Brief Report

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Postoperative Third Nerve Palsy after Endoscopic Endonasal Transsphenoidal Surgery for Pituitary Adenoma: Elucidating its Mechanism

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Abstract:

Third nerve palsy is a rare complication of transsphenoidal surgery and has been merely mentioned in different studies, but there is not any rigorous analysis focusing on this particular complication. The purpose of this study is to analyze this complication after transsphenoidal surgery for a pituitary adenoma to better understand its pathophysiology and outcome. The authors retrospectively analyzed 3 cases of third nerve palsy selected from the 377 patients operated via a transsphenoidal route between 2012 and 2021 at FLENI, a private tertiary neurology and neurosurgical medical center located in Buenos Aires, Argentina. The three patients who presented this complication were operated on via an endoscopic approach. It was observed that an extension into the cavernous sinus (Knosp grade 4) and to the oculomotor cistern was present in the three patients. The deficit was apparent immediately after surgery in two patients. For these two patients, the supposed mechanism of ophthalmoplegia was an intraoperative nerve lesion. The other patient became symptomatic in the 48 h following the surgery. The mechanism implied in this case was intracavernous hemorrhagic suffusion. The latter patient completely recovered the third nerve deficit in the 3 months that followed, while the other two recovered after 6 months postoperative. Oculomotor nerve palsy after transsphenoidal surgery is a very rare complication and appears to be transient in most cases. The invasion of both the cavernous sinus and the oculomotor cistern seems to be a major factor in its physiopathology and should be preoperatively analyzed on magnetic resonance imaging (MRI); recognizing such extension should play an important role in the surgeon's operative considerations.

Key Words:

Cavernous sinus, endoscopic, oculomotor nerve palsy, ophthalmoplegia, pituitary surgery, third nerve palsy, transsphenoidal

Key Message:

Postoperative oculomotor nerve palsy after transsphenoidal surgery is a very rare complication, transient in most reported cases. We present a rigorous analysis of this complication with an emphasis on the tumoral invasion of the oculomotor cistern.

Isolated third nerve palsy is a rare complication of transsphenoidal surgery, occurring at a rate of 0%–1% according to different series and in most cases is reported as transient.[1-9] However, at the present time, articles making a rigorous analysis of the mechanisms responsible for this phenomenon are scarce. This report aims to provide a detailed analysis of this issue by gathering reports from other authors and our practical experience with three patients presenting this complication in our department, to unify this information under a recognizable clinical entity to better understand its pathophysiology and outcome.

Materials and Methods

The authors retrospectively analyzed 3 cases of third nerve palsy selected from the 377 patients operated on via a transsphenoidal route between 2012 and 2021 at our center. The following patient characteristics were studied: age, sex, cavernous sinus invasion (Knosp classification), oculomotor cistern extension (OCE), ophthalmological symptoms, the severity of third nerve paralysis,

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affected side, type of surgery, the extent of resection, histology, the time of onset of paralysis, and recovery time.

We evaluated tumor growth into the oculomotor cistern on magnetic resonance imaging (MRI) T2-weighted coronal and axial images and fast-imaging, employing steady-state acquisition (FIESTA) sequences. The site at which the nerve pathway was no longer visible was determined to be the location of the compression.

All patients were operated on via a transsphenoidal approach, either microscopically or endoscopically.

Results

Three hundred seventy-seven patients were diagnosed with pituitary adenoma and had preoperative and postoperative specific pituitary protocol imaging available for review. Fourteen patients (6 males and 8 females; ages 47–72 years; median 59 years) had pituitary macroadenoma with oculomotor cisternal extension (3.71% of total prevalence).

In this subset of 14 patients, the most common presenting symptom was visual deficit (71%; 10 patients); other symptoms were headache (21%; 3 patients), and symptomatic hypogonadism (7%; 1 patient). The visual deficits included visual field cuts and diminished visual acuity. Two patients (14%) presented with preoperative isolated oculomotor nerve palsy. Three cases (21.4%) without preoperative third nerve palsy presented postoperative transient deficit.

Case presentations

Case 1

The first case was a 35-year-old female patient with a history of a previous transnasal surgery 4 years before, for a non-functioning pituitary adenoma. During imaging follow-up, a recurrence was diagnosed and a new surgery was decided. His neurological examination was unremarkable. The patient's endocrinological examination was within normal values.

