callosum. The next step is the callosotomy, with a maximal expand of two centimeters which serves as the entrance to the

ventricle. The septal vein, the choroid plexus, the thalamostriate vein and the caudate nucleus vein lead to the interventricular foramen. Then the tela choroidea of the lateral ventricle is prepared, beneath this structure lies the 3. ventricle, which serves as the entrance to the thalamus and mesencephalon.(32,41,48,49)

4.7.1.5.8 Endoscopic, transsphenoidal, transclival approach

Indication

The general indications for a transsphenoidal approach are lesions in the sella region, but a transclival approach also grants access to lesions of the ventral pons. The benefits of this approach are minimal trauma to the brain, no need for brain retraction, no creation of visible scars and it has a lower surgically related morbidity than transcranial approaches.(48,49)

Procedure

The patient is positioned supine with the head elevated above the heart level. In case of neuronavigation a three-pin fixation device is recommended. The head should be positioned with the neck slightly flexed. A desinfection of the nose and oropharynx is performed. For local anesthesia and hemostasis, a mixture of lidocaine and epinephrine is infiltrated into the mucosa of the nose. A hockey stick incision is made in the mucosa overlying the septum and the mucosa is scraped of the septum. Subsequently the septum is fractured and dislocated to the other side. The sphenoid sinus is opened and the mucosa within should be removed meticulously. After that, depending on the lesion location the bottom of the sphenoid sinus can be opened at the needed direction.(41,48,49)

4.7.1.6 Safe entry zones

Safe entry zones are relatively safe but narrow surgical corridors into the brainstem parenchyma with few critical neural structures and no perforating arteries getting in the way. Most commonly, the exposed brainstem surface shows a xanthochromic coloration at the site of the cavernoma and an additional small, dark-blue area corresponding to the bulging hematoma. In such cases, the entry zone depends on the exact site of the cavernoma or hematoma on the brainstem surface. But if the lesion is deep and separated from the surface by a parenchymal layer, however thin it may be, the safe entry zones provide a proper alternative approach.(18,27,29,38,39,41)

Anatomic research shows the safe entry zones mainly at the dorsal brainstem (Figure 4.7-5) but there are also some at the ventral brainstem (Figure 4.7-6). The various safe entry zones at the dorsal side of the brainstem are: 1) Supracollicular, localized inferior to the pineal gland and above and between the superior colliculi. 2) infracollicular, localized between and inferior to the inferior colliculi and above the trochlear nerve. 3) The lateral mesencephalic sulcus, which divides the midbrain into the anterolateral midbrain and the posterior midbrain and runs from the medial geniculate body above to the pontomesencephalic sulcus. 4) The median sulcus, at the floor of the fourth ventricle at a point between the facial colliculus and abducens nucleus. 5) The suprafacial triangle, bordered rostrally by the base of the frenulum veli, caudally by the facial colliculus and laterally by the cerebellar peduncle. 6) The infrafacial triangle, bordered caudally by the rostral margin of the hypoglossal triangle, laterally by the vestibular area and rostrally by the facial colliculus. 7) The posterior median, 8) intermediate- and 9) lateral sulcus. The two safe entry zones at the ventral side of the brainstem are: 1) The peritrigeminal area and 2) the inferior olivary nucleus. In cases of intrinsic cavernomas separated from the ependymal surface, it is recommended to map the floor of the fourth ventricle with to identify and avoid functionally important areas before incision.(18,27,29,34,38,39,41)

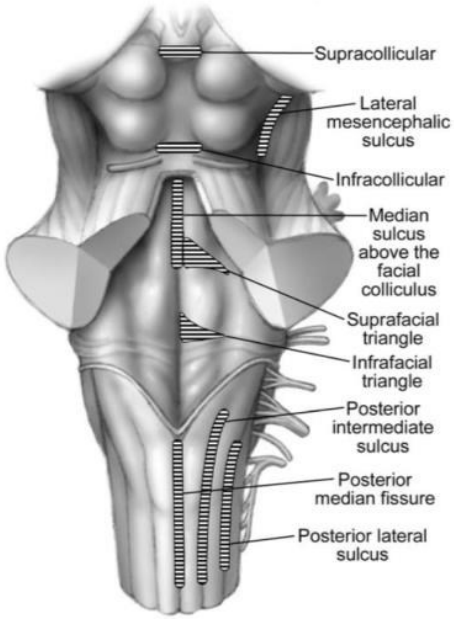

Figure 4.7-5: : safe entry zones posterior view (Giliberto, Guliano. Brainstem cavernous malformations: anatomical, clinical, and surgical considerations. copyright 2010 by Neurosurgical focus)

Figure 4.7-6: safe entry zones ventral view (Giliberto, Guliano. Brainstem cavernous malformations: anatomical, clinical, and surgical considerations. copyright 2010 by Neurosurgical focus)

4.7.1.7 Intraoperative Neuromonitoring

Nowadays, brainstem surgery is almost impossible without the aid of intraoperative neuromonitoring. This technique plays an important part in the possibility to minimize injury to critical structures and therefore reducing surgery related morbidity and permanent and potentially severely disabling neurological deficits. The role in detecting cranial nerve nuclei hence identifying the safe entry zones of the brainstemis essential for surgical procedures of the brainstem,especially in BSCMs.(22,34)

With techniques like motor evoked potentials, somatosensory evoked potentials and auditory evoked potentials, structures such as the corticospinal tract in the cerebral peduncle, CN nuclei (CNs VII, IX, X, and XII), the facial colliculus, and hypoglossal and vagal trigones on the floor of the fourth ventricle can be mapped, identified and their function monitored. Pandey et al. describe a gain of knowledge in early detection of excessive retraction and manipulation of critical structures with the use of intraoperative monitoring and mapping techniques. They therefore recommend an intraoperative

neuromonitoring protocol which includes electroencephalogram, bilateral somatosensory evoked potentials and auditory evoked potentials for every patient and cranial nerve nuclei mapping when appropriate.(1,34)

4.7.2 STEREOTACTIC RADIOSURGERY

General notes

The basic principle for using stereotactic radiosurgery in cavernous malformations derives from the treatment of AVMs, where radiosurgery induces a hyalinization and thickening of blood vessel walls which results in a thrombosis and obliteration of the targeted vessels, that can be confirmed by angiography.(10,19,22,43,47)

