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Original article

Holmes tremor in a monocentric series of resected brainstem cavernomas

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ABSTRACT

Object. – Several scientific papers report clinical symptoms, indications, complications and outcomes of brainstem cavernous malformation (BSCM) surgery without reporting on the occurrence of postoperative Holmes tremor (HT). Our purpose is to report our experience with HT in a monocentric series of resected brainstem cavernomas.
Methods. – We reviewed all the BSCM surgical records between 2002 and 2018 at Saint-Luc University Hospital's Department of Neurosurgery, Brussels and selected patients developing HT postoperatively. Patients' demographics, symptoms, pre- and postoperative imaging, recurrence and complications were analysed. A PubMed literature review was performed to compare our results with those in the existing literature.
Results. – In a total series of 18 resected BSCM, 5 patients: 1 male and 4 females, with a median age of 51 years (range 29–59 years), developed HT. The median preoperative mRS score was 2 (range 1–4). GTR was achieved in all patients without surgery-related death. BSCM were located in the mesencephalon in 4 patients (80%) who developed HT. Tremor was noticed between ten days and one year after surgery. One patient saw significant improvements to the point of stopping treatment. The median follow-up period was 2 years (range 1–14 years). At the last follow-up, 40% of our patients showed a worse mRS score, 40% stayed unchanged, and 20% improved.
Conclusion. – We are reporting an original single-center series of patients suffering from HT after BSCM surgery. The risk for HT after surgery is significant for midbrain BSCM. A spontaneous favorable evolution is possible.

Mots clés :
Cavernome du tronc
Tremblement rubral
Tremblement de Holmes

RÉSUMÉ

Objectifs. – Nombreux articles scientifiques décrivent les symptômes, les indications chirurgicales, les complications et les résultats postopératoires des cavernomes du tronc cérébral sans rapporter l'apparition de tremblement de Holmes. Notre objectif est de rapporter ici notre expérience avec le tremblement de Holmes dans une série monocentrique de cavernomes du tronc cérébral opérés.
Méthodes. – Nous avons revu les dossiers de tous les patients opérés d'un cavernome du tronc cérébral dans le service de neurochirurgie des cliniques universitaires Saint-Luc, Bruxelles et avons sélectionné tous les patients qui ont présenté un tremblement de Holmes dans la période postopératoire. L'âge et le sexe des patients, leurs symptômes, leurs imageries pré- et postopératoires, les récidives et les complications postopératoires ont été analysées. Une revue de la littérature existante sur la plateforme PubMed a été réalisée afin de comparer nos résultats avec ceux déjà publiés.

Abbreviations: BSCM, brainstem cavernous malformation; CNS, central nervous system; DTI, diffusion tensor imaging; ERP, event-related potential; DBS, deep brain stimulation; GPi, internal globus pallidus; GTR, gross total resection; HOD, hypertrophic olivary degeneration; HT, Holmes tremor; MRI, magnetic resonance imaging; mRS, Modified Rankin Score; STN, subthalamic nucleus; VIM, ventral intermediate nucleus of the thalamus; VPS, ventriculo-peritoneal shunt.

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Résultats. – Dans une série de 18 cavernomes du tronc cérébral opérés, 5 patients : 1 homme et 4 femmes, avec un âge médian de 51 ans (allant de 29 à 59 ans), ont présenté un tremblement de Holmes dans les suites d'une chirurgie pour un cavernome du tronc cérébral. Le score mRS préopératoire médian était 2 (score de 1 à 4). Une résection macroscopiquement complète a été obtenue chez tous les patients sans décès liés à la chirurgie. Quatre (80 %) des cinq patients ayant développé un tremblement de Holmes présentaient un cavernome situé dans le mésencéphale. Un patient a présenté une amélioration significative de son tremblement au point de pouvoir arrêter son traitement. Le suivi postopératoire médian a été de 2 ans (allant de 1 à 2 ans). Au dernier contact, 40 % des patients présentaient une aggravation de leur clinique par rapport à la période préopératoire, 40 % étaient stables et 20 % présentaient une évolution favorable.

Conclusion. – Nous décrivons une série monocentrique originale de patients souffrant d'un tremblement de Holmes après l'exérèse d'un cavernome du tronc cérébral. Le risque de développer cette complication est significatif après résection d'un cavernome mésencéphalique. Une évolution spontanément favorable est possible.

1. Introduction

Cavernous malformations are low-flow, low-pressure lesions formed by sinusoidal vascular channels lined with endothelium without brain parenchyma [1–5]. Their incidence is reported to be between 0.39% and 0.9% [6–10], and in most cases are not located within the brainstem (5%–35%) [3–6,8,9,11–18]. However, brainstem cavernous malformations (BSCM) are of particular concern. Even the slightest volume variations can result in severe and damaging neurological symptoms, more so than with less eloquent supratentorial locations, because of the concentration of fiber tracts and cranial nerve nuclei [6,11–13,15,19]. Additionally, an increased incidence of hemorrhage and rehemorrhage is reported for BSCM compared to other areas [2,5,12,13,20–22].

The estimated risk of a first hemorrhage from BSCM varies between 0.7% and 10.6% per year, per lesion [7,13]. Nevertheless, a history of one or multiple previous events entails a higher risk of rebleeding that ranges from 5% to 60% per year [7,8,11,18–20,23,24].

It is noteworthy that surgical removals can produce similar effects to those of a hemorrhage. Cranial nerve and sensory deficits, hemiparesis and ataxia are commonly reported following BSCM surgery [7,14,25]. However, very few authors have reported on postoperative Holmes tremor (HT). HT is a unique form of symptomatic tremor, which results from lesions of the central nervous system (CNS), and is characterized by three components: it is present at rest, postural and intentional. The proximal upper limbs are the main targets of HT [26–33].

Gordon Holmes was the first to depict this kind of tremor in 1904. The current definition of HT is the result of a consensus statement made by the Movement Disorder Society on Tremor in 2018 [32]. It is described as a 3–5 Hz oscillation, present at rest, exacerbated with posture and intensified with action. It typically occurs from proximal and distal rhythmic muscle contraction. HT generally appears between 1 and 24 months after a CNS insult [28,29,31,32]. It has received several names (such as rubral, midbrain, thalamic, and cerebellar outflow), however, due to their similar symptoms despite lesions located in different regions of the brain, the umbrella term of "Holmes tremor" is now more commonly used.

In this paper, we will report an original single-center series of postoperative HT, confirmed by a senior neurologist, after the surgical resection of the midbrain cavernomas.

2. Methods

Institutional research ethics board (IRB: 00001530) approval for this study was request. Patients were retrospectively identified by examining hospital records of all intracranial cavernoma surgeries between 2002 and 2018, at St-Luc University Hospital's Department of Neurosurgery in Brussels.

We selected all patients who presented a HT after surgery for BSCM.

Surgery was offered to all patients with symptomatic BSCM or those who had iconographic growth during follow-up. Patients were given time to think about surgery before deciding, except in case of severe neurological deterioration.

