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Indication for surgery in prolactinomas and factors influencing the postoperative remission

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Abstract:
Objective: *to determine the current indications for trans-sphenoidal surgery in patients with Prolactinomas and determine the factors that influence post-operative remission.*
Trans-sphenoidal surgery may be indicated in patients with resistant prolactinoma and/or in case of intolerance to treatment with dopamine agonists (DA).
Patients and methods:
We performed a retrospective review of the medical records of 160 patients with prolactinoma over a period of 12 years (2009-20021).
Results: *This is a series of 160 prolactinomas, 90 women (mean age of 38 years; ranging from 20 to 56) and 70 men (mean age of 41.5 years; ranging from 18 to 65) and all presented with hyperprolactinemia.*
The majority of women presented with headache (94.4%), dysmenorrhea (38.8%) and galactorrhea (38.5%), while most men had hypopituitarism (86.4%) and headaches (88.5%). The majority of women (93.5%) and men (85.6%) had been treated with at least one form of DA before surgery. The median duration of follow-up for all patients was 67.5 months.
Imaging showed the presence of microadenomas (diameter of largest tumor < 1.0 cm) in 17.5% of patients (n = 28) and macroadenomas (larger diameter P 1.0 cm) in 68.7% of patients (n=111).
We found that 33 patients (20.6%) presented with a cystic form, apoplexy in 79.3% of patients (n=127) with suprasellar extension in 27 (79.3%) patients.
The surgical indication was proposed for all the patients of the series but the percentage depends on different criteria like resistance, intolerance, pregnancy, preference of the patient and others.
The preoperative prolactinemia varies between 114 and 6735 ng/mL and the average was 516.5 ng/mL.
Only endonasal endoscopic trans-sphenoidal approach was used in all patients without exception, the most common immediate postoperative complication was rhinorrhea (45 patients), most of the patients benefited from daily lumbar puncture until the total disappearance of the rhinorrhea over a few days (4-5 days), only 10 patients underwent surgical revision to repair the meningeal breach (we use abdominal fat and biological glue).
Conclusion: *Trans-sphenoidal surgery is indicated in patients with Prolactinoma who are resistant to anti-dopaminergic therapy, intolerance to the side affects of dopamine, or both.*
Some factors that determine the postoperative remission rate must be taken into account before surgery.
Key words: *Prolactinoma, anti-dopaminergic, intolerance, resistance, endoscopic approach.*

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I. Introduction:

Prolactin-secreting adenomas are the most common subtype of all primitive pituitary tumors, accounting for approximately 40% of all pituitary adenomas (1). Prolactinomas are pituitary tumors that can be successfully treated with medical methods. Dopamine (DA) agonists have been used for many years, with bromocriptine (BRC) as the treatment of choice. Bromocriptine was tested in 1985 as part of a multicenter prospective trial for the treatment of macroprolactinomas (2). Prolactin levels were normalized in two-thirds of the patients, and tumor size decreased by more than half in 46% of patients, by half in 18% of cases and by a quarter in 36% patients over a period of 6 weeks (2). For some time, bromocriptine has been replaced by cabergoline (CAB) as first-line DA treatment due to certain benefits like lower side effects, increased half-life and convenience of administration (3.4). When the prolactin level does not normalize, or when there is no reduction in volume tumor after medical treatment, these tumors are classified as resistant to DA treatment, and surgery may become the best option (5-6-7). Resistance to BRC has been defined as the inability to normalize prolactin levels when the patient receives a daily dose of 15 mg of BRC for 3 months (5-8-9) In addition, surgery is recommended to relieve symptoms in case of cystic adenomas and/or has a stroke. A recent meta-analysis reported that 73.7% of patients with

microadenomas and 32.4 % of patients with macroadenomas had normal prolactin levels 1 to 3 months after surgery (10-11).

Factors that influence disease remission after surgical treatment of a prolactinoma are not yet established. These determinants of postoperative remission are not well determined and evaluated in the literature (12-13).

However, to our knowledge, no meta-analyses aimed at distinguishing clinical factors associated with remission after surgery for prolactinoma exist.

Knowledge of these determinants such as preoperative prolactin levels (PRL), tumor size, volume of tumor growth, and prior use of AD may influence the individual prognosis of each patient with Prolactinoma and determines the need for the recourse to surgery.

II. Material And Methods:

This is a series of 160 patients with Prolactinoma who underwent endoscopic trans-sphenoidal surgical resection between 2009 and 2021 in two neurosurgery departments at EHS Ali ait Idir and Cherchell EHS of Neurosurgery.