For Cavernomas categorized as inoperable because of a high surgical risk because of location in eloquent areas such as deep seated BSCMs, radiosurgery, using either heavy charged particles (proton ions) or photons (linear accelerator and gamma knife radiosurgery), has been introduced as a potential alternative in analogy to the successful radiosurgical treatment of AVMs.(10,19,43)

The main goal of radiosurgery is a significant reduction of bleeding risk. The latency period for reaching this goal is defined for 2 years. This delay stems from experiences with radiosurgical treatment of AVMs, because investigations in AVMs after radiosurgery show that after a time period of 2 years, effects of the treatment were verifiable.(19,22)

The hypothesis behind the effect ofradiosurgery proposed by Hasegawa et al. is that the endothelium-lined channels undergo progressive hylinization leading to thickening and eventual closure of the lumen, perhaps via the chronic inflammatory response typical for radiation-induced vasculopathy. The limitation of this theory is, that there are just a few reports on the histology of cavernous malformations after radiation, therefore more histological studies of cavernous malformations after radiosurgery are needed to determine the influence of radiosurgery.(47)

Pros of stereotactic radiosurgery

In the study of Hasegawa et al. results were published in which the study population, containing 82 patients, was treated with radiosurgery and presented after this intervention with a reduced risk of hemorrhage during a 2-year latency interval, followed by a return to baseline risk. Before intervention the yearly risk of hemorrhage in that study population was about 33,9%, within the following 2-years after radiosurgery, the risk of hemorrhage was reduced to 12,3% per year and after the 2 years of latency interval, the yearly risk of

hemorrhage was further reduced to 0,76%. But the study of Hasegawa et al. had to deal with severe criticism because of the design of the study, in which the patients were analyzed in a series-connected way and therefore acted as their own control group, hence the results of the study have to be interpreted critically.(47)

Cons of stereotactic radiosurgery

One problem in reviewing the results of stereotactic radiosurgery is, that in contrast to AVMs, MRI sequences such as time of flight as well as angiography cannot be used to follow up cavernoma patients. Hence, assessing the bleeding risk and therefore an obvious end point in evaluating the treatment results does not exist. The only way of assessing the efficacy of the treatment is the clinical observation of hemorrhage rates before and after treatment.(19)

The most commonly found values in the literature related to the rebleeding rate after radiosurgical intervention range between 9 to 44% during the latency period of 2 years.(19,22,41,43,47) In one of the biggest and most cited studies dealing with radiosurgery in CMs, Hasegawa et al. published a value of 17 rehemorrhages in 13 patients within the latency period of 2-years, from which they calculated an annual hemorrhage rate of 12.3%. This is a higher rehemorrhage ratecompared with the rate of 5,2% after conventional surgery. A noteworthy aspect is, that lesions which hemorrhaged after radiosurgery were significantly larger than those that did not (2,7 versus 1,7 cm^3, $P< 0,05$), which is in contrast with the natural history of cavernomas, where the size does not influence the rehemorrhage rate.(22,41,43,47)

The major statement of studies supporting stereotactic radiosurgery of CMs is, that after the 2-years latency period with the higher risk of hemorrhage compared to conventional surgery, the hemorrhage rate decreases to a baseline as low as 0,8%.

But natural history studies show that hemorrhage frequency among aggressive lesions may abate after a natural 2-years latency period, therefore the efficacy of radiosurgery remains unproven and may merely reflect the natural history of the lesions. Hence Goss et al. rank stereotactic radiosurgery as an alternative forobservation but not for surgery in the case of aggressive lesions.(41)

In the study of Hasegawa et al. the follow-up imaging studies for an observation period of 10 years show an increase in size and a high signal intensity on T1-weighted images.(47)

The problems of radiation in the area of the brainstem are on the one hand the fact, that in most patients cavernomas appear much bigger on MRI scans due to the hematoma than the

actual cavernoma really is, therefore the target of radiation is unprecise. On the other hand, in an eloquent area like the brainstem, which is highly sensitive to swelling and manipulation and therefore to radiation, even the relatively low dose of radiation used in current stereotactic radiosurgery protocols have to be limited (<15 Gy) to avoid damage to the brainstem, so complete obliteration of the cavernoma vessels is difficult to obtain.(27)

Adverse effects of radiation

Besides the question of utility, there are neurological sequelae after radiosurgery. The values found in the literature regarded to permanent neurological deficits range from 12% to 16%, all occurred within the first year after radiosurgery and were due to necrosis or posttreatment hemorrhage. In the study of Pollock et al. a temporary and permanent radiation-related complication rate of 59% and 41%, respectively, was published.(43) Even fatal cases have been reported, with mortality rates ranging from 0% to 13%.(41) In the study of Hasegawa et al. a correlation between a significantly higher marginal dose (17,45 versus 16,05 Gy) as well as a higher rate of previous hemorrhages and radiosurgical complications have been observed. Furthermore, the rate of complications was higher in CMs localized in the brainstem or the diencephalon than in other regions.(19,41,43,47) Finally, the morbidity of radiosurgery in angiographically occult vascular malformations significantly higher when compared with the morbidity on treatment of AVMs.(19,41,43,47)

Hasegawa et al. blame the inaccurate targeting of stereotactic radiosurgery for the high risk of morbidity. They claim a significant decrease in treatment related morbidity due to improvement of the targeting, and that since the use of more accurate targeting no neurological deficit occurred in 50 treated patients since 1992.(47) Furthermore, one has to keep in mind, that if surgery is needed after stereotactic radiosurgery, this previous treatment makes the surgical resection more difficult, by making the cavernomas more adherent to the surrounding tissue and the dissecting plane less clear.(27)

The place of radiosurgery after all

These days the use of radiosurgical treatment for cavernous malformations is controversial. There is still no study which was able to prove the hemorrhage preventive effect of radiosurgery in CMs. The problem in an objective follow-up after this treatment is, that cavernous malformations are angiographically occult lesions and no other clinical test or imaging can confirm whether the cavernomas are obliterated or not. Therefore, long term follow up stays the only criteria to evaluate the effectiveness of radiosurgery. The

statement of decreased hemorrhage rate after a 2-years latency period past radiosurgical treatment lies in contrast to the observed pattern of temporal clustering. This phenomenon is discussed of being the natural history in BSCMs, which implies that BSCMs have the tendency to bleed multiple times during a 1- or 2-year period and then cease bleeding. The majority of the authors thus conclude that if radiosurgery is incorporated into a treatment algorithm, it should be reserved for deep-seated symptomatic lesions in eloquent regions, which do not fulfil enough criteria for surgical resection and executed with modest doses of under 15 Gy to lower the risk of complications.(10,19,27,34,41,47)