MRI indicated a sellar tumor stretching into the right cavernous sinus with complete encasement of the intracavernous internal carotid artery (ICA) (Knosp grade IV) and tumor extension to the oculomotor cistern [Figure 1a-c]. The histopathology indicated a diagnosis of non-functioning pituitary adenoma.

Forty-eight hours after surgery, the patient developed incomplete third nerve palsy with mild diplopia, ptosis, and anisocoria reactive to light. Computed tomography (CT) scan showed compressive postoperative hematoma in the cavernous sinus and tumor bed, which resolved spontaneously within 12 days [Figure 1d, e]. The patient completely recovered the third nerve palsy before the 3-month postoperative follow-up evaluation. An MRI captured one year following the surgery demonstrated a subtotal resection with decompression of the oculomotor cistern and residual tumor contained within the cavernous sinus [Figure 1b-f]. The residual tumor in the cavernous sinus was treated with a gamma knife (maximum dose 32 Gy, marginal dose 16 Gy). MRI revealed no regrowth after 2 years.

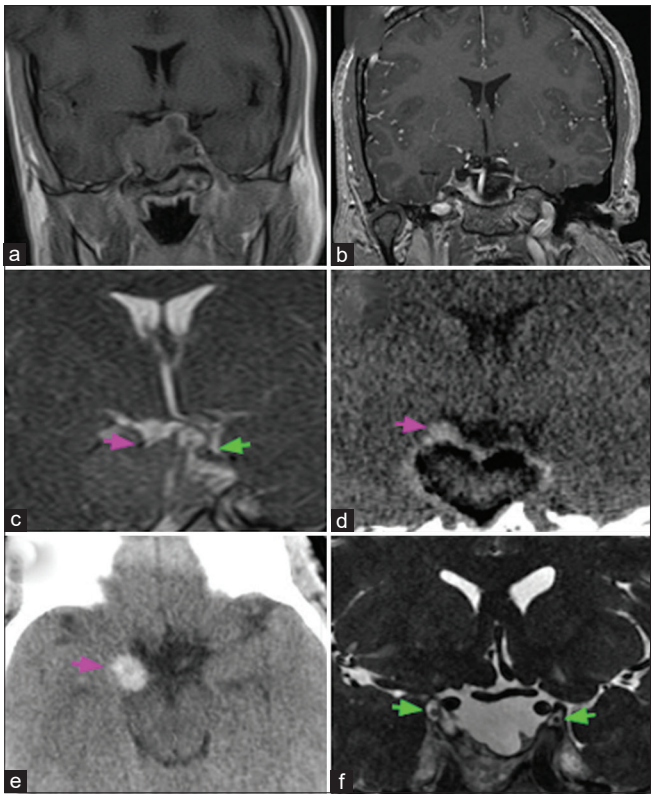

Figure 1: Case one: (a) Preoperative and (b) postoperative coronal MRI demonstrating the subtotal removal of a pituitary adenoma, a remnant is noted in the right cavernous sinus (b). Preoperative axial T2-weighted MR image (c) illustrating tumor extension posterolaterally into the right oculomotor cistern (pink arrow). The preserved anatomy of the left oculomotor nerve and cistern (green arrow) can be seen. Postoperative CT scan images (d and e) showing a compressive postoperative hematoma in the oculomotor cistern. At 3 months after the tumor removal, the right oculomotor nerve (green arrow) is visible (f)

Case 2

The second case was a 78-year-old male patient with a history of a previous transnasal surgery 6 years before, for a non-functioning pituitary adenoma. He had permanent panhypopituitarism afterwards. During imaging follow-up, a recurrence was diagnosed and a new surgery was decided. His neurological examination was unremarkable. MRI showed a sellar/suprasellar lesion, with a Knosp IV extension into the left cavernous sinus and compromising the ipsilateral oculomotor cistern [Figure 2a-c]. The tumor was excised under general anesthesia via the endoscopic transsphenoidal route.

