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Original Investigation

Cerebrovascular-Endovascular

Brainstem Cavernoma: A Benign Lesion in a Malignant Location

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ABSTRACT

AIM: To present our surgical experience with brainstem cavernomas and to emphasize the importance of the brainstem's internal structures.

MATERIAL and METHODS: Based on the clinical data of 25 symptomatic patients who underwent surgery for brainstem cavernomas, we reviewed their radiological findings, surgical indications, surgical timing, postoperative remnants, and outcomes. We also performed a statistical analysis of seven parameters that, based on our clinical experience, may influence outcomes in these challenging cases.

RESULTS: There were 14 male and 11 female patients, with a mean age of 36.6 years (range: 20–66 years). All patients were symptomatic and had experienced at least one episode of bleeding. Complete resection was achieved in 23 patients (92%), while two (8%) required reoperation for residual cavernoma. Postoperative mortality occurred in one patient (4%) due to malignant hyperthermia. As a result, the mean modified Rankin Scale (mRS) scores at admission, discharge, and last follow-up were 2.44, 2.14, and 1.86, respectively. Statistical analyses demonstrated that preoperative neurological status was an important parameter affecting outcome (p=0.002).

CONCLUSION: Brainstem cavernoma is a benign pathology, but it occurs in a malignant location. Therefore, advanced techniques, such as tractography, neuronavigation and neuromonitoring, should be employed in these challenging cases. However, we believe that a thorough knowledge of brainstem neuroanatomy and meticulous surgical technique are even more critical.

KEYWORDS: Brainstem, Cavernoma, Safe entry zone

ABBREVIATIONS: DSA: Digital subtraction angiography, **DTI:** Diffusion tensor imaging, **DVA:** Developmental venous anomaly, **MRI:** Magnetic resonance imaging, **mRS:** Modified rankin scale

INTRODUCTION

The first resection of a brainstem cavernoma (cavernous malformation, cavernous hemangioma) was reported almost 100 years ago by Walter Dandy (19). However, owing to its dense concentration of cranial nerve nuclei and white matter tracts within a small cross-sectional area, the brainstem has long been regarded as "terra incognita" (no man's land). Since the 1990s, brainstem surgery has been performed more safely due to advances in neurosurgical techniques, modern neuroimaging methods, and an improved understanding of the brainstem's internal structure (7,11,22).

Complications in brainstem cavernoma surgery primarily arise while entering the brainstem and/or cavernoma resection. Therefore, neurosurgeons must possess a detailed understanding of both the external and, especially, the internal structures of the brainstem. Brainstem lesions, resulting from surgical trauma, may lead to severe cranial nerve dysfunctions, motor/somatosensory deficits, cerebellar symptoms, and even death.

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We retrospectively reviewed our series of brainstem cavernoma surgeries, focusing on surgical indications, surgical timing, postoperative remnants, and factors affecting outcomes. We also aimed to highlight the importance of safe entry zones and the brainstem's intrinsic structures.

MATERIAL and METHODS

Between 1996 and 2019, 25 patients underwent surgery for symptomatic brainstem cavernoma. All surgeries were performed by the senior author (S.I.) using high magnification with a surgical microscope (Pentero, ZEISS, Oberkochen, Germany). The patients' files, surgical reports, radiological examinations, surgical videos, and follow-up data were reviewed. Ethics committee approval and informed consent were not required, as this study was conducted retrospectively.

All patients underwent preoperative brain MRI with standard sequences. Diffusion tensor imaging (DTI) with tract reconstruction was also performed in patients who underwent surgery in more recent years. Digital subtraction angiography (DSA) was performed in only two patients to rule out an arteriovenous malformation.

Throughout the series, we operated exclusively on symptomatic patients. Our surgical indications were: 1) cavernomas with repeated intralesional hemorrhages causing progressive neurological deficits; 2) symptomatic cavernomas reaching the pial surface or the fourth ventricular ependyma; and 3) cavernomas with acute hemorrhage extending beyond the lesion and causing mass effect.

All patients were started on corticosteroid therapy upon hospital admission. Preoperatively, patients and their relatives were informed about the estimated risk of rebleeding, potential surgical complications, and the high morbidity rates associated with the procedure.

Early postoperative MRI was obtained in all patients using the same sequences and planes as the preoperative scans and compared accordingly.

Patients' neurological status at admission, discharge, and last follow-up was assessed using the modified Rankin Scale (mRS) (0–6). Scores of 0–2 were considered a good outcome, while scores ≥ 3 were classified as an unfavorable (poor) outcome. These evaluations were performed by neurosurgery residents or junior neurosurgeons who had not participated in any of the surgeries included in this study.

Surgical Technique

In most cases, the appropriate surgical approach was selected using the two-point method described by Brown et al (8). In exophytic cavernomas or those adjacent to the pia mater (or ependymal surface), the lesion itself dictated the entry zone. Once the safe entry zone was reached, the pia mater was incised with microsurgical scissors, and the superficial parenchymal layer was gently dilated using the tip of bipolar forceps. After evacuating the hematoma, the cavernoma was internally decompressed, gently dissected from the surrounding neural tissue, and resected in a piecemeal manner. During resection, en bloc removal was avoided to prevent injury to the surrounding ascending/descending tracts and cranial nerve nuclei. Bipolar cauterization was not used unless obligatory. If present, the developmental venous anomaly (DVA) was preserved to prevent venous infarction. No attempt was made to remove hemosiderin-stained tissue. After meticulous hemostasis, the surgical area was carefully examined for cavernoma remnants.