We included patients with a pituitary adenoma who had undergone resection surgery and had immunohistochemical confirmation of tumor cells secreting prolactin.

Medical records were reviewed for the following data: age at the time of surgery, gender, preoperative symptoms, preoperative and postoperative endocrine status (including pre and postoperative levels of prolactinemia), type and duration of treatment, preoperative medical examination, the preoperative radiological presentation (maximum dimensions, estimated tumor size, degree of supra-sellar extension), the reasons for indicating surgery (symptoms drug intolerance and/or resistance to medical treatment / no reduction in tumor volume), surgical technique (trans-sphenoidal, microscopic versus endoscopic), sample of pathological findings (Microscopic description, typical or atypical characterics, immunohistochemistry, MIB-1 proliferation index), and postoperative evolution (evolution , length of hospitalization, hormone replacement therapy, adjuvant chemotherapy or radiotherapy, total or partial resection with postoperative imaging.

III. Results:

This is a series of 160 prolactinomas, 90 women (mean age of 38 years; ranging from 20 to 56) and 70 men (mean age of 41.5 years; ranging from 18 to 65) and all presented with hyperprolactinemia. The majority of women presented with headache (94.4%), dysmenorrhea (38.8%) and galactorrhea (38.5%), while most men had hypopituitarism (86.4%) and headaches (88.5%). The majority of women (93.5%) and men (85.6%) had been treated with at least one form of DA before surgery. The median duration of follow-up for all patients was 67.5 months (Table1).

Imaging showed the presence of microadenomas (diameter of largest tumor < 1.0 cm) in 17.5% of patients (n = 28) and macroadenomas (larger diameter P 1.0 cm) in 68.7% of patients (n=111).

We found that 33 patients (20.6%) presented with a cystic form, apoplexy in 79.3% of patients (n=127) with suprasellar extension in 27 (79.3%) patients (Table 1).

The surgical indication was proposed for all the patients of the series but the percentage depends on different criteria like resistance, intolerance, pregnancy, preference of the patient and others.

The preoperative prolactinemia varies between 114 and 6735 ng/mL and the average was 516.5 ng/mL. Only endonasal endoscopic trans-sphenoidal approach was used in all patients without exception, the most common immediate postoperative complication was rhinorrhea (45 patients), most of the patients benefited from daily lumbar puncture until the total disappearance of the rhinorrhea over a few days (4-5 days), only 10 patients underwent surgical revision to repair the meningeal breach (we use abdominal fat and biological glue).

Caractéristics	**Female N=90**	**male N=70**	**Total N=160**
-Age	**39 (20-59)**	**50(35-65)**	**44,5(20-65)**
-Symptoms :			
***headache**	**85**	**62**	**147**
***Galactorrhea**	**35**	**4**	**39**
***Gynécomastia**	**40**	**0**	**40**
***Dys ou aménorrhéa**	**35**	**0**	**35**
***Sexual impotence**	**0**	**5**	**05**
***Weight gain**	**10**	**15**	**25**
*** Visual impairment**	**8**	**7**	**15**
***Cognitive disorders**	**0**	**2**	**02**
***Psychological disorders**	**0**	**1**	**01**
-hormonal assessment :			
***Thyroid hormones**	**15**	**8**	**23**
*** Cortisol**	**6**	**7**	**13**

***Pre-op prolactinemea**	**516.5 ng/mL(114 à 6735 ng/mL)**	**516.5 ng/mL**	
-medical treatment AD			
***Pre-op AD**	**180**	**180**	
***Post-op control (months)**	**67,5 (3-132)**	**67,5 (3-132)**	
-Tumor characteristics :			**28**
Micro adenoma	**14**	**14**	**110**
Macro adenoma	**75**	**35**	
***Invasion (knops)**	**23**	**10**	**33**
***Cyst**	**67**	**60**	**127**
Apoplexy	**15**	**12**	**27**
*** suprasellar extension**	**20**		
Surgery indications :			**24**
***Resistance**	**10**	**14**	**24**
***Intolerance**	**17**	**7**	**48**
***Resistance and intolerance**	**35**	**13**	**45**
***Apoplexy**	**20**	**25**	**10**
***patient preference**	**05**	**05**	**05**
***pregnancy**	**05**	**00**	**160**
Total	**90**	**70**	

Table 1: Preoperative clinical characteristics of patients with Prolactinoma, tumors and surgical indications.