4.7.3 CONSERVATIVE MANAGEMENT

Patient selection for observation

The hallmarks of conservative management are a symptoms oriented therapy, continuous imaging protocols and clinical observation. The indications for conservative management found in the literature are: patients diagnosed with a CM who present without gross hemorrhage, asymptomatic patients, normalization of a pathologic neurological status sometime after the bleeding event, small deep lesions without contact to the surface in asymptomatic patients, uncertain diagnosis of cavernoma hemorrhage, relatively asymptomatic patients in whom lesions are detected incidentally and older patients (>65 years) an patients with high anesthesia related risk.(12,19,27,35)

The decision between treatment and observation is not simple, the task is to balance the pros and cons and the estimation if the risk of clinical deterioration due to recurrent hemorrhage outweighs the surgery-related risks and possible postoperative morbidity.(12,19,27,35)

Wang et al. state a course of action in which hemorrhages in brainstem cavernomas are assumed to have such a high rebleeding rate, which in consideration of the eloquent area will almost certainly lead to new or more permanent neurologic deficits, that they decide for the benefit of a surgical resection of the BSCM.(27)

Clinical course of conservative management

In the study of Chen et al. a group of 20 patients underwent conservative management. After a mean follow-up of 44 months, the results of the study yileded 7 lesions with rehemorrhage of which 4 lesions were left untouched because of their difficult location and in the 3 remaining cases a surgical resection was performed. However, 13 of the 20 lesions

remained quiet after the period of follow-up. In the study of Chotai et al. including 5 patients with poor neurological status in the conservative group, 40% demonstrated improvement and 60% had no change in mRS at one-year follow up.(39,44)

Comparing conservative management and surgical treatment

A noteworthy observation is depicted in the study of Chen et al. In their two groups of surgically treated and conservatively managed patients, they found no significant difference in the initial and final neurological states. Although they emphasize the satisfactory prognosis of surgically treated patients harboring a deep BSCM, satisfactory if it is reachable via the safe entry zones. But they also underline that BSCMs might become quiet after the onset of bleeding, and this phenomenon was especially observed for deep-seated BSCMs. (39)

The place of conservative management after all

The long-term outcomes of conservative treated patients may be worse than in surgically treated patients, 42% and 9%, respectively.(22) In special selected patients, as described above, conservative treatment can play an important role. However, it is important to inform the patient of the estimated individual bleeding risk and all treatment options and possible morbidities which specific for each treatment. In Bozinov et al. that they never encountered a life-threatening bleeding in moren than 60 conservatively managed patients harboring minor- or non-hemorrhagic lesions.(22)

5 PATIENTS AND METHODS

5.1 DESIGN OF THE STUDY

We conducted a retrospective analysis of 26 patients with BSCMs who underwent surgical and conservative treatment at the Neurosurgical Department of the Medical University of Graz, during the 12-year period from March 2004 to November 2016. For ethical reasons, we do not have a control group in our study. The Ethical Review Committee of the Medical University of Graz approved this study, EK-number: 28-274 ex 15/16.

5.2 STUDY POPULATION

During the 12-year period from March 2004 to November 2016, 24 patients underwent microsurgical resection for BSCMs, one patient was treated radiosurgically and one patient was treated conservatively at the Neurosurgical Department of the Medical University of Graz. There were no age limitations for inclusion. Patients were excluded if the if the symptomatic lesion was not located in the brainstem (midbrain, pons or medulla oblongata).

5.3 DATA COLLECTION

The Hospital Information System openMEDOCS, a SAP-product, was used to collect the patient's charts. The collected data involves sex, age, date of admission, date of surgery, number of surgeries, date of discharge, localization of the lesion, number of CM's, number of hemorrhagic events, therapy modality, maximum diameter of the lesion, size of the lesion in volume, presence of DVAs, determined by radiographic films and operative notes, operative approach, usage of neuronavigation and intraoperative neuromonitoring, the pre- and postoperative condition of the patient

the pre- and postoperative modified Rankin Scale "mRS" and Glasgow Outcome Scale "GOS" score for each patient the period of follow up in each case, the time form hemorrhage till operation and the surgical complications. The occurrence of a hemorrhagic event was assumed by the appearance of new neurological symptoms, the deterioration of previously existing neurological symptoms and the radiological signs of an acute hemorrhage in the specific lesion.

5.4 DATA ANALYSIS AND STATISTICS

Descriptive analysis with median, mean, standard deviation, and maximum and minimum values was performed. Contingency tables were compiled for the pre- and postoperative mRS and GOS, the patient's symptoms, and the number of hemorrhagic events dependent on the localization. To compare the pre- and postoperative scores a Wilcoxon test was used. Additionally, the mRS and GOS variables were dichotomized into favorable (mRS≤2, GOS≥4, coded as 0) vs. unfavorable (mRS>2, GOS<4, coded as 1). A McNemar test was used to investigate the outcome using the dichotomized variables. With a Mann-Whitney Test, the association of the outcome of absolute binary mRS, with the size of the lesion was tested. The size of the lesion was evaluated with the DICOM-viewing software OsiriX Lite (by Rosset and Heuberger). Data was analyzed using IBM SPSS Statistics 23.