Statistical Analysis

The following seven parameters, which in our experience may influence patient outcomes, were statistically analyzed: age, sex, preoperative mRS score, cavernoma location, cavernoma size, cavernoma depth, and surgical timing. All analyses were performed using SPSS version 23 (IBM Corp., Armonk, New York, USA). Data were analyzed using Fisher's Exact Test or the Pearson Chi-Square Test, as appropriate. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 14 male and 11 female patients, with a mean age of 36.6 years (range: 20–66 years), were included. The patient's demographic characteristics are summarized in Table I.

One patient had previously undergone V/P shunt placement at another hospital due to obstructive hydrocephalus. Another patient had also previously received radiotherapy at a different hospital under the suspicion of a brainstem glioma.

In this series, all patients experienced at least one bleeding episode. Thirteen patients (52%) presented with a single preoperative bleeding episode, 10 patients (40%) had two episodes, and two patients (8%) had three previous hemorrhages. In total, 39 hemorrhagic episodes were observed over 915

Table I: Characteristics of the Patients.

	Total/Average
Number of operated patients	25
Male	14
Female	11
Age at admission (years)	Mean 36.6 (20-66)
Cavernoma size (mm)	5-21
Hemorrhagic Event*	
1	13
2	10
3	2
Mean mRS score at admission	2.44
Mean mRS score at discharge	2.14
Mean mRS score at last follow-up	1.86
Mortality	1
Follow-up (months)	Mean 83.4 (2-128)

**According to past medical history of the patients and magnetic resonance imaging findings.*

patient-years. Thus, the annual hemorrhage rate was 4.2% per patient per year. The median time from the last hemorrhage to surgery was 22.4 days (range: 3–120 days). Based on measurements from Tl-weighted MRI, the maximal size of the cavernomas ranged from 5 mm to 21 mm.

The most common clinical presentation was motor and sensory deficits (80.0%), followed by cranial nerve deficit(s) (72.0%), cerebellar symptoms (36.0%), headache (28.0%), and vertigo (24.0%). Interestingly, one patient with mesencephalic cavernoma presented solely with Holmes tremor (4.0%). Another patient presented with symptoms of obstructive hydrocephalus caused by a cavernoma obstructing the aqueduct of Sylvius (Figure 1).

The cavernomas were located on the mesencephalon (10 cases, 40%), the pons (11 cases, 44%), and the medulla oblongata (4 cases, 16%). Of the 25 lesions, 16 were intrinsic, eight were partially abutting the pial surface or fourth ventricular ependyma, and only one was exophytic. The surgical approaches used throughout this series and the corresponding safe entry zones are presented in Table II.

DVA was observed intraoperatively in 10 cases (40%) and was preserved in all. However, DVA had been identified on preoperative MRI in only six cases (24.0%). Complete resection of cavernoma was achieved in 23 patients (92%), as confirmed by early postoperative MRI. One patient with a residual cavernoma on postoperative MRI underwent reoperation on the second postoperative day, resulting in complete excision of the remnant. One patient developed a hematoma, causing hemiparesis on the second postoperative day. The hematoma was evacuated on the same day, and the residual cavernoma was also excised (see illustrative Case 11). In another patient, postoperative MRI revealed a suspicious remnant, but reoperation was not performed. This patient underwent MRI surveillance for 4 years.

In all patients, the diagnosis of cavernoma was confirmed by histopathological examination of the surgically resected tissue.

Complications

There were no significant intraoperative complications affecting the prognosis. Intraoperative air embolism developed in one patient operated in the sitting position, but it did not affect the course of the surgery. Postoperative pneumocephalus developed in another patient in the same position. One patient developed a supratentorial subdural effusion postoperatively