Clinical data was obtained from electronic charts and imaging analysis, including patients' demographics, signs and symptoms, pre- and postoperative imaging, recurrence and complications. Functional status was assessed using the modified Rankin Scale (mRS) (range 0–6), with a score between 0 and 2 suggesting a good outcome. The mRS score was recorded before surgery, early after surgery and at the last follow-up. Each patient's operation note was reviewed to obtain a full description of the surgeon's findings. Follow-up assessments were performed either in person during clinic or remotely by phone call. Due to the retrospective nature of our study, informed consent was not required.

3. Results

From 2002 to 2018, a total of 18 patients, underwent surgery for a BSCM in our department, being referred after at least one episode of brainstem hemorrhage. Table 1 shows patient demographics, as well as the location and the size of the lesions. The size of the hematomas, including the cavernoma, varied from 10 to 35 mm. Five of those patients (1 males and 4 females with a median age of 51 years (range 29–59 years)), developed HT during follow up period.

3.1. Holmes patients

3.1.1. Clinical presentation

The median preoperative mRS score was 2 (range 1–4). All patients exhibited a focal neurological deficit. Cranial nerve deficits were the most common (80%), followed by motor and sensitive deficits and ataxia (60%). None of them suffered from alterations of consciousness.

3.1.2. Radiological findings

All patients underwent a magnetic resonance imaging (MRI) scan. All lesions were at least partially located in the mesencephalon, one patient (20%) exhibited BSCM partially located in the diencephalon (thalamus) and a second one (20%) mostly in the metencephalon (Table 2). All those BSCM were exophytic.

Table 1
Patient's demography, cavernoma's locations and surgical outcomes.

N°	Age at surgery (y)	Sex	Preop mRS	Preop symptoms							MRI						Postop mRS evolution				
											Location				Size (mm)		Early	Late			
				GCS	Headache	N^+/V^+	Mo D	Se D	CN D	Cer D	di	mes	met	myel	<30	≥30		Y	Worse[a]	Stable	Improve
1	39	F	0	N	–	–	–	–	–	–		+			?	?	5	12	2		
2	42	M	2	N	+	–	–	+	–	+			+		21		4	14	4		
3	7	M	0	N	–	–	–	–	–	–			+		17		4	6		0	
4[b]	51	F	2	N	+	+	–	+	+	+			+		25		4	14	4		
5	34	F	4	N	–	–	+	+	+	+			+		17		4	3			1
6	18	F	1	N	–	–	+	–	–	–	+				25		3	2		1	
7	52	M	1	N	–	–	–	+	–	–				+	13		1	6		1	
8	30	F	1	N	–	–	–	+	+	+				+	10		1	10		1	
9	45	F	1	N	–	–	+	+	–	–	+					35	2	1			0
10	39	F	1	N	+	–	+	+	–	+			+		13		2	5		1	
11[b]	29	F	1	N	–	–	+	–	+	–		+			24		2	2		1	
12	30	F	0	N	–	–	–	–	–	–		+			12		0	1		0	
13	34	M	1	N	–	–	–	–	+	–			+		21		1	LtFu		1	
14	65	M	5	10	–	+	+	–	+	+			+		27		5	3			1
15	31	F	3	N	–	–	–	+	+	+			+	+	22		3	2			2
16[b]	31	F	4	N	–	–	+	+	+	+		+				30	3	2			2
17[b]	59	F	1	N	–	–	–	–	+	–		+			14		5	1	4		
18[b]	56	M	2	N	–	–	+	+	–	+	+	+			29		2	2		2	
n (%)					3 (17)	2 (11)	8 (44)	10 (56)	9 (50)	9 (50)	3 (15)	6 (30)	8 (40)	3 (15)	15 (88)	2 (12)			4 (22)	9 (50)	5 (28)
Mean	38		1.6												18	33	2.8	5	1.5		

mRS: modified Ranking Scale; MRI: magnetic resonance imaging; di: Diencephalon; mes: Mesencephalon; met: Metenchephalon; myel: Myelencephalon GCS: Glasgow coma scale; N: normal; Mo D: Motor deficit; CN D: cranial nerves deficits; Se D: sensory deficits; Cer D: cerebellar deficits; N^+/V^+: nausea/vomiting; LtFU: lost to follow up; Y: years.

[a] Worsened patients: No 1: Diplopia on Parinaud syndrome; No 2: unable to walk unassisted because of cerebellar ataxia; No 4: Diplopia on internuclear ophthalmoplegia and cerebellar ataxia; No 17: severe Holmes' tremor.

[b] Holmes patients.

Table 2
Locations and size OF 18 BSCM.

no	Location				Size (mm)	
	di	mes	met	myel	< 30	≥ 30
1		+			?	
2			+		21	
3			+		17	
4[a]		+	+		25	
5			+		17	
6	+				25	
7				+	13	
8				+	10	
9	+					35
10			+		13	
11[a]		+			24	
12		+			12	
13			+		21	
14			+		27	
15			+	+	22	
16[a]		+				30
17[a]		+			14	
18[a]	+	+			29	
n (%)	3 (15)	6 (30)	8 (40)	3 (15)	15 (88)	2 (12)
Mean					18	33

di: Diencephalon; mes: Mesencephalon; met: Metenchephalon; myel.
[a] Holmes patients.

Table 3
Surgical details.

N°	Surgeon	Approach	DTI	ERP
1	A	Trans-tentorial	–	–
2	A	Trans-Magendie	–	+
3	A	Trans-Magendie	–	–
4	A	Subvermian	–	+
5	A	Trans-Magendie	–	–
6	A	Trans-sylvian	–	–
7	A	Subvermian	–	+
8	A	Trans-Magendie	–	+
9	B	Trans-T2	+	–
10	B	Trans-vermian	–	–
11	A	Trans-sylvian	–	–
12	A	Supra-cerebellar	–	–
13	B	Retro-sigmoïdal	+	–
14	B	Retro-sigmoïdal	–	–
15	A	Trans-tonsillar	–	–
16	A	Supra-cerebellar	–	–
17	A	Fronto-orbito-zygomatic	–	–
18	A	Trans-frontal	+	–

A: CR; B: GV; DTI: diffusion tensor imaging (DTI); ERP: event-related potential.

3.1.3. Interventions

All but one patient were operated on after their neurological condition had been stabilized. A surgical preoperative planning was performed using neuronavigation (Brainlab®, Feldkirchen, Germany). Table 3 shows surgical approach, operator, diffusion tensor imaging (DTI) and event-related potential (ERP) implementation.

3.1.4. Surgical outcome and complications

GTR was achieved in all patients and there were no surgery-related deaths. Histopathological examinations confirmed the cavernoma diagnosis in all cases.

In the immediate postoperative period, the neurological status of three (75%) patient worsened, which was temporary in two cases.

The median hospital stay was 16 days (range 7–28 days), and the median follow-up period was 2 years (range 1–14 years). For two patients (40%), the neurological evaluation at the last follow-up was the same, one patient (20%) had improved compared to the preoperative period. For 60% of HT and 83% of all BSCM patients, the mRS score at the last follow-up was good (≤ 2). Fig. 1 shows patients' clinical evolution according to BSCM location and Table 4 illustrates the evolution of tremor severity over time.

Table 4
Holmes severity evolution.

Patient	Holmes severity (months)		
	1	3	12
4	0	0	2
11	0	2	1
16	0	1	2
17	2	3	3
18	0	2	2

0: none; 1: light; 2: moderate; 3: severe.