6 RESULTS

6.1 PATIENT CHARACTERISTICS

There were 14 females and 12 male patients included in this retrospective analysis. Ages ranged from 16 to 71 years (mean, 43,1 years; median, 40 years). The occurrence of a hemorrhagic event was assumed by the appearance of new neurological symptoms, the deterioration of previously existing neurological symptoms and the radiological sings of an acute hemorrhage in the specific lesion. Therefore 11 (42,3%) patients had a single hemorrhagic event and 15 (57,7%) suffered from multiple hemorrhagic events. Thus, all patients were symptomatic before surgery. Multiple hemorrhagic events were distributed as follows, 7 (46,7%) in the pons, 5 (33,3%) in the mesencephalon and 3 (20%) in the medulla oblongata. The distribution of the hemorrhagic events depending on the size showed a minimum in volume of 0,23cm^3 and a maximum of 7,9cm^3 with a median of 4,8cm^3 for multiple hemorrhagic events and a minimum volume of 0,26cm^3 and a maximum of 6,7cm^3 a median of 0,86cm^3 for single hemorrhagic events. Therefore, these findings show a higher bleeding tendency in bigger lesions (Figure 6.1-1). Three patients (11,5%) had a single brainstem cavernoma in combination with additional cavernous malformations elsewhere in the brain. From these three patients, one harbored three additional cavernomas, another patient two and one patient harbored a single additional cavernous malformation. One patient presented initially with a symptomatic cavernoma in

the cerebellum withpostoperative images indicating a partial resection of the cavernoma. The lesion recurred three more times, each time the cavernoma appeared at a slightly different localization drifting towards the medulla, where after several years a BSCM was diagnosed. 4 (16,7%) patients were operated two times and 1 (4,2%) patient was operated three times because of recurrence of the lesion. None of the patient's lesions were treated preoperatively with radiation or stereotactic radiosurgery. One patient with a cavernous malformation localized in the pons was treated radiosurgically with Leksell® LINAC. One patient with a cavernous malformation also located in the pons was treated conservatively.

At admission, the mRS score ranged from 0 to 4 (mean 2, standard deviation 1) and the GOS score ranged from 2 to 5 (mean 5, standard deviation 1). 17 patients (65,45%) presented with cranial nerve disturbances, 2 patients (7,7%) with only sensory cranial nerve deficits, 7 patients (26,95%) with only motor cranial nerve deficits and 5 patients (19,25%) with combined sensory and motor cranial nerve deficits. 21 patients (80,85%) presented with sensory and motor neurological deficits, whereof 4 patients (15,4%) had a pure sensory deficit, 6 (23,1%)patients presented with a pure motor deficit and 10 patients (38,5%) presented with a combined sensory and motor neurological deficit.

The general intention was to operate the lesion within the subacute state after a hemorrhagic event, the median time from a hemorrhagic event to surgery was 28 days, the mean was 41 days with a standard deviation of 38 days. One patient presented as a statistical outlier, so the patient was excluded from calculation of the median, mean and standard deviation. The patient received surgery 12 years after an initial event because of progression in growth indicated on MRI scans.

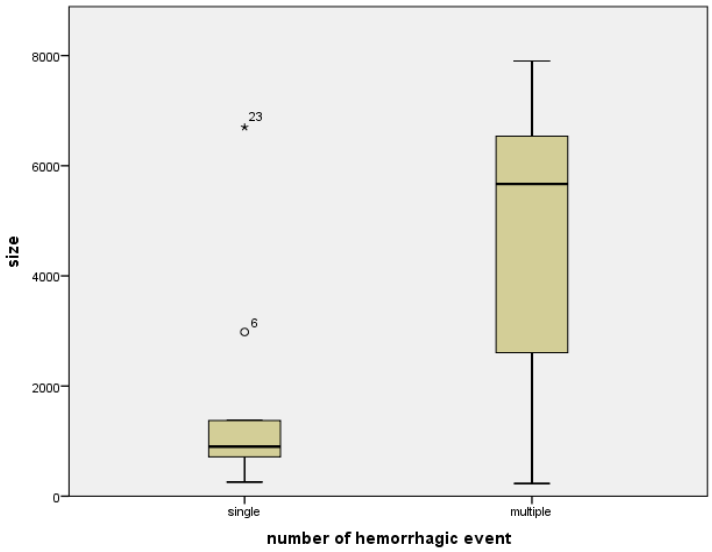

Figure 6.1-1: number of hemorrhagic event; satistical outliers case number 6 and 23

6.2 LESION CHARACTERISTICS

Of all BSCMs, 14 (53,9%) were located in the pons, 6 (23,1%) in the medulla oblongata and 6 (23,1%) in the midbrain. The size of the BSCMs ranged from 0,231 to 7,9 cm^3. The distribution of the size referred to the location of the lesions wasa mean of 3,81 ± 2,67 cm^3, a median of 3,31 cm^3, a max. volume of 7,47 cm^3 and a min. volume of 1,37 cm^3 for BSCMs in the mesencephalon. The volume of the cavernomas located in the pons was resulted in a mean of 3,05 ± 2,77 cm^3, a median of 2,01 cm^3, a max. volume of 7,90 cm^3 and a min. volume of 0,24 cm^3. The volume of the cavernomas located in the medulla was calculated with a mean of 1,7 ± 2,57 cm^3, a median of 0,80 cm^3, a max. volume of 6,27 cm^3 and a min. volume of 0,23 cm^3 (Figure 6.2-1). In 7 patients (26,95%) a DVA could be identified intraoperatively. All cavernomas were histologically verified.