The patient developed an isolated complete third nerve palsy with ptosis and mydriasis non-reactive to light in the hours following the surgery. CT scan showed no signs of hematoma. With neurorehabilitation, his deficit was completely resolved after 5 months. The one-year follow-up MRI demonstrated a subtotal resection with decompression of the oculomotor cistern and residual tumor contained within the sellar and suprasellar region [Figure 2b-d].

Case 3

A 34-year-old male consulted at our institution with a 2-month history of visual impairment. His neurological examination was unremarkable. MRI showed a sellar tumor extending

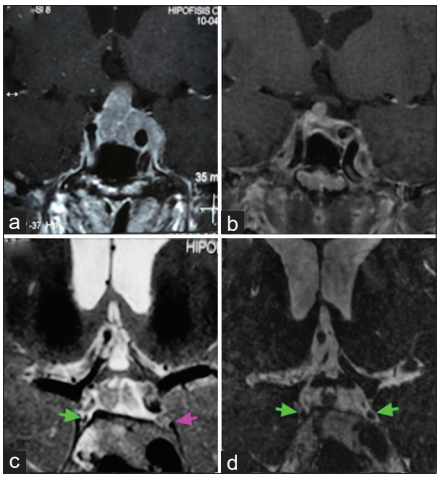

Figure 2: Case two: (a) Preoperative and (b) postoperative coronal MRI demonstrating the subtotal removal of a pituitary adenoma. Preoperative axial T2-weighted MR images (c) illustrating tumor extension posterolaterally into the left oculomotor cistern (pink arrows). Postoperative coronal T2-weighted MR image (d) after the tumor removal, the left oculomotor nerves (green arrows) are now visible in the oculomotor cistern

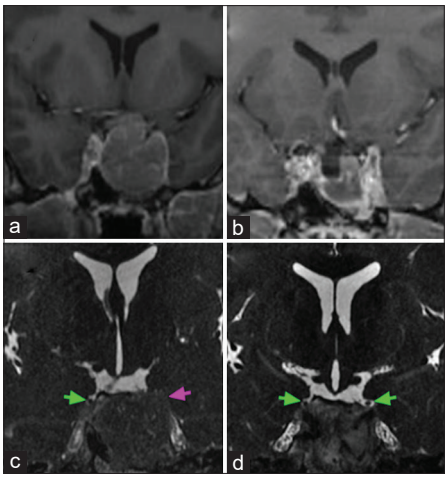

Figure 3: Case three: (a) Preoperative and (b) postoperative coronal MRI demonstrating the subtotal removal of a pituitary adenoma. Preoperative axial T2-weighted MR images (c) illustrating tumor extension posterolaterally into the left oculomotor cistern (pink arrows) of two different patients. The preserved anatomy of the right oculomotor nerve and cistern (green arrow) can be seen. Postoperative coronal T2-weighted MR image (d) after the tumor removal, the left oculomotor nerves (green arrows) are now visible in the oculomotor cistern

into the left cavernous sinus with complete encasement of the intracavernous ICA (Knosp grade 4) with extension into the oculomotor cistern [Figure 3a-c]. The patient histopathology informed a non-functioning pituitary adenoma.

In the immediate postoperative period, the patient developed an isolated complete third nerve palsy with ptosis and mydriasis non-reactive to light. CT scan showed no signs of hematoma. At the sixth-month follow-up evaluation, the patient had completely recovered from the ophthalmoplegia. The one-year follow-up MRI demonstrated a subtotal resection with decompression of the oculomotor cistern and residual tumor contained within the left suprasellar and parasellar region [Figure 3b-d].

Discussion

Third nerve palsy as a complication of transsphenoidal surgery is seen at a rate of 0%–1%, being transient in most cases.[7,10-13] The three previously described cases exemplify this postoperative complication which is rare but nonetheless important and to date there are only a few studies that discuss this issue thoroughly. In our series, we encountered this complication in 3 (0.95%) of the 377 patients recorded in our database. We summarized in Table 1 the data regarding postoperative third nerve palsies in our series and in a review of the literature for patients with pituitary lesions that were surgically treated via a transsphenoidal approach.