Interestingly, the mean postoperative mRS of patients with HT was higher than that of all patients, which shows the impact of this symptom on quality of life. No rebleeding or cavernoma recurrence occurred during the follow-up period.

3.1.4.1. Patient 1. A 51-year-old woman (patient 4) was diagnosed with a left metencephalic cavernoma six years before surgery following a hemorrhage. During the follow up period she experienced three additional hemorrhages, which led to diplopia on VI left cranial nerve palsy, headache, nausea, sensory deficits and cerebellar ataxia.

We offered her surgical intervention due to her progressive neurological deterioration and the increasing size of the cavernoma.

During the postoperative course, her symptoms, notably diplopia, worsened and she was unable to walk without assistance. Postoperative MRI showed a GTR and she left the hospital for rehabilitation 16 days after surgery.

At the three months follow-up, she described a slow, but progressive improvement of her walking aptitudes while the neuro-ophthalmologist was taking care of her diplopia. Unfortunately, she ended up leaving our country and her aftercare was interrupted. At the fourteen years follow-up she complained about a right-hand tremor that appeared one year after surgery. The tremor was barely visible at rest but increased significantly with movement which mad writing and daily activities impossible. During periods of emotional stress, the tremor spreads to the entire right upper limb. A new MRI showed a bilateral hypertrophic olivary degeneration (HOD), which appeared to be more severe on the left side and left red nucleus hemosiderin deposits (Fig. 2).

Neurology follow-up has been scheduled in order to start treatment, but the patient did not wish to try any medication.

3.1.4.2. Patient 2. Five months before being admitted into our center, this 29-year-old woman (patient 11) developed upward gaze diplopia, left hemiparesis and vertigo. A cranial MRI showed a hematoma in the right thalamo-mesencephalic junction (Fig. 3). Another institution had started treating it with corticosteroids and obtained the almost complete resolution of the symptoms. Two months later, following an early pregnancy, she developed a recurrence of her symptoms. A second MRI showed a probable tegmentum cavernoma within the hematoma, which had grown in size. The pregnancy was interrupted, she recovered from her motor deficits and was operated on two months later by a transylvian transuncal approach [18].

Immediately after surgery, she suffered from left hemiparesis (grade 4) and from right III and VII cranial nerve palsies (House–Brackmann 3/6), as well as cerebellar dysmetria. She left our department to go to rehabilitation eight days after surgery. A postoperative MRI showed a GTR without surgery-related complications, with no involvement of the red nucleus but with a fading of its T2 hypo-signal compared to the other side (Fig. 4).

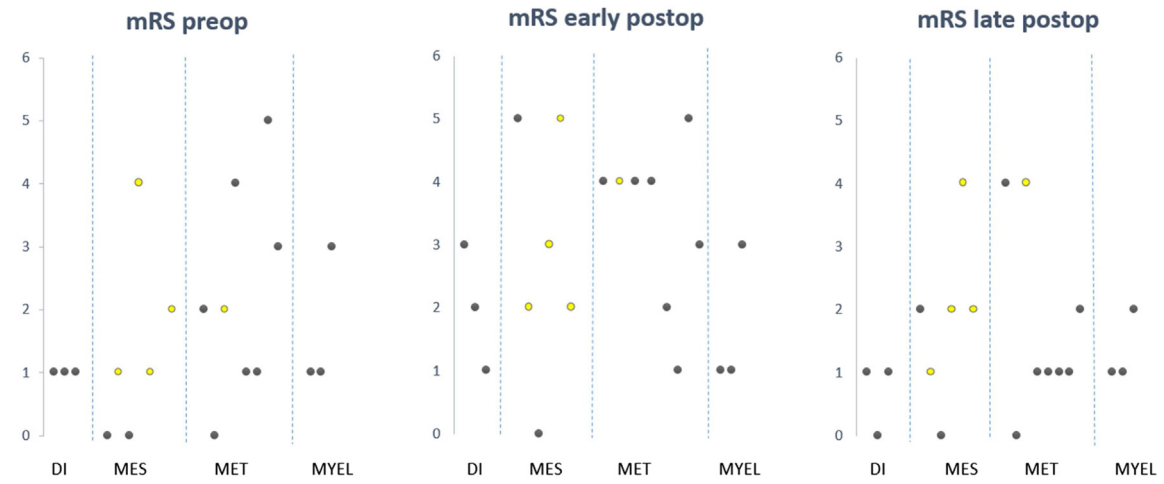

Fig. 1. Clinical evolution (mRS) according to cavernoma location. Holmes, DI, Diencephalon; MES, Mesencephalon; MET, Metenchephalon; MYEL, Myelencephalon; mRS, modified Rankin Scale.

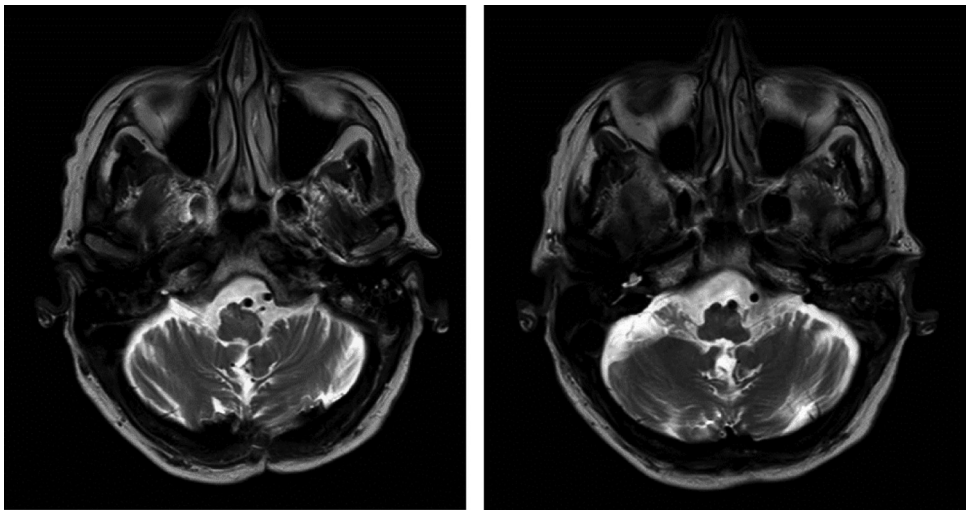

Fig. 2. Patient 4: Postoperative last FUp T2-weighted brain MRI showing HOD with hyperintensity of both inferior olivary nuclei.