IV. Discussion:

Medical treatment in the form of DA has long been the first line of treatment for patients with prolactin-secreting pituitary adenomas. Most of the authors agree that these drugs provide good biochemical control in 80% to 85% of cases. (14)

However, some patients are refractory to DA, and their tumors are resistant to the effects of medications. These patients never had a significant reduction in prolactinemia after 6 to 12 weeks of treatment, their tumors show no reduction in tumor volume (15) Failure to normalize prolactin levels is in the order of 25% of patients treated with bromocriptine and 10-15% of those treated with cabergoline (15-16-6).Failure to achieve at least a 50% reduction in tumor volume occurs in approximately 30 % of people treated with bromocriptine and 10 to 15% for those treated with cabergoline (15-16-6).

Trans-sphenoidal surgery is indicated in case of intolerance or resistance to antidopaminergic treatment, in case of the mass effect of adjacent structure or according to patient preference.(17-18 -2.3)

Although ADs are the first-line treatment, several studies have recommended surgery of the Prolactinoma as a safe alternative for medical treatment, especially for microadenomas.(20). Long-term medical treatment with ADs can overwhelm patients with many side effects such as nausea, headache and postural hypotension, potential association with heart valve disease, fibrosis, psychiatric symptoms and impulsivity and a significant financial burden. (21).

The determinants of postoperative remission and recurrence after prolactinoma surgery have been largely overlooked and unstudied in the literature.

Some authors have shown that microadenomas are associated with higher rates of postoperative complications and remission.

Some have reported other additional predictors of disease remission that are as follows: absence of tumor extension, absence of cavernous sinus invasion, female sex and the lack of preoperative use of AD. Kyla Wright et al found that microadenomas had higher rates of remission compared to macroadenomas (76.4% versus 47.1% respectively).

In the studies by Kruljac et al and Babey et al respectively, microadenomas had higher remission rates and in conclusion, tumor size was established as a determinant of surgical remission .(22-23) Zamanipoor et al, observed a long-term postoperative remission in 83% of microadenomas and 57% macroadenomas. Similarly, a meta-analysis by Qianquan et al.7 found that long-term remission was 91% in patients with microadenomas and 77% in patients with macroadenomas.(23) Female gender was also associated with higher remission rates in this study. Additionally, several studies have shown that prolactinomas in men can be biologically more aggressive than those of females, with increased proliferative capacity and the probability of invasion.

Raverot et al (24) found that tumor invasiveness was a predictor of results in prolactinomas, while tumor size was not. Han et al. have stated that tumor size and invasiveness were independently associated with postoperative remission (12).

The study by Rudnik et al was the only series that reported postoperative remission rates compared to the Knosp score, noting that 100% remission is for grade 0 of Knosp tumors, 87.5% for grade I, 1/1 grade II, 0/1 grade III and 0/2 grade IV(25).

Three studies reported that preoperative prolactin levels were lower in patients in remission.(24) Mean preoperative prolactin levels in patients in remission ranged from 238 at 433 ng/mL, whereas the average levels of prolactinemia in patients where the tumor persists or in case of postoperative recurrence ranged from 1470 to 4764 ng/mL.Remission rates in patients with a preoperative prolactin that was inferior to100 ng/mL ranged from 55% to 77% of cases. (24)

The postoperative remission rate in patients with a preoperative prolactinemia inferior to 200 ng/mL ranged from 50% to 71% of cases for the 2 series; and from 29% to 40% of cases in patients who have a preoperative prolactinemia superior to 200 ng/mL. Postoperative remission has been reported in 9.7% of patients with preoperative PRL levels that's superior to 500 ng/mL in the first series and 20 to 34 % in patients with a preoperative prolactin level that's superior to 1000 ng/mL in the other study (26).

Three individual studies reported lower postoperative remission rates in patients who received preoperative anti-dopaminergic therapy according to a review by Carija et al.(24)

Vermeulen et al proposed a scoring system to identify subgroups of patients, finding male sex, large tumor, long time until PRL normalization and presence of cysts, hemorrhagic or necrotic intra-tumor components to be predictors of DA-resistant prolactinoma (24).

V. **Conclusion:**

Trans-sphenoidal surgery is indicated in patients with Prolactinoma who are resistant to anti-dopaminergic therapy, intolerance to the side affects of anti-dopaminergic, or both.

Recent advances in endoscopic technology and the familiarity of surgeons with this technique only make the transsphenoidal procedure safer, faster and more effectie.

Some factors determining the postoperatie remission rate must be taken into account before the surgery.

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