Several mechanisms may have been proposed for third nerve palsy in the postoperative period in patients undergoing transsphenoidal surgery that can be grouped into two categories[18]:

A- ***Compressive Etiology:***
- Postoperative hematoma[1,2]
- Excessive packing of the sella with fat or muscle[19]
- Interstitial hemorrhage and swelling in the tumor remnant.[1,2]

B- ***Intraoperative Nerve Injury:***
- Direct injury to cranial nerves during tumor removal[10]
- Injury to the carotid artery and meningohypophyseal trunk.[11]

In our series, the first case, which presented a delayed onset oculomotor nerve transient palsy, had a hematoma in the postoperative CT, apparently causing compression of the oculomotor cistern on the second day after surgery. In this case, because of the small volume of the hematoma, the patient did not undergo an evacuation procedure, but in similar cases with larger intrasellar compressive hematomas, reoperation should be considered.[1] The most probable cause for this transient complication was that the hemorrhagic suffusion in the cavernous sinus in the hours following the procedure caused a swelling process affecting the third cranial nerve in the first days after surgery.

In the remaining two patients, there was no evidence of bleeding in postoperative images. In these patients, the onset of the third cranial nerve deficit was immediate after surgery and its recovery was slower. In agreement with what has been reported by Magro *et al*.,[2] we believe that the transient palsy, in this case, was most probably caused by interstitial hemorrhage in the tumor remnant or in the cavernous sinus, rather than the curettage and direct injury of the intracavernous oculomotor nerves. The partial resection of the cavernous extension of the adenoma might lead to postoperative swelling of the residual tumor causing compression over the oculomotor cistern. Because there is no direct nerve damage intraoperatively, as the swelling resolves, the deficit recovers.

Regarding the fact that all patients had locally aggressive tumors with cavernous sinus invasion, a Knosp grade III or IV could be considered a risk factor for postoperative oculomotor nerve palsy.[1-4,12] The three patients reported also had an extension of the adenoma into the oculomotor cistern, a narrow space where the oculomotor nerve enters

Table 1: Third nerve palsy as a postoperative complication in our series and a review of the literature

Authors and Year	Patients w/Oculomotor N. Palsies		Surgical Technique	Transient or Permanent
	%	No./total		
Wilson and Dempsey, 1978[4]	0.4	1/250	Microscopic	Transient
Semple and Laws, 1999[10]	0.95	1/105	Microscopic	Transient
Cappabianca *et al*., 2002[14]	0.68	1/146	Endoscopic	Transient
de Divitiis *et al*., 2003[15]	0.43	1/233	Endoscopic	Transient
Mortini *et al*., 2005[6]	0.26	3/1140	Microscopic	Transient
Frank *et al*., 2006[16]	10	1/10	Endoscopic	Transient
Barzaghi *et al*., 2007[7]	0.48	6/1240	Microscopic	Transient
Wang F *et al*., 2010[3]	1.06	4/375	Endoscopic	Transient
Kassam *et al*., 2011[17]	0.125	1/805	Endoscopic	Transient
Halvorsen *et al*., 2014[8]	0.4	2/506	Endoscopic	Unspecified
Wang *et al*., 2015[3]	0.08	1/1116	Endoscopic	Transient
Smith *et al*., 2015[9]	1.22	1/82	Endoscopic	Transient
Magro *et al*., 2016[2]	2.67	8/300	Endoscopic	Transient
Florea *et al*., 2019[1]	0.6	10/1694	Endoscopic	Transient
Thakur *et al*., 2021[5]	0.2	1/514	Endoscopic	Permanent
Present Series	0.95	3/317	Endoscopic	Transient

the cavernous sinus. This cistern is located within the so-called oculomotor triangle in the posterior aspect of the cavernous sinus roof and is limited anteromedially by the interclinoidal ligament, posteromedially by the posterior petroclinoidal ligament, and laterally by the anterior petroclinoid ligament [Figure 4a-d].[12,13] Along this triangle the nerve is hidden posterolaterally to the posterior clinoid process, in the lateral wall of the cavernous sinus, making it extremely difficult to expose with the endoscopic endonasal technique, constituting what Akar *et al*.[20] called the "blind spot."[21] Extension of a pituitary adenoma into this particular anatomical area has been probably underreported in the medical literature. In a series of 170 patients with pituitary macroadenomas by Hoang *et al*.,[22] OCE incidence was 4.1%.[3] In our series, we found 14 cases with OCE (3.71%), and was associated with postoperative third nerve palsy in 3 cases (21,4%). Compression of the third nerve at this site by the tumor, followed by excessive bending of the nerve during surgery or by a hematoma seems to be a reasonable cause of postoperative third nerve palsy. The fact that our three patients recovered from the neurological deficit, and that the postoperative MRI showed decompression of the nerve in the oculomotor cistern, seems to support this concept.