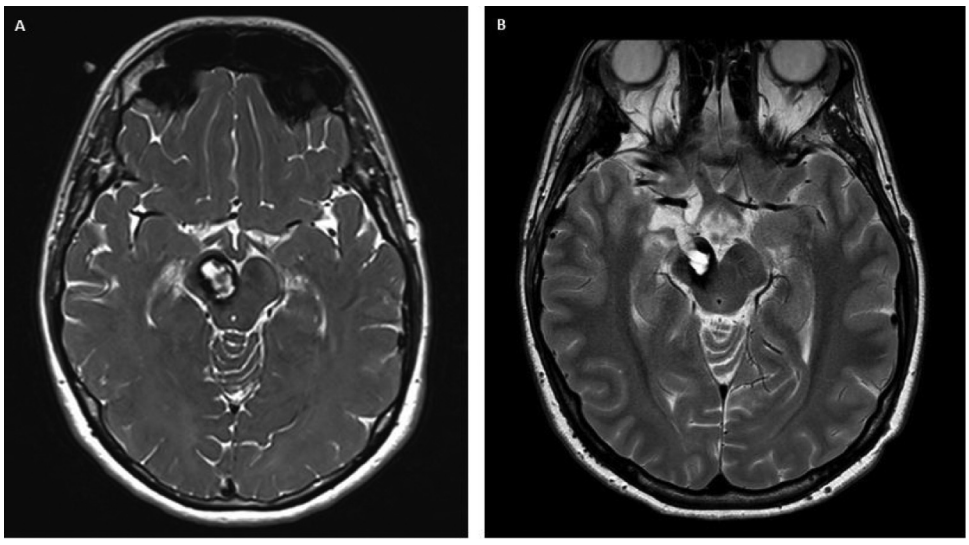

Fig. 3. Patient 11: A. Preoperative axial T2-weighted MR image showing a cavernoma in the right part of crux cerebri and midbrain tegmentum. B. Postoperative last FUp T2-weighted brain MRI showing GTR.

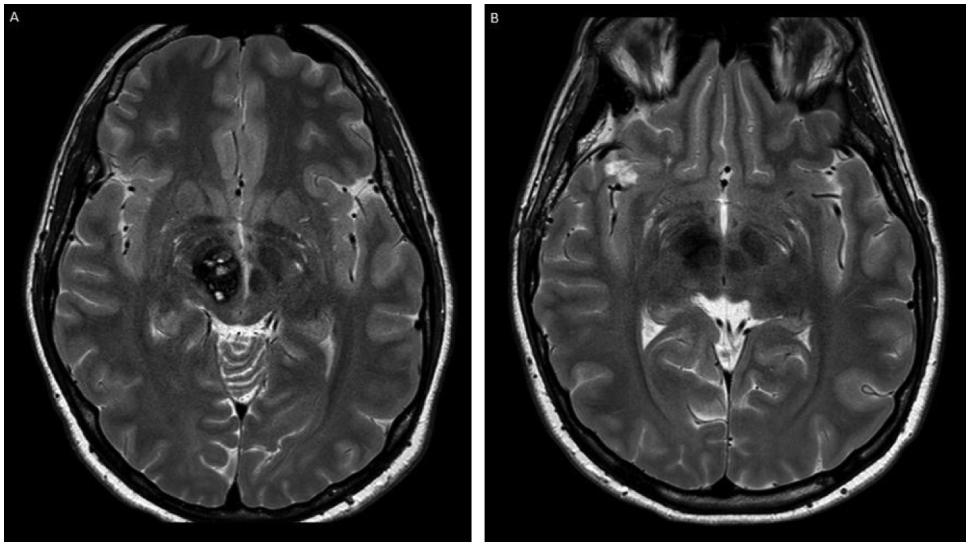

Fig. 4. Patient 11: A. Preoperative T2-weighted MR image showing right red nucleus invaded by the BSCM. B. Postoperative T2-weighted MR image showing well individualized right red nucleus but surrounded by hemosiderin and presenting a fading of its physiological T2 hypo-signal compared to the other side.

Ten days after surgery, while she was recovering from motor deficits, she developed a left upper limb HT that was rapidly controlled with Levodopa treatment. At the last follow-up, she had returned to work as veterinarian and was planning on a second pregnancy. For this reason, she stopped Levodopa despite the return of a discreet tremor, compatible with her daily activities.

3.1.4.3. Patient 3. This 31-year-old woman (patient 16) was referred to us following the discovery of a left mesencephalic cavernoma, which led to the sudden onset of dysarthria and paresthesia of her right hemiface (Fig. 5).

At that time, she was 28 weeks pregnant and neurological monitoring was offered in order to continue the gestation up to 34 weeks. Unfortunately, the progressive deterioration of her neurological state (appearance of right dysmetria, diplopia with III and VI cranial nerve palsies, right hemiparesis (grade 4), sensory ataxia and dysphagia) forced her to undergo a c-section under general anesthesia. This was followed by a complete macroscopic resection of the cavernoma by a supra-cerebellar approach at 32 weeks of pregnancy.

After the surgery, her state gradually improved, and all her symptoms progressively disappeared. She was able to walk with assistance when she left the hospital for rehabilitation 18 days after surgery. A postoperative MRI (Fig. 6) showed a GTR without complications, and the presence of a hemosiderin ring surrounding the red nucleus and involving the substantia nigra.

Four months later, she began to experience HT in the right upper limb. This was already present at rest but increased with movement and during emotional stress. A year after surgery, it was no longer present at rest, but remained severely disabling in her everyday life. She started a treatment with Levodopa and showed a slight symptomatic improvement, even after trialing the medication at the maximum dosage. After some time on Primidone treatment at 250 mg, her tremor improved enough to allow her to take care of her child but remained too severe to return to work.

3.1.4.4. Patient 4. Two years before surgery, this 59-year-old woman (patient 17) was diagnosed with a left midbrain cavernoma following a hemorrhage, which led to an upward gaze diplopia.

A conservative treatment with Propanolol was initiated, but due to the aggravation of her vertical strabismus and the increasing size of the cavernoma, a surgical intervention was proposed (Fig. 7), with an eventual transuncal approach being carried out. She could not be extubated until the second postoperative day because she was slow to regain consciousness.

During the postoperative period she suffered from a right facial palsy (5/6 on House–Brackmann scale), a complete paralysis of the left oculomotor nerve, dysarthria, right hemiparesis (grade 2) and swallowing disorders (requiring the placement of a nasogastric tube). Two weeks after surgery, while she was slowly recovering from her deficits, she started to experience right upper limb HT. She began treatment with Levodopa and showed signs of improvement. HT was already present at rest, but increased significantly during posture, and especially in stressful and anxious states. She was transferred to the rehabilitation center 28 days after surgery.

While the medulla looked preserved on the initial study, a postoperative MRI showed a GTR and the appearance of a bilateral hypertrophic olivary degeneration (HOD), which was more severe on the left side (Fig. 8). One year after surgery, the patient had almost completely recovered from her hemiparesis, but still exhibited a complete paralysis of the left oculomotor nerve, as well as severe dysarthria. Despite trialing Levodopa at the maximum dosage and the concomitant Gabapentin, she still suffered from a predominantly located in the right-side HT, which was exacerbated by emotional situations. The patient was forced to leave work and remains dependent on others for daily living. A possible treatment with DBS has been proposed, but so far, it has been refused by the patient.

3.1.4.5. Patient 5. This 56-year-old man (patient 18) was followed for four years for a left thalamo-mesencephalic cavernoma involving the red nucleus and substantia nigra. He had suffered from two bleeding episodes. Surgical treatment was offered due to the increasing size of the cavernoma as well as the appearance of dysarthria, lingual paresthesia, dysmetria and fine motor disorders which made it impossible for him to write, despite a Propanolol treatment. A heterolateral trans-frontal transventricular approach was carried out. A postoperative MRI confirmed GTR (Fig. 9). During the postoperative course, the preoperative symptoms persisted, with a slight improvement in writing, but the appearance of de novo right hypoesthesia.