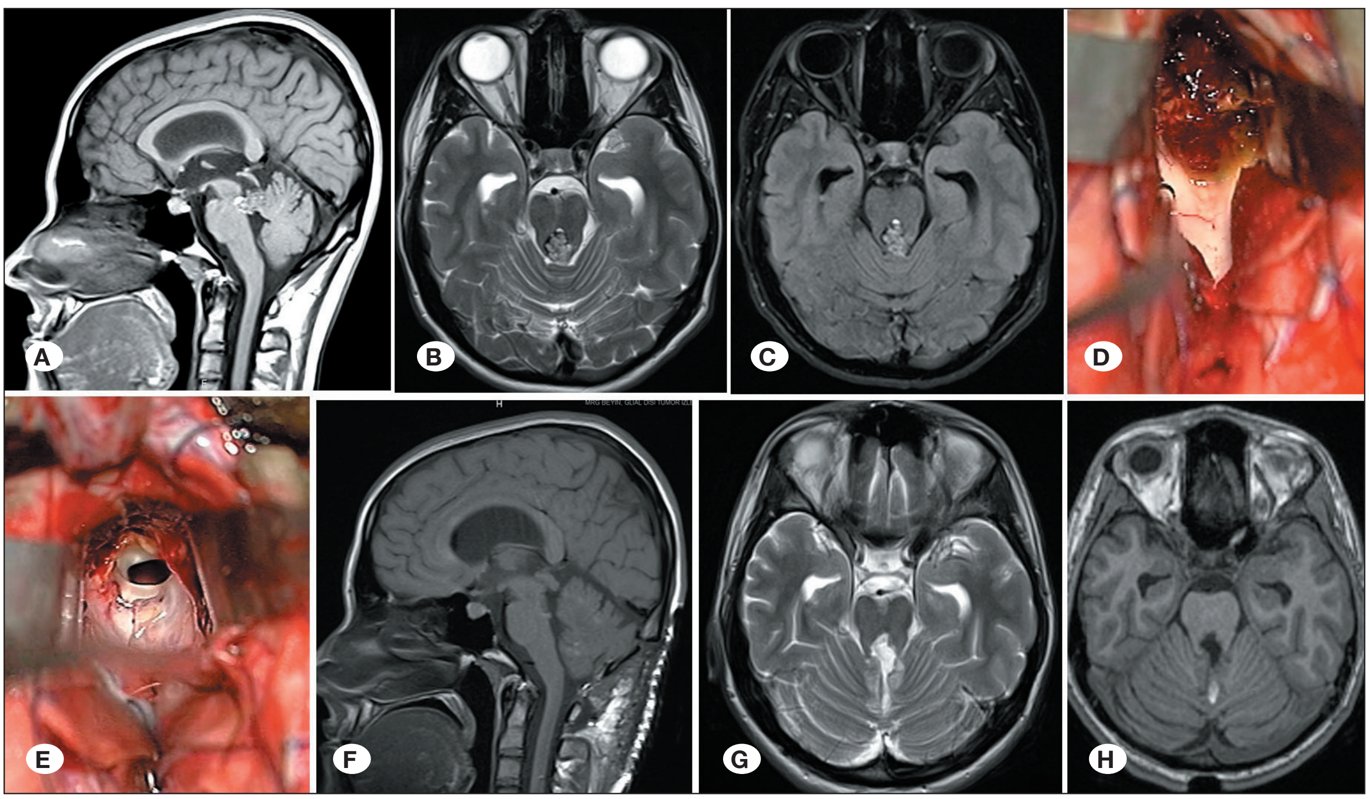

Figure 1: A 19-year-old female patient presented with a headache for several days. Magnetic resonance imaging (MRI) revealed obstructive hydrocephalus from a cavernoma within the aquaductus Sylvii (**A:** sagittal T1-weighted, **B:** axial T2-weighted, **C:** axial T1-weighted images). The patient was operated via midline suboccipital craniotomy. The vermis was partially split and the cavernoma obstructing the aqueduct was seen at the highest point of the 4th ventricle **(D)**. Gross total resection of the cavernoma was performed and the aquaductus was opened **(E)**. Post-operative MRI showed no residual lesion (**F:** sagittal T1-weighted, **G:** axial T2-weighted, **H:** axial T1-weighted images). The patient was discharged with normal neurological examination. She was still neurologically intact at her latest follow-up 36 months after surgery.

Table II: Basic Operative Approaches to Brainstem Cavernomas Used in the Study

Location	Sub-location	Approaches	Number	Used Safe Entry Zone
Mesencephalon	Ventral	Pterional/transsylvian	4	Perioculomotor
	Lateral	Subtemporal	4	Lat. Mesecephalic Sulcus
	Dorsal	Supracerebellar infratentorial	2	Infra collicular
Pons	Lateral	Retrosigmoid Subtemporal	4 2	Peritrigeminal Peritrigeminal
	Dorsal	Suboccipital transvermian Suboccipital telovelar	3 2	Suprafacial Infrafacial
Medulla Oblongata	Dorsal	Median suboccipital Median suboccipital	2 1	Post. Median fissure Post. Intermediate sulcus
	Lateral	Far lateral	1	Trans olivary

and required drainage with a burr hole. In the other patient, temporary postoperative CSF leakage occurred from the wound but did not require surgical intervention.

Outcome

Based on patients' preoperative neurological status, postoperative neurological symptoms improved in nine patients (36%), remained unchanged in 11 patients (44%), and worsened in four patients (16%). There was no surgery-related mortality. However, during the early years of this series, one patient (4%) with known myotonic dystrophy died postoperatively due to malignant hyperthermia.

Follow-up

Follow-up data were obtained for all surviving 24 patients. At followup (mean: 83.4 months; range: 2–128 months), no patient experienced clinical regression, and no rehemorrhage was observed. Two of the four patients whose postoperative status had deteriorated returned to their preoperative neurological status, while the other two remained unchanged.

As a result, the mean mRS scores at admission, discharge, and last follow-up were 2.44, 2.14, and 1.86, respectively.

Statistical Results

Seven potential parameters that may affect outcomes were evaluated using univariate analysis. The effects of six of these parameters—age, sex, location, size, depth, and timing of surgery—on the unfavorable outcomes were not statistically significant (Fisher's Exact Test). Only the preoperative mRS score was identified as a high-risk factor for unfavorable outcome ($p=0.002$, Pearson ChiSquare Test) (Table III).