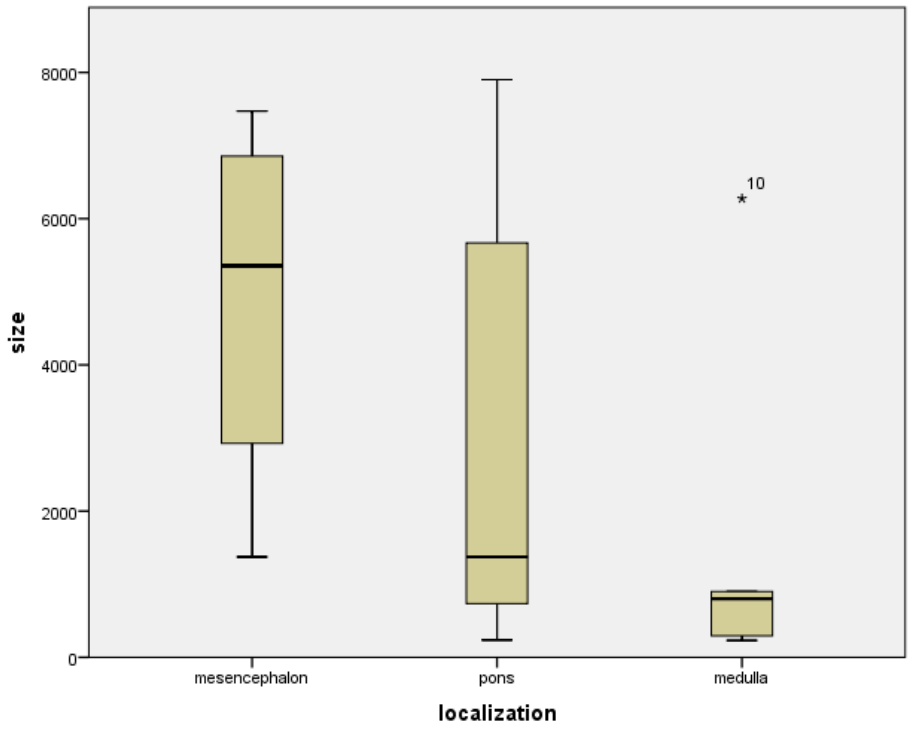

Figure 6.2-1: Boxplot localization; statistical outlier case number 10

6.3 SURGICAL OUTCOME

A total resection was achieved in 18 patients (69,2%), a subtotal resection, which is defined as the removal of at least 85% of the cavernoma, in 1 patient (3,8%), a partial resection in 4 patients (15,4%), in 1 (3,85%) patient the cavernoma was inaccessible, 1 (3,85%) patient was treated radiosurgically and 1 (3,85%) patient was treated conservatively. Reappearance of a cavernoma in the resection cavity was detected in 4 (16,67%) patients based on MRI findings. The first patient (male, age at the first surgery 51 years, location of the cavernoma pons), experienced another symptomatic episode. Because of lesion growth and progressive symptoms, this patient underwent a second procedure with total removal of the cavernoma. The second patient (female, age at first surgery 17 years, location of the cavernoma medulla oblongata), presented with new neurological deficits and a progression in growth of the lesion, 3 years after the surgery with partial removal of the cavernoma. At the second intervention, a total removal of the lesion could be achieved. The third patient (male, age at the first surgery 37 years, location of the cavernoma mesencephalon), underwent a second surgery 2 years after a partial resection of the cavernoma. Also in the second intervention, just partial removal of the lesion could be achieved. The fourth patient (female, age at the first surgery 29 years, location of the cavernoma pons), in the second surgery a total removal of the cavernoma could be achieved. In one patient (male, age at the first surgery 45 years, location of the cavernoma mesencephalon) the cavernoma exposed as inaccessible during surgery, one month later a different approach was attempt but also failed to provide a good accessibility to the cavernoma, therefore no removal of the cavernoma was possible. Surgical complicatons occurred in 6 (25%) patients. These complications involved liquor fistula in four patients and rhinoliquorrhea in two patients. After a mean follow-up of 26 months, compared to the preoperative status, 22 patients (91,67%) improved or were stabilized, 1 patient (4,17%) was worse and 1 patient (4,17%) was lost to follow-up. The one patient who deteriorated (female, age at surgery 73 years old, location of the cavernoma pons) decreased in the mRS score from preoperative 2 to postoperative 3. No patient was severely disabled or died. At last follow-up postoperatively, the mRS score ranged from 0 to 4 (mean 1, standard deviation 1) and the GOS score ranged from 3 to 5 (mean 5, standard deviation 0,5).

Two methods were used to assess the statistical significance between the outcomes of mRS score and GOS score. For the first method, a Wilcoxon-test was used, and for the second

method, the mRS and GOS variables were dichotomized into favorable (mRS≤2, GOS≥4, coded as 0) vs. unfavorable (mRS>2, GOS<4, coded as 1) and these binary variables were used to perform a McNemar-test. The results from the Wilcoxon-test show that mRS scores improved significantly (p=0,006) after the surgical treatment, whereas the Wilcoxon-test did not show a statistically significant improvement (p=0,031) when the condition of the patient was assessed with the GOS. This results from the more inexact structure of the GOS. The dichotomization of the mRS and GOS into favorable (mRS≤2, GOS≥4, coded as 0) vs. unfavorable (mRS>2, GOS<4, coded as 1). With the dichotomized mRS variables a McNemar-test was used to investigate the improvement after surgical intervention, the test showed no statistical significance (p=0,289).

6.4 OUTCOME PREDICTORS

With a Mann-Whitney Test, the association of the outcome of absolute binary mRS, with the size of the lesion was tested. The results did not show a statistical significant correlation (p=0,698). In the graphical illustration, a tendency was inferable showing that the unfavorable outcome correlated with a higher median in size of the lesion. (Figure 6.4-1)