Three months after the surgery, he began to experience a HT in the right upper limb. It was refractory to treatment with Levodopa, Gabapentin and Primidone titrated to maximum doses. A left GPi

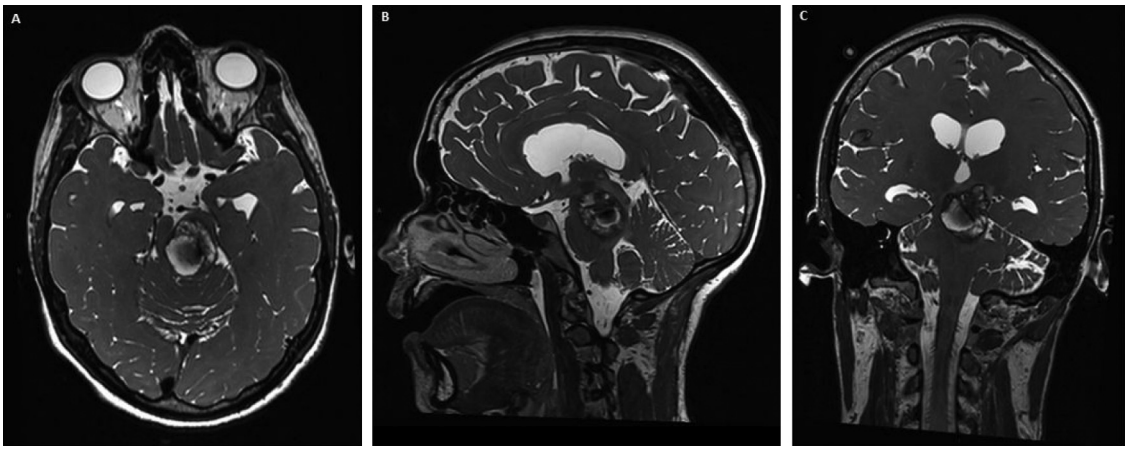

Fig. 5. Patient 16: A. preoperative axial; B. Sagittal and C. Coronal T2-weighted brain MRI showing a 2.3 × 3 × 3 cm left mesencephalic cavernoma with extension in the pons.

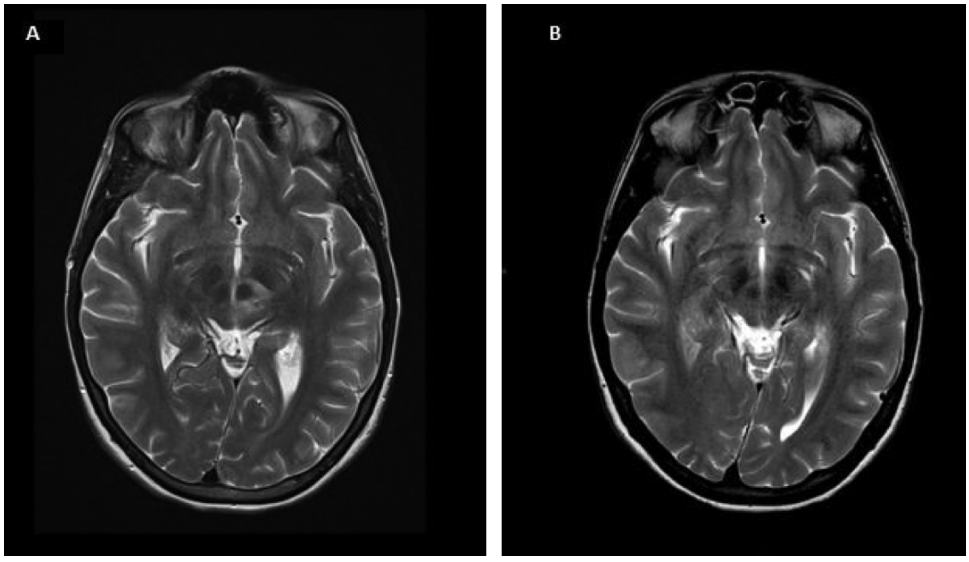

Fig. 6. Patient 16: A. Preoperative axial T2-weighted brain MRI showing left red nucleus smaller than the contralateral side and surrounded with edema. B. Postoperative axial T2-weighted brain MRI showing disappearance of the edema but the presence of hemosiderin around the nucleus and in the substantia nigra.

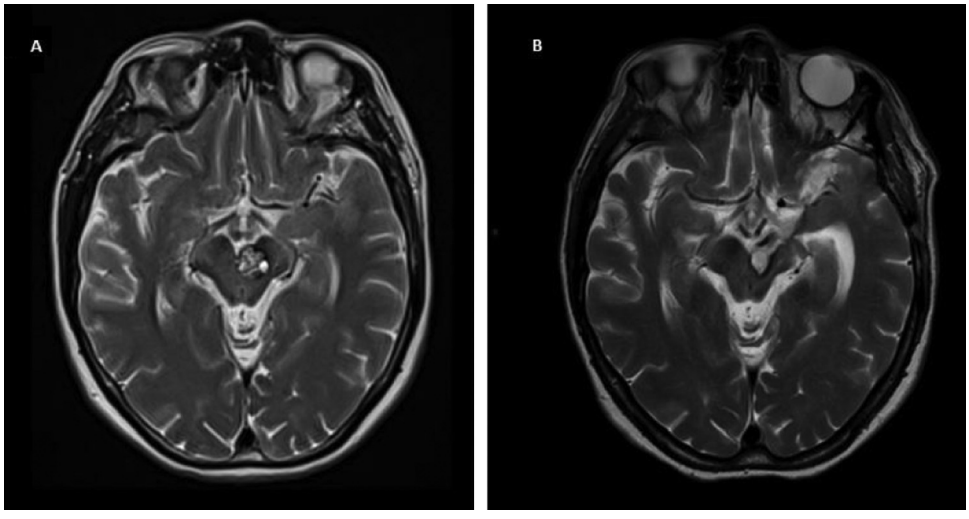

Fig. 7. Patient 17: A. preoperative axial T2-weighted MR image showing a cavernoma in the left antéro-médian midbrain. B. Postoperative lastFUp T2-weighted brain MRI showing GTR by transuncal approach

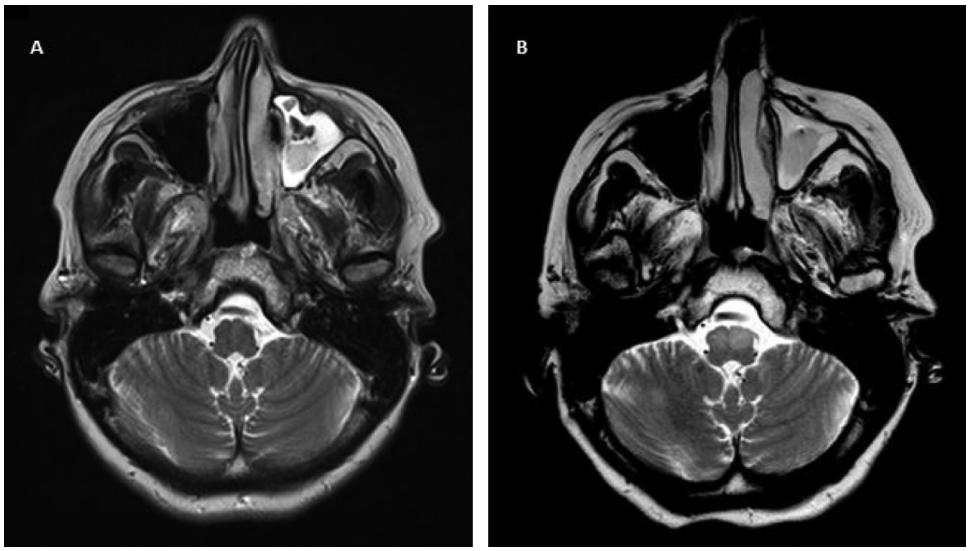

Fig. 8. Patient 17: A. preoperative axial T2-weighted MR image showing normal bulbar olives. B. Postoperative last FUp T2-weighted brain MRI showing HOD with hyperintensity of both inferior olivary nuclei.