Illustrative Cases

Case 11: A 31-year-old male patient presenting with sudden headache, left eyelid drooping, double vision, and right-sided eye weakness was referred to us. His past medical history revealed a similar but milder episode 3 months ago. MRI demonstrated a cavernoma located in the left ventral mesencephalon with an old hematoma (Figure 2A, B). DTI tractography demonstrated lateral displacement of the left corticospinal tract. Surgery was performed via left pterional craniotomy using the transsylvian approach. The left oculomotor nerve was traced to the brainstem. The left ventral surface of the mesencephalon, the exit of the oculomotor nerve, the posterior cerebral artery, and the superior cerebellar artery were visualized (Figure 2C). The surface of the mesencephalon appeared entirely normal (Figure 2D). A small incision was made just lateral to the oculomotor nerve using the tip of the bipolar forceps, reaching and draining the hematoma approximately 2 mm deep (Figure 2E). The cavernoma was then easily identified and excised in piecemeal fashion. No venous anomalies were observed. The cavity was carefully examined for any residual lesions. After achieving hemostasis, the wound was closed in the usual manner. The patient was transferred to the intensive care unit with his preoperative symptoms. On the second postoperative day, his hemiparesis worsened. MRI revealed a small hematoma and a possible residual cavernoma. The patient underwent reoperation, the hematoma was evacuated, and a small remnant located in the postero-lateral part of the cavity was excised. Postoperative MRI confirmed complete excision of the cavernoma (Figure 2F, G). In the postoperative period, his hemiparesis improved sufficiently to allow unaided walking, but oculomotor paresis remained unchanged. At his last follow-up, 8 months after surgery, he was able to walk independently. His oculomotor paresis had improved slightly but persisted.

Case 18: A 26-year-old male patient was admitted with left hemihypoesthesia that began 10 days earlier and hiccups that started 2 days prior. MRI revealed a hematoma and cavernoma on the left dorsal aspect of the medulla oblongata (Figure 3A, B). DTI-tractography demonstrated displacement of the pyramidal tract (Figure 3C). The patient was operated on via low medial suboccipital craniotomy and C1 laminectomy. Upon opening the dura, the surface of the medulla oblongata appeared completely normal (Figure 3D). Based on the multiplanar MRI findings, a small vertical myelotomy was performed along the posterior intermediate sulcus, likely overlying the hematoma. The hematoma was reached at a depth of approximately 1 mm and evacuated. The small cavernoma

Table III: Factors that May Affect Unfavorable Outcome and Results of Statistical Analysis

Factors		No. of patients	No. of unfavorable outcome (%)	p-value
Age (years)	1-40	16	8 (50)	0.677*
	>40	9	3 (33)	
Sex	Male	14	7 (50)	0.689*
	Female	11	4 (36.6)	
Preop. mRS score	0-2	12	1 (8.3)	**0.002****
	3-5	13	10 (76.9)	
Location	Mesencephalon	10	5 (50)	0.757*
	Pons	11	4 (45.4)	
	Medulla Oblongata	4	1 (25)	
Size (mm)	5-10	11	3 (27.2)	0.227*
	11-21	14	8 (57.1)	
Depth of cavernoma	Superficial	9	2 (22.2)	0.208*
	Deep	16	9 (56.2)	
Timing of surgery (weeks)	< 2	5	3 (60)	0.856*
	2-6	15	6 (40)	
	> 6	5	2 (40)	