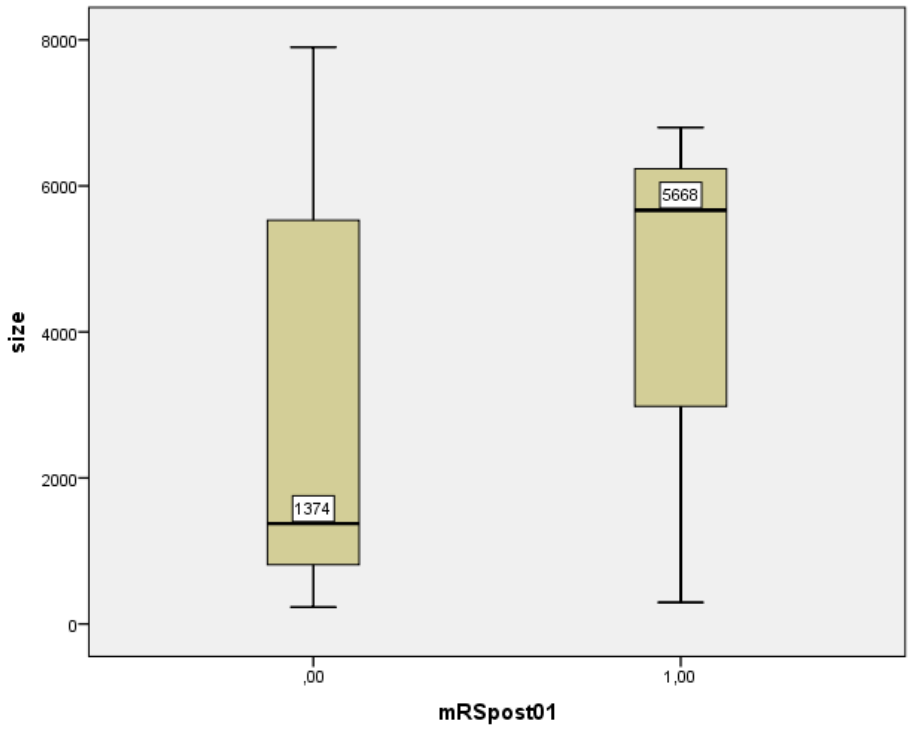

Figure 6.4-1: Boxplot correlation outcome with size of the lesion

6.5 SURGICAL APPROACHES

The choice of the surgical approach was made using the 2-point method described by Brown et al., also considering the patient specific variations in the anatomic location and planning the approach with the intention of minimize the damage of the surrounding structures of the brainstem and provide a trajectory which facilitates best conditions for total removal of the lesion. For planning the approach T1 MRI scans were used. To access the cavernomas, the following approaches were used: median suboccipital, retrosigmoid, occipital interhemispheric, pterional, subtemporal and supracerebellar infratentorial. The median suboccipital approach was the most common approach in our series (54,2%). The second most common approach in our series was the retrosigmoid approach (16,7%).

7 DISCUSSION

7.1 SURGICAL INDICATIONS

Most authors propose to use symptoms as an indication for surgery.(18,27,29,44)

Some add the acuteness of the presentation. Some divide the symptoms in their origin and recommend surgery in case of mass effect derived symptoms. Others stay to the principle for recommending surgery in case of progressive neurologic deficits. From our point of view, further considerations which may contribute to the decision making if a surgery is indicated and finally benefits the patient, can be done. One is, to elicit for how long do the symptoms already persist and therefore how big for the chance for improvement is. One has to keep in mind, that if symptoms occur through mass effect, they may vanish according to the natural history of organization of the hematoma and may remain the only symptomatic period the patient has ever encountered. Moriarity et al. (7) showed that a single hemorrhagic event is not necessarily accompanied with a higher risk of further hemorrhagic events. Furthermore, in some natural history studies a benign course of CMs has been described, hence Gross et al. even recommend to wait for a second hemorrhagic event, to define if the lesion tends to have an aggressive course, or as mentioned before a benign one.(41) But on the other hand, if the symptoms already persist for a long time, and a recovery of the neurological deficits can't be expected, neither naturally nor through surgery, the neurosurgeon has to weigh the risks which derive from a BSCM surgery against the doubtful benefits of the surgery. Another criterion to consider when it comes to the question of surgical indications is the location of the lesion. Most authors indicate the location as a selection criterion for surgery, but interestingly, the grade when they recommend a surgical intervention based on the location varies notably. The surgical recommendation reaches from clearly superficial lesions that can be reached without crossing healthy tissue (18,29,32) to lesions within 2-3 mm of the brainstem pial surface (27,44). In cases where the lesion does not initially present to such a surface, especially in cases of a first time hemorrhagic event, a conservative management can be considered(25),.The results of several studies show that surgeries of lesions which present to the ependymal surface or which are exophytic are well tolerated.(25) However, surgery of lesions which are covered by thin layers of healthy brain parenchyma can result in devastating neurological deficits. Some authors only recommend surgery in deep BSCMs when the lesion is accessible through a small incision of the anterolateral pontine surface (18). The strategies in deep BSCMs also vary. Chotai et al. treat every deep BSCM, if it can be approached by a safe trajectory (44) while Ferroli et al. prefer a more conservative way and monitor the patients and treats them surgically only if they exhibit severe progression of symptoms or if they develop neurological deficits such as those that would have been expected to result from surgery (18). Two other strategies, one from Gross et al.

the other from Ohue et al. will be highlighted here. Gross et al. combine the location of the lesion and the clinical course of the patient. They first evaluate the distance from lesion to pial or ependymal surface, measured on T1-weighted MRI scans and then combine these findings with the expectation of life- threatening emergent cases and with significant, progressive neurological deterioration in patients.(41) Ohue et al. perform surgery in patients with any neurological deficit and a lesion location to a surgical surface such as the floor of the fourth ventricle or the lateral or posterior aspects of the brainstem.(38) Our strategy is to include a presumable improvement in neurological deficits and a location of the lesion, which is either exophytic, or with a pial or ependymal presentation, or is reachable through an approach using a safe entry zone, determining the location of the lesion by T1-weightet MRI sequences, based on the phenomenon of ferromagnetic blooming. A common published indication for surgery is the hemorrhage in CMs. Some authors use the number of hemorrhagic events as a criterion, and therefore operate only after a second hemorrhage. Others use the acuteness of a hemorrhage as the decisive criterion, based on findings on MRI scans. Others again recommend surgery in acute, subacute or delayed hemorrhage, hence in every cavernous malformation. Abla et al. try to specify the consequences of the hemorrhage based on the findings at the MRI scans, namely if a hemorrhage is acute and extents outside the lesion capsule and further try to associate repeated hemorrhages with the progression of neurological deficits.(32) Abla et al. as well as Oliveira et al. try to distinguish between intralesional hemorrhage and extralesional/gross hemorrhage, and therefore try to identify a mass effect associated with an intralesional hemorrhage.(29,32) In the majority of proposed indications for surgical treatment, the acuteness or the number of hemorrhages are mentioned. But one has to keep in mind, that in the theory of origin of CMs, two types of continuous bleeding, in particular the “slow ooze” and the “intralesional hemorrhage or thrombosis” play an important role in the appearance and growth of CMs. Therefore, in the most cases the lesion will present with different states of hemorrhage, which in the case of the “slow ooze” and the “intralesional hemorrhage or thrombosis” have no magnificent influence of the clinical presentation of the lesion. Yet the bleeding type of “gross hemorrhage”, which is logically compared with the two previous mentioned types, relatively rare, but is thought to be responsible for causing acute symptoms by the destruction of the surrounding tissue. Precise radiological differentiation between these bleeding patterns stays difficult in the majority of the cases, so to use a supposed acute or second bleeding based on radiological findings as an indication for surgery, may in some cases not reliably reflect the true