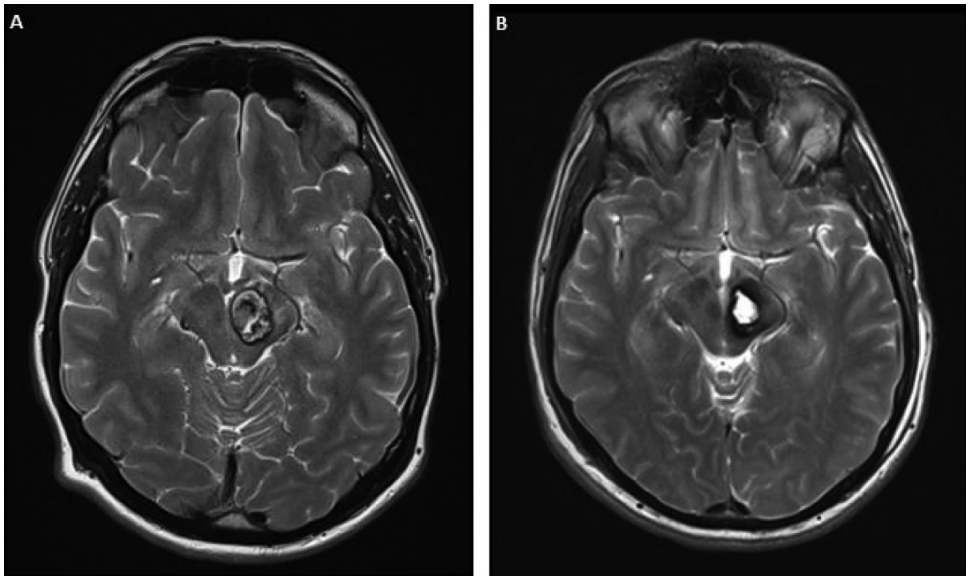

Fig. 9. Patient 18: A. preoperative T2-weighted brain MRI showing the mesencephalic cavernoma with involvement of red nucleus and substantia nigra. B. Postoperative T2-weighted brain MRI showing the resection cavity undertaking the normal localization of the red nucleus.

and VIM DBS treatment was implanted under general anesthesia. The position of the electrodes was confirmed by an intra-operative cone beam cranial CT. The results of Vim and GPi stimulation was assessed independently and in combination. At six months follow up the greatest improvement was achieved with stimulation of the GPi alone, resulting in a 67% reduction in tremor evaluated with the Fahn–Tolosa–Marin tremor rating scale.

4. Discussion

Because of the high threat of neurological impairment after a hemorrhage and the increasing risk of rebleeding, most authors recommend surgery after at least one bleeding episode from an accessible symptomatic BSCM [1,3–5,7,11–14,16,19,22]. In our institution, we initially proposed a conservative treatment with Propanolol, but due to the lack of evidence on the effectiveness of this treatment, we are currently recommending surgical management after several hemorrhages.

A correlation between the incidence of cavernous malformation hemorrhages and being female has been reported, as well as an increased incidence of these occurring during pregnancy [10,11,13,34]. In our center we found a female preponderance, with two patients suffering from hemorrhages during pregnancy. HT was also preponderant in female patients in our series as well as in the largest series of HT reported [31]. The majority of patient with HT after BSCM surgery reported in the literature are women [18,28,32].

4.1. Rebleeding

Complete resection was achieved in all our patients. GTR associated with minimal normal brain involvement was the main goal of surgery, considering that partial resection exposes the patient to an increased risk of neurological deficits due to rebleeding. As reported by Cenzato et al. [23], BSCM remnants present a hemorrhage rate of at least 40%. However, rebleeding may arise even after

a complete resection [15,16]. De Oliveira [25] et al. reported a 15.5% recurrence rate after a MRI confirmed the GTR, and for this reason, in our hospital institution, we recommend follow-up imaging for several years after surgery as a way to identifying any progression or recurrence.

4.2. Holmes tremor

HT has been described in association with multiple different etiologies affecting cerebellar outflow pathways or the area of the red nucleus: trauma, tumors, neurodegenerative disease, radiotherapy, infectious or vascular conditions [29,31,32,35]. We researched the presence of tremor in a large literature review of BSCM studies, with only three authors reporting this complication in their papers.

Huang et al. [13] reported a rubral tremor in one patient that was operated on via a trans-vermian approach, but failed to mention the exact location of the cavernoma. Zaidi et al. [16] reported two rubral tremors in their surgically treated BSCM study, one of the largest series in the literature to date.

Wang et al. [34] described preoperative red nucleus tremor in three patients with midbrain lesions. According to the literature, all our patients with HT had BSCM located in the mesencephalon. Although despite a long preoperative follow-up, none of them presented HT before surgery.

A specific literature search looking for the association of HT and cavernomas only found case-reports.

Seidel et al. [28] described HT nine months after surgery for a left-sided mesencephalic cavernoma on a 16-year-old-girl. Just like in our series, her tremor worsened during times of emotional distress and ceased during sleep. The resting component of her tremor improved with a Pramipexole treatment and her postural tremor improved with an additional dose of L-Dopa. As reported in previous studies [29–31], HT shows an involvement of not only the red nucleus, but also of the dopaminergic nigrostriatal and cerebellothalamic systems that produce the combination of rest and kinetic tremor.

Rojas et al. [32] reported a left sided HT a few weeks after a surgery for an extensive cavernous angioma involving the right mesencephalon with diencephalic and thalamic extension on a 33-year-old right-handed female, without any relevant medical history prior to the BSCM bleeding. Her tremor did not respond to classical drugs used in HT patients such as Pramipexole, Levodopa/Carbidopa, Valproic acid, Levetiracetam, Quetiapine, Gabapentin, Clonazepam and Agomelatine, all of them titrated to their maximum dosage. Instead, an improvement of her tremor was observed after titration of Topiramate to 100 mg/day.

Raina et al. [31] reported in the largest series of HT in the literature to date, a series of 29 patients with different etiologies. Three patients from this series exhibited HT after hemorrhages from a BSCM. Like in our series, all patients had at least one associated neurologic manifestation involving the same body region as the tremor. They describe a 54.16% improvement due to a Levodopa treatment, in our series only one patient (25%) presented significative improvement under Levodopa treatment. No significant differences were found in the doses of Levodopa used on the group which improved when compared with the group with no response.