**Fisher's Exact test, **Pearson Chi-Square test.*

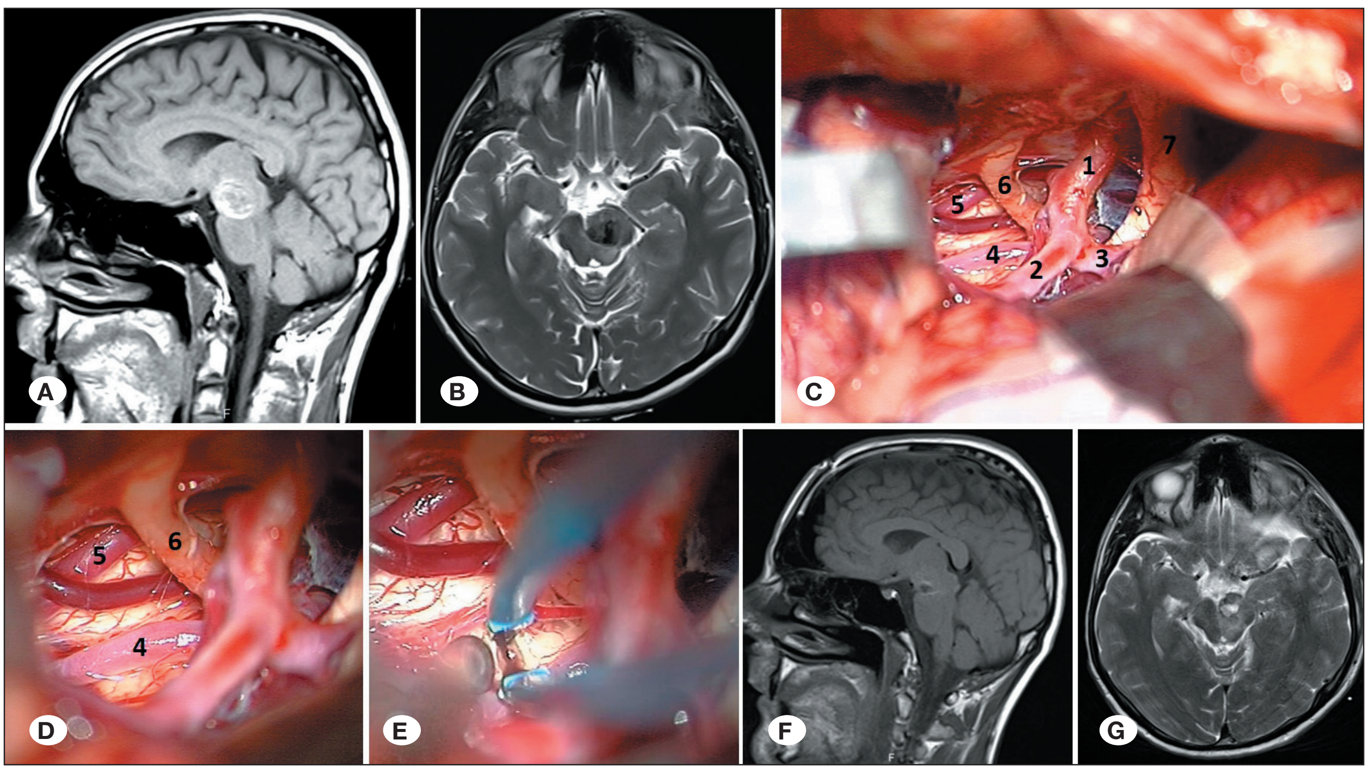

Figure 2: Case #11. **A)** T1-weighted sagittal magnetic resonance imaging (MRI) shows ventral mesencephalic cavernoma, **B)** T2-weighted axial MRI, **C)** intraoperative picture after fully splitting the left Sylvian fissure (1: ICA, 2:MCA, 3:AI, 4: Post. Cerebral Artery, 5: Sup. Cerebellar artery, 6: The oculomotor nerve, 7: The optic nerve), **D)** view of the surgical field with higher magnification, **E)** a small incision in the perioculomotor safe entry zone and drainage of the hematoma, **F)** postoperative T1-weighted sagittal image, **G)** postoperative T2-weighted axial image.