situation. Therefore, not an assumed bleeding should be used as an indication, but an "hemorrhagic event" which is characterized by suspect radiological findings as well as signs and symptoms in patients. At this point, also the facts should be mentioned, in which a surgery is not recommended and a conservative treatment would be the therapy of choice. There is generally consensus about asymptomatic patients, which may never experience hemorrhage from their cavernous malformation, that in such cases a conservative treatment is the option of choice.(18,34,41) Abla et al. goes one step further and recommends observation even in patients with mild symptoms, in case the cavernoma is deep seated.(32) It is obviously, that in the case of a BSCM neither the symptomatic presentation, nor the localization nor the MRI appearance of a hemorrhage can determine a surgical treatment. Because the eloquence of the brainstem requires a tailored treatment plan in every patient, which includes the analysis of all parameter which can influence the outcome of the surgery. With modern techniques like the intraoperative monitoring as well as neuronavigation, procedures which were impossible then, are now performed routinely with outstanding results hence the restraint in operating these lesions decreased. But the consultant has to counsel the patient regarding the risks and benefits of surgery as well as rehemorrhage rates in conservative management, so that the final decision is made by a thoroughly briefed the patient.(18,32,34,41)

7.2 TIMING OF SURGERY

The fact that there is an optimal timing, derives from several factors which influence the outcome of surgery. The right time for surgical intervention can facilitate the procedure for the surgeon and is also accompanied with a better outcome for the patient.(35) The better outcome may arise because of the benefits of facilitated surgery, but may also arise because of early mass effect reduction, most probably it is the combination of both. Known factors which influence the optimal time for surgery are, the presence or absence of hemorrhage, the presence or absence of intractable seizures, the acuteness and the mass effect of hemorrhage and the patient's clinical condition and probably the most important factor is the delay of the last hemorrhage. The best time for surgery seems to be the subacute state after a hemorrhagic event. And the theory behind this phenomenon is accompanied with the observation and empirical knowledge from AVM surgery. In cases of AVMs a condition was observed in which a hemorrhage facilitates the surgery by separating the AVM from adjacent brain. During surgery, the hematoma can be sucked off and therefore provides a working space which enables the surgeon to access the nidus with

less traction and manipulation on healthy brain tissue and allows to reach parts of the malformation which otherwise would not have been able to access. The same phenomenon was assumed in cavernous malformations, which is verified by evidence now.(9,35) An additional fact is under discussion to influence the outcome in a positive way, and this is the removal of the hematoma in an early stage and therefore releasing the mass effect derived by the hemorrhage, thus leading to improvement of neurological symptoms. This phenomenon of improvement hence volume reduction is observed rather in early than in late surgery.(34) There is general consensus about the exact process which facilitates the surgery. It is about the liquefaction of the hematoma and hence the created clean dissection plane, plus the reduction of the early posthemorrhage edema. This situation provides intraoperatively the best conditions for the surgeon, which allows safe excision of cavernoma without unnecessary retraction on the healthy neuro tissue. (18,27,33,41) On the other side, if the surgery is scheduled delayed, in term to the last hemorrhagic event, there are following obstacles the surgeon has to struggle with. Over time the hematoma organizes, which means fibrosis, calcification, glial scarring and hyaline degeneration may develop, hence it obscures the dissection plane and therefore making the surgical resection more difficult.(27,41,44) This phenomenon of complicated surgery also occurs after multiple bleeding episodes and with a long clinical history. In the study of Ferroli et al. the obstacles which derive from multiple bleeding are described as that the lesions are more compact, as well as an increased occurrence of small vascular anomalies in the surrounding tissue, which is accompanied with more difficult resection and suspected to be the cause of rebleeding episodes.(18) In the study of Bruneau et al. a retrospective non-randomized study was performed, which demonstrated with statistically significant results the better outcome in patients with early surgery.(35) Therefore they also recommend early surgery but with the hint of the necessity for further validation of these results by a prospective randomized study. Many authors recommend surgery in the subacute stage, particularly in eloquent areas such as the medulla or the pons, but when it comes to the question of the precise time interval, the different opinions split up.(38,43) Wang et al. recommends to operate between 1 to 2 weeks after subsidence of the brainstem edema and before the hematoma becomes organized.(27) In the study of Bruneau et al. they published a mean time of 21.6 days, between the last bleeding event and surgery.(35) Giliberto et al. recommend to operate within 2 to 3 weeks after a symptomatic hemorrhage, argued with the known benefits of a partial liquefied hematoma, hence providing a well zoned working plane and therefore a reduced risk of surgery related trauma.(1) Chen et al. postulates that

the hematoma would not be absorbed until 6 weeks after hemorrhage and recommend therefore surgery after the lesion is demonstrated on MRI scans and within 6 weeks after hemorrhage.(39) In the study of Pandey et a. they observed a better outcome in patients operated within 8 weeks compared with those operated on after 8 weeks and therefore recommend with, the exception of an acute worsening of the patient with the necessity of immediate surgery, to schedule the surgery between 4 to 8 weeks after a hemorrhagic event.(34) And interesting aspect is depicted in the study of Chotai et al., where they did not found a significant correlation, between surgery scheduled early or delayed after a hemorrhagic event and the postoperative course of the patient. But they found a correlation between timing and postoperative outcome. When the patient was in a good and stable clinical condition preoperatively, then the postoperative results were better in early operation, but when the preoperative clinical condition was poor, the delayed operation was associated with a better outcome. Therefore, to make a valid decision for the right timing of surgery, they recommend to include other factors such as the progression of neurological symptoms, the preoperative neurological status, the size and the location of the CM, the age of the patient as well as other co-morbidities.(44) But there are also contraindications for surgery in the subacute state, namely if the patient is in coma or cardiorespiratory instable, in this instance, emergent surgical evacuation is required. (27) Samii et al. publish contrary results comparing to the majority of authors. They did not found a statistically significant difference referred to the long-term outcome of patients, when they compared the group which underwent surgery within 3 months after a hemorrhagic event, with those in whom resection was performed after 3 months.(12) Maybe this observation derives from the method of comparing groups with surgery within and after 3 months, so that even within three months, the organization of the hematoma was already developed or at its beginning. Hence, the difference of the grade of organization between the two groups may be too little to observe a significant difference in postoperative outcome. Therefore, it may be possible that the best results are achieved, when the surgery is scheduled between 2 to 4 weeks after a hemorrhagic event.