Still being studied is pathogenesis of HT with the involvement of dopaminergic nigrostriatal and cerebellothalamic systems having been described in previous studies [28,29,31,36]. Furthermore, it appears that a dysfunction of the olivocerebellar system is also thought to be responsible for HT. Even if it is usually associated with palatal tremor, HOD in HT patients had previously been reported [37–39]. In our series two HT patients showed HOD on the postoperative MRI. Interestingly patient nº 17 developed HT two weeks after surgery while patient nº 4 did not notice the onset of the tremor until a year after surgery. Cosentino et al. reported two cases of midbrain vascular lesions at the level of the commissure of Wernekinck associated with HT and bilateral HOD without palatal tremor. Bilateral HOD can be seen after lesion of both superior cerebellar peduncle and central tegmental tract or, in the event of midline injury located at the level of commissure Wernekinck. HOD is considered to be associated to the late occurrence of HT, the delay between brainstem lesion and HT varies in the literature but generally arise at around four weeks to two years. This may be associated to trans-synaptic degeneration, secondary to disruption in the dento-rubro-olivary pathway referred to as the Guillain-Mollaret triangle [29,36–38].

For other authors the latent period before occurrence of HT is induced by the plasticity of the affected systems, particularly the nigrostrial system [29].

The heterogeneity of the responses to the medical treatment and the tremor improvement to different classes of drugs indicates that multiple patho-physiological phenomena may lead to the development of HT. This observation is even more important when considering surgical treatments such as DBS. Indeed, VIM stimulation, although very effective in some patients, has shown very limited reduction in the proximal component of HT and in the action component of distal tremor in other subjects [26,29,31] Aydin et al. [29] reported the case of a 30-year-old man with a left upper limb HT six months after resection of a right posterior ponto-mesencephalic cavernoma by a trans-telovelar approach. As in our series, they described an involvement of the contralateral tegmentum, red nucleus and substantia nigra. L-dopa and Keppra treatment were ineffective. Starting from the idea that HT is related to both the motor striatal and thalamic circuits, they implanted DBS electrode at two different targets (VIM and GPi) for the neuromodulation of these circuits. Following the same idea, we used those targets for patient 18. Interestingly, in our patient, the greatest improvement was not obtained from combined stimulation but with GPi alone.

When we analyze the outcome after BSCM surgery at our institution, even if most patients had maintained a stable neurological status at the last follow-up, we note a neurological degradation of 15% of those who have not developed HT, compared to 40% of patients presenting this complication. This observation allows us to understand the adverse effect of HT on quality of life.

This underlines the importance of additional studies to better recognize the role of lesions in each different pathway in the pathogenesis of HT in order to find the best surgical targets and improve chances of a successful surgery.

5. Limitations

The major limitation of this study is the small number of patients and its retrospective nature. Clinical outcomes were determined on a retrospective evaluation of chart data, which can be difficult as they are susceptible to information bias.

This study reports only on surgically treated BSCM without any comparison to the conservative treatment, which prevents the highlighting of irrefutable indications.

6. Conclusion

Performing surgery to treat BSCM is a challenging procedure, associated with potentially severe morbidity. It remains however the first treatment option after symptomatic hemorrhage, considering the high rebleeding rate. The risk for HT after surgery is significant for midbrain BSCM. We report an original single-center series of patients presenting with HT following midbrain cavernoma surgery. Our series shows the heterogeneity of the treatment response and the possibility of spontaneous favorable evolution.

Further investigation and a DBS implantation on a larger series could provide treatment guidelines to improve the quality of life of patients suffering from drug-refractory HT.

Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s) and/or volunteers.

Disclosure of interest

The authors declare that they have no competing interest.