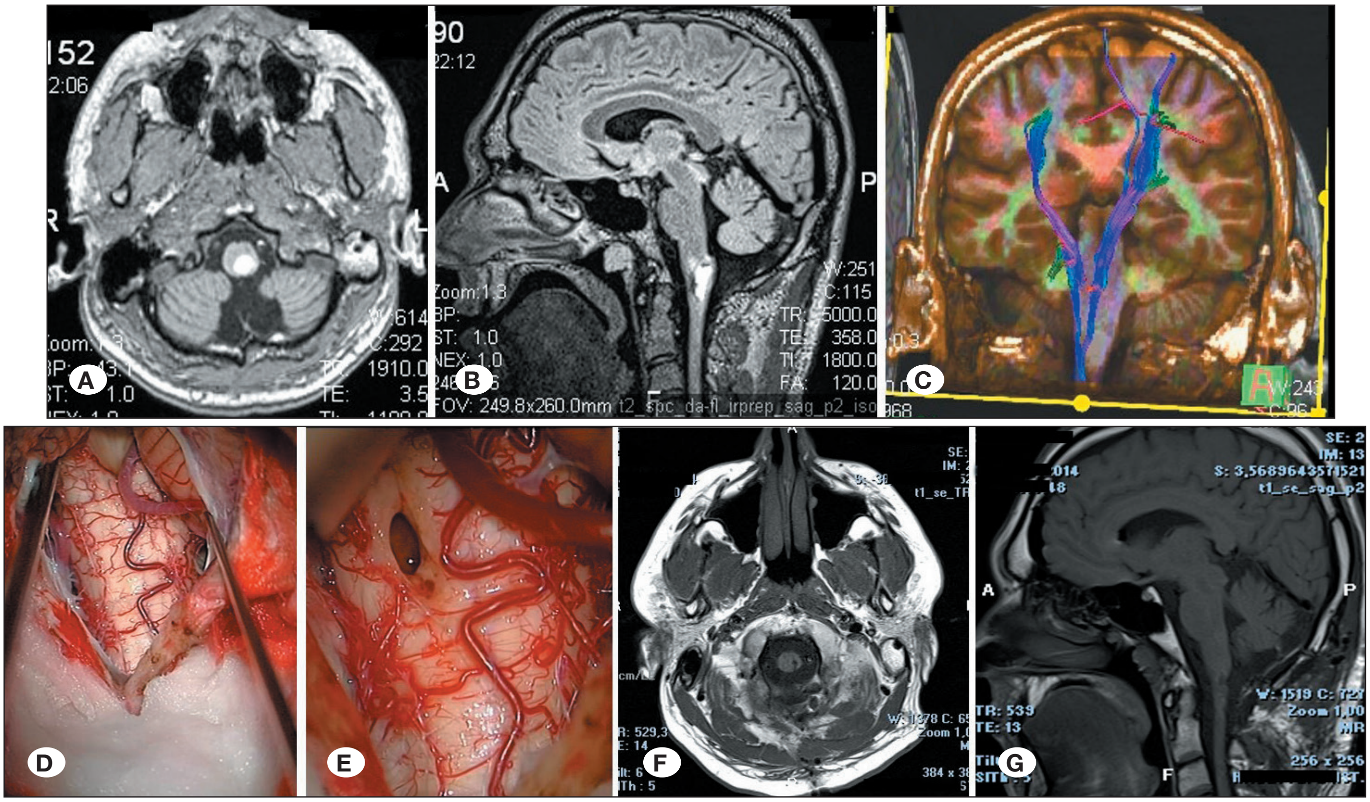

Figure 3: Case #18. **A)** T1-weighted axial magnetic resonance imaging (MRI) shows a cavernoma on the left dorsal surface of the medulla oblongata, **B)** sagittal MRI, **C)** DTI-tractography shows displacement of the pyramidal tract, **D)** the dorsal surface of the medulla oblongata was entirely normal, **E)** the cavernoma was excised with a small incision but the hemosiderin ring was left intact, **F)** axial, and **G)** sagittal T1-weighted postoperative MR images showed complete resection.

was then easily resected; however, the surrounding hemosiderin-stained tissue was not removed (Figure 3E). Postoperative MRI confirmed gross total resection of the cavernoma (Figure 3F, G). His hiccups resolved completely in the early postoperative period, and the hemihypoesthesia had also resolved by the last follow-up, 17 months later.

DISCUSSION

Brainstem surgery has several important disadvantages compared to surgeries performed in other regions of the brain: 1) the surgical corridor is longer; 2) the surgical field of view is coneshaped and gradually narrows; 3) there is little or no possibility of using a static retractor during surgery; and 4) this region contains a high density of critical tracts and cranial nerves nuclei. In conclusion, a brainstem cavernoma is a benign pathology, but it is located in a surgically malignant localization. Consequently, the morbidity rate in brainstem cavernoma surgery remains high, even in experienced hands (20,39,41,51).

Neuroradiological Imaging

MRI is the most sensitive and specific method for diagnosing brainstem cavernomas. Preoperative multiplanar MRI should be carefully reviewed, with particular attention to the following aspects: I) If the MRI is more than a few days old, a new scan should be obtained preoperatively. 2) The size of the cavernoma, rather than the hematoma, should be measured. 3) The relationship of the cavernoma to the pial or ependymal surface should be carefully assessed. This relationship is best evaluated on TI-weighted images. T2-weighted images may falsely suggest pial involvement due to blooming artifacts, even when the cavernoma is actually embedded within the brainstem (9,20,26). 4) Identification of some anatomical landmarks on the brainstem surface is important for accurate localization, including the exits of the cranial nerves, the lateral mesencephalic vein, the facial colliculus, the superior and inferior colliculus, and the olive. 5) DTI with reconstruction should be performed to demonstrate displacement of surrounding white matter tracts and to minimize the risk of surgical injury to these critical structures (21,33,47). 6) The presence of any associated DVA should be noted.

The use of neuronavigation is an important advantage, especially for deeply located cavernomas. However, it was not used in most cases in this series, as it was not available in our department at that time. While neuronavigation is valuable, it cannot replace careful evaluation of the MRI or, more importantly, detailed knowledge of the intrinsic brainstem anatomy. Therefore, the neurosurgeon needs to maintain a clear understanding of the three-dimensional anatomy of both external and, especially, internal brainstem structures during surgery.

Surgical Indication

The prevailing view among neurosurgeons is that asymptomatic patients should not undergo surgery, a position we also support (4,5,10,26,41,52). Although there is strong consensus that brainstem cavernomas causing hemorrhage and neurological symptoms warrant surgical intervention, the specific criteria for surgical intervention remain controversial. In detailed literature reviews of brainstem cavernoma surgery reported by Gross et al. (27), and Kearns et al. (32), the overall rates of complete resection were 91% and 92.3%, respectively. At long-term follow-up, the rate of improved or stable clinical symptoms was also 84% and 92.3%, respectively. Despite these satisfactory results, there remains no consensus on the specific criteria for surgical indication.

In 2021, an international consensus report on the surgical treatment of brainstem cavernomas was published (17). To summarize the report: l) asymptomatic patients or those with mild symptoms and difficult access to the cavernoma should not undergo surgery; 2) patients with multiple symptomatic hemorrhages, progressive deficits, and easy access to the cavernoma should undergo surgery; 3) patients experiencing first symptomatic hemorrhage with severe progressive deficits and mass effect should also undergo surgery; and 4) other patients who do not meet these criteria may be treated either surgically or conservatively. The decision should take into account the patient's general condition and the characteristics of the cavernoma.