The preoperative finding of OCE of pituitary macroadenomas on MRI, although uncommon, raises surgical and clinical management questions. This extension can limit gross-total resection,[12,22] and in our series presented a high prevalence of postoperative third nerve palsy (21.4%) using the transsphenoidal approach alone. Given the limitations of access to the region of the oculomotor cistern using a transnasal approach, the tumor growth pattern should be identified preoperatively, and counsel given to the patient about the plan for subtotal resection, and posterior observation or adjuvant treatment postoperatively.[22] In cases where a gross total resection is sought, to protect the oculomotor nerve and the rest of the cavernous sinus structures, a combined transcranial and transsphenoidal approach can provide excellent access to this region for direct decompression of the oculomotor cistern and dissection of the tumor within the subarachnoid space.[23]

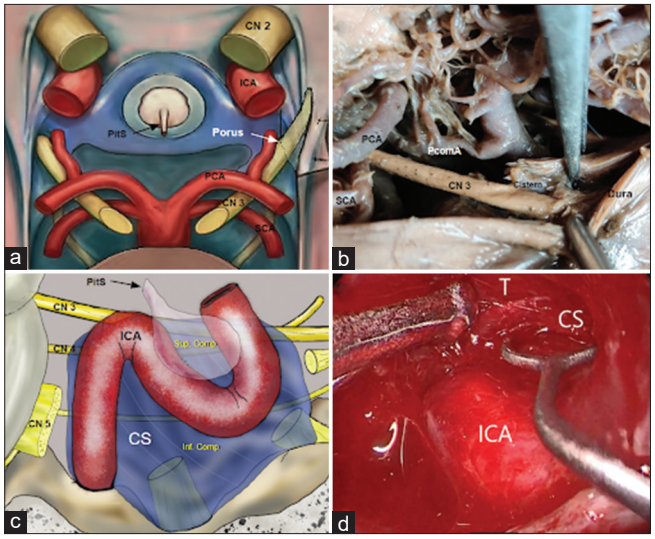

Figure 4: Anatomy of the oculomotor cistern. (a) Schematic illustration of the sellar and parasellar region seen from above showing the oculomotor nerves entering the cavernous sinus roof. On the right side, the dura is retracted laterally to expose the oculomotor cistern running toward the anterior clinoid process. (b) Lateral anatomic dissection of the cisternal and cavernous portions of the right oculomotor nerve. The dura covering the oculomotor cistern has been opened to depict the nerve within the cistern. (c) Schematic illustration of a medial-to-lateral view of the cavernous sinus (CV). The superior compartment of the CV which lies superior to the horizontal cavernous ICA and posterior to the anterior genu is the access point to the roof of the CV. (d) Intraoperative picture showing access to the cavernous sinus with identification of the cavernous ICA; the superior compartment located above the horizontal segment of the ICA is accessed by a large opening through the medial wall of the cavernous sinus created by the tumor. CN 2 = optic nerve; CN 3 = oculomotor nerve; CN 4 = trochlear nerve; CN 5 = trigeminal nerve; ICA = internal carotid artery; PCA = posterior cerebral artery; PcomA = posterior communicating artery; T = tumor; CS = cavernous sinus

When the OCE of the tumor is small and not immediately adjacent to the optic apparatus, transsphenoidal removal of the medial main mass, followed by stereotactic radiosurgery of the cisternal part may be a possible strategy[22] as in Case 1 of our series.

Conclusion

Third nerve palsy after transsphenoidal surgery is one of the least common complications of the procedure and appears to be transient in most cases. The possible causes may be categorized as compressive, direct nerve damage, or postoperative ischemic injury. The invasion of both the cavernous sinus and the oculomotor cistern seems to be a major factor in its physiopathology and should be preoperatively analyzed on MRI; recognizing such extension should play an important role in the surgeon's operative considerations.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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