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Author contributions

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References

[1] Chen LH, Zhang HT, Chen L, Liu LX, Xu RX. Minimally invasive resection of brainstem cavernous malformations: surgical approaches and clinical experiences with 38 patients. Clin Neurol Neurosurg 2014;116:72–9, http://dx.doi.org/10.1016/j.clineuro.2013.10.012.
[2] Schwartz C, Grillhösl A, Schichor C, et al. Symptomatic cavernous malformations of the brainstem: functional outcome after microsurgical resection. J Neurol 2013;260(11):2815–22, http://dx.doi.org/10.1007/s00415-013-7071-3.
[3] Bradac O, Majovsky M, De Lacy P, Benes V. Surgery of brainstem cavernous malformations. Acta Neurochir (Wien) 2013;155(11):2079–83, http://dx.doi.org/10.1007/s00701-013-1842-6.
[4] Ren Y, Li J, Tao C, et al. Surgical treatment of cavernous malformations involving the midbrain: a single-center case series of 34 patients. World Neurosurg 2017;107:753–63, http://dx.doi.org/10.1016/j.wneu.2017.08.117.
[5] Nathal E, Patiño-Rodriguez HM, Arauz A, et al. Risk factors for unfavorable outcomes in surgically treated brainstem cavernous malformations. World Neurosurg 2018;111:e478–84, http://dx.doi.org/10.1016/j.wneu.2017.12.105.
[6] Bruneau M, Bijlenga P, Reverdin A, et al. Early surgery for brainstem cavernomas. Acta Neurochir (Wien) 2006;148(4):405–14, http://dx.doi.org/10.1007/s00701-005-0671-7.
[7] François P, Ben Ismail M, Hamel O, Bataille B, Jan M, Velut S. Anterior transpetrosal and subtemporal transtentorial approaches for pontine cavernomas. Acta Neurochir (Wien) 2010;152(8):1321–9, http://dx.doi.org/10.1007/s00701-010-0667-9.
[8] Chen L, Zhao Y, Zhou L, Zhu W, Pan Z, Mao Y. Surgical strategies in treating brainstem cavernous malformations. Neurosurgery 2011;68(3):609–20, http://dx.doi.org/10.1227/NEU.0b013e3182077531.
[9] Dukatz T, Sarnthein J, Sitter H, et al. Quality of life after brainstem cavernoma surgery in 71 patients. Neurosurgery 2011;69(3):689–95, http://dx.doi.org/10.1227/NEU.0b013e31821d31b7.
[10] Li D, Yang Y, Hao SY, et al. Hemorrhage risk, surgical management, and functional outcome of brainstem cavernous malformations. J Neurosurg 2013;119(4):996–1008, http://dx.doi.org/10.3171/2013.7.JNS13462.
[11] Li H, Ju Y, Cai BW, Chen J, You C, Hui XH. Experience of microsurgical treatment of brainstem cavernomas: Report of 37 cases. Neurol India 2009;57(3):269–73, http://dx.doi.org/10.4103/0028-3886.53269.
[12] Ohue S, Fukushima T, Kumon Y, Ohnishi T, Friedman AH. Surgical management of brainstem cavernomas: selection of approaches and microsurgical techniques. Neurosurg Rev 2010;33(3):315–24, http://dx.doi.org/10.1007/s10143-010-0256-7.
[13] Huang AP-H, Chen J-S, Yang C-C, et al. Brain stem cavernous malformations. J Clin Neurosci 2010;17(1):74–9, http://dx.doi.org/10.1016/j.jocn.2009.06.009.
[14] Abla AA, Lekovic GP, Garrett M, et al. Cavernous malformations of the brainstem presenting in childhood: surgical experience in 40 patients. Neurosurgery 2010;67(6):1589–98, http://dx.doi.org/10.1227/NEU.0b013e3181f8d1b2.
[15] Li D, Hao SY, Tang J, et al. Surgical management of pediatric brainstem cavernous malformations: clinical article. J Neurosurg Pediatr 2014;13(5):484–502, http://dx.doi.org/10.3171/2014.2.PEDS13536.
[16] Zaidi HA, Mooney MA, Levitt MR, Dru AB, Abla AA, Spetzler RF. Impact of timing of intervention among 397 consecutively treated brainstem cavernous malformations. Neurosurgery 2017;81(4):626, http://dx.doi.org/10.1093/neuros/nyw139.
[17] Xie MG, Xiao XR, Li D, et al. Surgical treatment of the medullary cavernous malformations: 53 cases. World Neurosurg 2018;118:e449–59, http://dx.doi.org/10.1016/j.wneu.2018.06.213.
[18] Delaunois J, Vaz G, Raftopoulos C. Transsylvian transuncal approach for an anterior midbrain cavernous malformation resection: a case report. Oper Neurosurg 2018;14(3):E38–43, http://dx.doi.org/10.1093/ons/opx116.
[19] Hauck EF, Barnett SL, White JA, Samson D. Symptomatic brainstem cavernomas. Neurosurgery 2009;64(1):61–70, http://dx.doi.org/10.1227/01.NEU. 0000335158.11692.53.
[20] Maurer AJ, Bonney PA, Strickland AE, Safavi-Abbasi S, Sughrue ME. Brainstem cavernous malformations resected via miniature craniotomies: Technique and approach selection. J Clin Neurosci 2015;22(5):865–71, http://dx.doi.org/10.1016/j.jocn.2014.10.028.
[21] Farhoud A, Aboul-Enein H. Surgical management of symptomatic brain stem cavernoma in a developing country: technical difficulties and outcome. Neurosurg Rev 2016;39(3):467–73, http://dx.doi.org/10.1007/s10143-016-0712-0.
[22] Zhang S, Lin S, Hui X, Li H, You C. Surgical treatment of cavernous malformations involving medulla oblongata. J Clin Neurosci 2017;37:63–8, http://dx.doi.org/10.1016/j.jocn.2016.11.014.
[23] Cenzato M, Stefini R, Ambrosi C, Giovanelli M. Postoperative remnants of brainstem cavernomas: incidence, risk factors and management. Acta Neurochir (Wien) 2008;150(9):879–86, http://dx.doi.org/10.1007/s00701-008-0008-4.
[24] Hauck EF, Barnett SL, White JA, Samson D. The presigmoid approach to anterolateral pontine cavernomas: clinical article. J Neurosurg 2010;113(4):701–8, http://dx.doi.org/10.3171/2010.1.JNS08413.
[25] De Oliveira JG, Lekovic GP, Safavi-Abbasi S, et al. Supracerebellar infratentorial approach to cavernous malformations of the brainstem: surgical variants and clinical experience with 45 patients. Neurosurgery 2010;66(2):389–99, http://dx.doi.org/10.1227/01.NEU.0000363702.67016.5D.
[26] Dec-Cwiek M, Tutaj M, Pietraszko W, et al. Posterior subthalamic area deep brain stimulation for treatment of refractory holmes tremor. Stereotact Funct Neurosurg 2019;97(3):183–8, http://dx.doi.org/10.1159/000502563.
[27] Martins WA, Marrone LCP, Fussiger H, et al. Holmes' tremor as a delayed complication of thalamic stroke. J Clin Neurosci 2016;26:158–9, http://dx.doi.org/10.1016/j.jocn.2015.09.014.
[28] Seidel S, Kasprian G, Leutmezer F, Prayer D, Auff E. Disruption of nigrostriatal and cerebellothalamic pathways in dopamine responsive Holmes' tremor. J Neurol Neurosurg Psychiatry 2009;80(8):921–3, http://dx.doi.org/10.1136/jnnp.2008.146324.
[29] Aydin S, Abuzayed B, Kiziltan G, et al. Unilateral thalamic vim and GPi stimulation for the treatment of Holmes' tremor caused by midbrain cavernoma: Case report and review of the literature. J Neurol Surgery 2013;74(4):271–6, http://dx.doi.org/10.1055/s-0032-1322549 [Part A Cent Eur Neurosurg].
[30] Inci S, Celik O, Soylemezoglu F, Ozgen T. Thalamomesencephalic ossified cavernoma presenting with Holmes' tremor. Surg Neurol 2007;67(5):511–6, http://dx.doi.org/10.1016/j.surneu.2006.06.057.
[31] Raina GB, Cersosimo MG, Folgar SS, et al. Holmes tremor. Neurology 2016, http://dx.doi.org/10.1212/WNL. 0000000000002440.
[32] Rojas NG, Cesarini M, Etcheverry JL, Da Prat G, Viera Aramburu T, Gatto EM. Holmes tremor partially responsive to topiramate: a case report. Tremor Other Hyperkinet Mov (N Y) 2018;8:565, http://dx.doi.org/10.7916/D82C0FFN.
[33] Yoon JH, Yong SW, Lee JS. Spontaneous disappearance of Holmes' tremor in a patient with a midbrain cavernous hemangioma. Neurol Sci 2015;36(11):2137–8, http://dx.doi.org/10.1007/s10072-015-2309-8.
[34] Wang CC, Liu A, Zhang JT, Sun B, Zhao YL. Surgical management of brain-stem cavernous malformations: report of 137 cases. Surg Neurol 2003;59(6):444–54, http://dx.doi.org/10.1016/S0090-3019(03)00187-3.
[35] Ramirez-Zamora A, Okun MS. Deep brain stimulation for the treatment of uncommon tremor syndromes. Expert Rev Neurother 2016;16(8):983–97, http://dx.doi.org/10.1080/14737175.2016.1194756.
[36] Kim MK, Cho BM, Park S-H, Yoon DY. Holmes' tremor associated with bilateral hypertrophic olivary degeneration following brain stem hemorrhage: a case report. J Cerebrovasc Endovasc Neurosurg 2014;16(3):299, http://dx.doi.org/10.7461/jcen.2014.16.3.299.
[37] Cosentino C, Velez M, Nuñez Y, et al. Bilateral hypertrophic olivary degeneration and holmes tremor without palatal tremor: an unusual association. Tremor Other Hyperkinet Mov (N Y) 2016;6:400, http://dx.doi.org/10.7916/D87944SS.
[38] Rosenblum JS, Nazari M, Al-Khalili Y, Potigailo V, Veznedaroglu E. Unilateral symptomatic hypertrophic olivary degeneration secondary to midline brainstem cavernous angioma: a case report and review of the literature. World Neurosurg 2018;110:294–300, http://dx.doi.org/10.1016/j.wneu.2017.10.061.
[39] Parker T, Raghu ALB, FitzGerald JJ, Green AL, Aziz TZ. Multitarget deep brain stimulation for clinically complex movement disorders. J Neurosurg 2020;1-6, http://dx.doi.org/10.3171/2019.11.JNS192224.