To our experience, the generalized recommendations in the literature should be considered when deciding on surgery for brainstem cavernomas; however, each patient must also be evaluated individually, taking into account the following factors: age, comorbidities, neurological symptoms, location/size of the lesion, and the surgeon's experience.

Timing of Surgery

The optimal surgical timing for brainstem cavernomas remains controversial, and there is no uniform consensus. Most authors recommend performing surgery in the subacute stage (2–6 weeks) for the following reasons: l) MRI can better differentiate between the hematoma and cavernoma itself; 2) during this period, the patient's neurological status becomes more stable; 3) this interval allows sufficient time for reduction of tissue edema; and 4) the hematoma liquefies within a few weeks and can be easily aspirated, making the cavernoma itself easier to identify within the cavity formed by the hematoma (10,26,28,36,40,42). However, some authors believe that surgery should be performed earlier because: 1) gliosis developing between the hematoma and neural tissue can make resection of the cavernoma more challenging; 2) neural tissue is relieved from compression in the early period; and 3) there is a risk of rebleeding during the waiting period (9,42,48).

According to a large series of 397 patients reported by Zaidi et al., patients treated within 6 weeks after hemorrhage derived the maximum benefit from surgical intervention (51). In a recently published large clinical series (49), patients who underwent surgery during the acute period (<3 weeks) or chronic period (>8 weeks) had poorer outcomes compared with those who underwent surgery during the subacute period (3–8 weeks). Similarly, a recently published international consensus report recommends that the preferred timing for resection is between 4 and 8 weeks after the last event (17). Interestingly, however, Samii et al. found no difference in outcomes between surgery performed in the subacute stage and surgery conducted more than three months after hemorrhage (39).

We prefer to perform this surgery in the subacute stage, provided the patient's condition is suitable. However, we operated on two patients with acute hematoma and associated severe neurological deficits at an early stage. In cases of life-threatening conditions, such as coma, hemi- or quadriplegia/paresis, rapidly deteriorating neurological status, or cardio/respiratory instability, emergency surgery should be considered (3,6,46). This approach can be lifesaving.

Surgical Tips and Tricks

Based on our experience and the literature, the following points should be considered in brainstem cavernoma surgery: 1) the aim of the surgery should be the complete resection of the cavernoma, while preserving all neurological structures and any associated venous anomaly. 2) The "two-point method" described by Brown et al. should be used to select the correct surgical approach (8). However, in brainstem surgery, the shortest route may not always be the safest or most effective. Therefore, the approach can be adapted to the individual anatomy of each patient. If the trajectory intersects delicate structures (venous anomaly, motor tract, or exiting cranial nerve), the entry point may be slightly modified to avoid these structures. Hence, the surgeon should choose not only the shortest but also the safest route. 3) Microsurgical resection is performed under high-power magnification. 4) When the safe entry zone is reached, the pial or ependymal incision should be smaller than the cavernoma itself, and the superficial parenchymal layer should be gently dilated using the tip of bipolar forceps. During this procedure, the bipolar forceps should be opened and closed parallel to the fibers to avoid injuring them. 5) If present, any extracapsular hematoma should be drained first using low suction power. Hematoma usually displaces or pushes white matter tracts but does not disrupt them (1,26). Therefore, if the surgeon remains inside the hematoma cavity, the probability of tract disruption decreases. 6) The cavernoma is then internally decompressed and gently dissected from the surrounding neural tissue. 7) The lesion should be removed in a piecemeal fashion. "En bloc" resection is generally not safe in this location. 8) The gliotic margins may be functional and should, therefore, not be handled aggressively. 9) Bipolar cauterization should be used in the brainstem only when necessary, due to the risk of thermal damage. Bleeding is usually low-pressure from the dilated sinusoidal spaces and can be easily controlled with gentle pressure. 10) The surrounding hemosiderin-stained tissue should not be removed (1,37,39,41). A study using DTI-MRI tractography demonstrated the presence of viable white matter tracts passing through the hemosiderin-stained tissue (12). 11) Any associated DVA should be preserved as much as possible to maintain normal venous drainage and avoid venous infarction (1,26). The rate of intraoperative identification of venous anomalies in brainstem cavernomas varies between 13.9% and 58.3% in the literature (24,28,34,40). We were able to detect and preserve the venous anomaly intraoperatively in only 10 cases (40.0%). However, according to the intraoperative findings from a very large series, this association rate is 100% (1). Additionally, a study conducted using a 7 Tesla MRI reported that cavernoma-associated venous malformations were observed in all cases (18). According to these results, the cause of unexpected postoperative worsening in some patients may be venous anomalies that are not visible during surgery and can, therefore, be injured. 12) Hemostatic agents may be used to control bleeding, but they should be removed after the procedure, as they can affect the appearance of the surgical site on postoperative MRI. 13) At the end of hemostasis, bleeding control should be confirmed by increasing venous pressure using the Valsalva maneuver. 14) The patient should be referred to the intensive care unit at least for 24 hours. If the lesion is close to the lower cranial nerves, extubation should be performed only after a satisfactory cough and gag reflex are observed.