7.3 SURGICAL RESULTS

One of the most important goals in CMs surgery is the complete resection of the lesion. A remnant of the cavernoma is accompanied with an increased rebleeding risk with reported values up to 43%.(21,22,32) In the literature, complete resection is accomplished between 86,4% and 92% in BSCM cases.(35,41) Therefore, every attempt should be made to be

sure that no residual of the lesion is left, techniques like the intraoperative MRI or intraoperative ultrasound may be useful in such cases.(41) Early after surgery an improvement of the neurological condition of the patients, derives according to the study of Bruneau et al.(35) from the release of tract compression and is given in a percentage of 52,2%. Davies et al.(25) also publishes an early postoperative improvement of the patients neurological condition with a percentage of 54,8%. Furthermore, from the same authors an unchanged neurological condition, at an early postoperative course is given by 21,7%(35) and 34,6%(25), respectively. The early postoperative morbidity is high in BSCM surgery. In the review of Gross et al.(41) they found that the early postoperative morbidity ranges in the literature from 29% to 67%. However, this deterioration is transient in the most cases. The cause of this phenomenon is thought to be a combination of postoperative edema, intraoperative manipulation and changes in microcirculation.(12,35,41) Tracheostomy and/or feeding tube is assumed to be necessary in 10% to 20% of patients, however often transient(41). Furthermore, the possibility of Ondine's course is given in BSCM surgery and therefore should be watched out for it(41). A neurological recovery or identical neurological status, in the long-term follow-up is reported to be 90,9% in the study of Bruneau et al.(35), 89,2% in the study of Wang et al.(27) and 87% in the study of Porter et al.(40). Kivelev et al. reported the poorest recovery potential for patients with cavernomas located in the fourth ventricle, with neurological improvement in only 29% of patients(37). A deterioration in the long-term follow-up was observed in the study of Bruneau et al. in 4,6%(35) and Gross et al. stated a 15% risk of long-term worsening even in the best of hands(41). Garcia et al. indicated an 8,7% rate of residual/recurrent lesions, with an estimated retrospective recurrent hemorrhage rate of 7.0% per year.(9) There were sever factors identified which influenced the postoperative outcome. Patients with anterolateral pontine lesions presented with better functional recovery.(41) In the study of Samii et al., patients with higher preoperative KPS scores, smaller lesions, or medulla oblongata cavernomas were observed to have better final outcomes, reflected by higher KPS scores.(12) Abla et al. identified in a series of 260 patients smaller lesion size, younger age and fewer preoperative hemorrhages as influencing factors which were accompanied with better outcomes.(32) In another big series of 134 patients, Pandey et al. detected age less than 40 years, male sex, surgery within 8 weeks of last hemorrhage and later surgical approach, as predictive factors for good outcomes.(34) In general, the postoperative outcome is poor in BSMCs, compared with CMs in other locations. Kivelev et al. states a percentage of only 49% of patients with a BSCM which stay not disabled. But proposes a

poor preoperative status to be responsible for the majority of morbidity and to a lesser extent the surgery itself.(37) Lesion location in, as well as surgical approach through the fourth ventricle is related to relatively worse long-term outcome.(41) Abla et al. lists new or worsened postoperative deficits in relation to BSCM location, with 41% in patients with medullary lesions, 58% in pontomedullary lesions, 55% in pontine lesions, 43% in pontomesencephalic lesions and 56% in midbrain lesions.(32) Garcia et al. emphasizes the similarity of outcome predictors for BSCMs and AVMs which they had found in their study. They stated that all factors used in the Spetzler-Martin and Lawton-Young grading systems for AVMs, with the exception of compactness or diffuseness which does not apply for CMs, seem to impact BSCM outcomes as well.(9) In contrast to the results of surgery are the observed natural courses, which show a complete neurological recovery between 20% in the study of Samii et al.(12) and 37% of complete resolution of neurological deficits in the study of Hauck et al.(43) Abla et al. claim that with surgery a permanent cure can be achieved, defined by prevention of recurrent hemorrhage.(32) But as long as the full etiology of cavernomas is not discovered, the statement of Perrini et al. referred to DVAs and the origin of CMs remains, which is, “it cannot be excluded that by treating the CM we are treating the result of the so-called “hemorrhagic angiogenic proliferation” and not the disease itself, which may indeed be the DVA”.(16)

8 CONCLUSION

Our results are reinforcing us, that in case of given indications, which are: 1) neurological symptoms with the chance of improvement through surgery 2) the location of the lesion is either exophytic, or with a pial or ependymal presentation, or reachable through an approach using a safe entry zone, determined by T1-weightet MRI 3) the appearance of a hemorrhagic event, surgical excision of the cavernoma is the first-choice treatment option. Our attempt is to perform surgery at the subacute state after a hemorrhagic event. Furthermore, through the fact that some authors described a benign course of BSCMs in natural history studies, waiting with surgery till a second hemorrhagic event can be considered in special selected cases. In our current study a statistically significant improvement through surgery could be achieved, using the modified Rankin scale and comparing the pre- and postoperative values with a Wilcoxon-test. Using the Glasgow

outcome scale, failed to show a statistically significant improvement. This results from the more inexact structure of the GOS. Therefore, we do not recommend the GOS for the investigation of the patient's condition related to a BSCM. With a Mann-Whitney Test, the association of the outcome with the size of the lesion was tested, despite the results were not statistically significant, in the graphical illustration a tendency was inferable, which shows a correlation with unfavorable outcome and a higher median size of the lesion. We also observed a higher bleeding tendency in bigger lesions. Further investigations are necessary to elucidate the origin of cavernous malformations and the role of DVA in this process, as well as the circumstances which provoke a first hemorrhagic event.

9 LIMITATIONS

Only patients with clinical symptoms were advised to undergo surgery. Therefore, we cannot assess the placebo effect or the effect of time passing. For ethical reasons, we did not have a conservatively managed control group. Although the majority of the patients were operated by the same surgeon, this is not a single surgeon study. Statistical limitations were on the one hand the low number of patients and on the other hand the inhomogeneity of the group, related to age, lesion size, lesion location, preoperative neurological condition and therefore an unfavorable requirement for comparing potential outcome factors. A further limitation is that there was no clearly structured follow-up protocol in terms of given clinical examination, specific time of follow-up and scheduled imaging.

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11 APPENDIX