Postoperative Remnants

Some cavernomas may be multilobulated (14,35). One of these lobules may not protrude into the surgical cavity and can be overlooked. In addition, if scar tissue has formed around the cavity due to old or multiple hemorrhages, it becomes difficult to fully inspect the cavity. For this reason, even in very experienced hands, the risk of remnant varies between 6.6% and 11% (1,24). In a systematic review published in 2019, which included 2,493 patients who underwent surgery (32), the rate of remnant was found to be 7.7%. In our series, the rate of remnant was 8%. Therefore, every neurosurgeon should consider this possibility, and postoperative MRI should be performed in all cases. If a hypo- or hyperintense blood-containing nodule is observed at the edge of or within the surgical cavity, a cavernoma remnant should be suspected. If a remnant is clearly identified on postoperative MRI, early reoperation should be considered, because, as in one of our cases, the risk of rebleeding from the remnant is high (1,10,20). According to the literature review by Gross et al., approximately two-thirds of patients with partially resected cavernomas experienced rebleeding (27).

However, early postoperative MRI is not very reliable for detecting small postoperative remnants. According to a detailed study on this subject (15), early postoperative MRI has a sensitivity of 66.6% for detecting cavernoma remnants, a specificity of 76.7%, a positive predictive value of 16.6%, and a negative predictive value of 97.0%. In other words, small remnants are not always visible on early postoperative MRI. This limitation has also been highlighted in large surgical series (24,43). Accumulated blood in the surgical cavity, tissue edema, or the use of hemostatic agents can contribute to this reduced imaging accuracy.

Factors Affecting Outcome

Recently, Garcia et al. developed a surgical risk grading system based on their experience with 104 operated patients (23). The system assigns points according to the following factors: lesion size (<2 cm, 0 point; > 2 cm, 1 point), crossing the axial midpoint (no, 0 point; yes, 1 point), presence of DVA (no, 0 point; yes, 1 point), age (<40 years, 0 point; > 40 years, 1 point), and hemorrhage acuity (0–3 weeks, 0 point; 3–8 weeks, 1 point; > 8 weeks, 2 points). According to this grading system, grades 0 and 1 are associated with universally favorable functional outcomes, whereas grades 6 and 7 are associated with universally unfavorable functional outcomes. We consider this grading system valuable and important. However, based on our clinical observations and statistical analyses, preoperative neurological status also emerges as a key prognostic factor influencing outcomes (p=0.002). In fact, several authors have also reported that the preoperative neurological status is a significant predictor of surgical outcome (14,29,39,45,51).

Another factor to consider is the depth of the cavernoma. Logically, surgery for deeply located brainstem cavernomas carries a higher risk, as it requires splitting of healthy brainstem parenchyma, increasing the likelihood of injury to the cranial nerve nuclei and long tracts. Many surgical series have already emphasized that surgical risk and morbidity are higher for deep-seated brainstem cavernomas compared with superficial ones (2,20,25,27). However, a few clinical series have reported contrasting findings. In the study by Bruneau et al., cavernoma location (deep, abutting the pial surface, or extrinsic) was not significantly associated with postoperative worsening (9). According to Huang et al., a deep intrinsic cavernoma location is not necessarily associated with an unfavorable outcome (30). In another study, although the terms “deep” and “moderate depth” were not clearly defined, patients with deep cavernoma were reported to have better outcomes than those with lesions of moderate depth (16).

Although the effect of cavernoma depth on unfavorable outcomes was not statistically significant in our study (p = 0.208), a notable difference was observed between patients with superficial and deep cavernoma (22.2% and 56.2%, respectively). Therefore, we believe that the impact of cavernoma depth on outcome remains controversial.

Safe Entry Zones and Related Intrinsic Structures

Recently, we published a comprehensive review on safe entry zones to the brainstem (31). To our knowledge, 21 safe entry zones have been described for accessing brainstem cavernomas, and our series utilized nine of them (50). While a detailed discussion of safe entry zones is beyond the scope of this article, we would like to briefly emphasize their importance.

In brainstem surgery, the brainstem surface is sometimes entirely normal, with no discoloration or dark-blue area indicating a bulging hematoma. In such cases, safe entry zones to the brainstem are essential. These zones represent entry points and trajectories where tracts and cranial nerve nuclei are relatively sparse (4,13,26,31,38,44). Performing brainstem surgery through these corridors minimizes the possibility of neurological deficit. Otherwise, serious cranial nerve dysfunctions, motor symptoms, cerebellar symptoms, and even death may occur. However, it should also be noted that these safe entry zones may “no longer be safe” if the normal anatomy is distorted by the cavernoma or associated hematoma.

Limitations of this study

The limitations of our study include its retrospective design and the relatively small number of patients.

CONCLUSION

Brainstem cavernoma is a benign pathology, but it occurs in a high-risk location. Therefore, advanced techniques, such as tractography, neuronavigation and neuromonitoring, should be employed in these challenging cases. Nevertheless, we believe that detailed neuroanatomical knowledge of the brainstem and meticulous surgical technique are even more crucial.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

Ethical approval: Ethics committee approval and informed consent were not required, as this study was conducted retrospectively.

AUTHORSHIP CONTRIBUTION

Study conception and design: SI
Data collection: SI, BB
Analysis and interpretation of results: SI, BB
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