

## CLINICAL CASE

## LONG-TERM FOLLOW-UP AFTER TRANSCRANIAL HYPOPHYSECTOMY IN MACROPROLACTINOMAS

Adina Ghemigian<sup>1,2</sup>, Mara Carsote<sup>1,2</sup>, Cristina Ghervan<sup>3,4</sup>, Anda Dumitrașcu<sup>2</sup>, Simona Elena Albu<sup>1,5</sup>, Carmen Emanuela Georgescu<sup>3,4</sup>, Ana Valea<sup>3,4</sup>

<sup>1</sup>The University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania

<sup>2</sup>“C.I. Parhon” National Institute of Endocrinology, Bucharest, Romania

<sup>3</sup>“I.Hatieganu” University of Medicine and Pharmacy

<sup>4</sup>The Clinical County Hospital, Cluj-Napoca, Romania

<sup>5</sup>The University Emergency Hospital, Bucharest, Romania

Corresponding author: Mara Carsote

Phone no. 0040213172041

E-mail: carsote\_m@hotmail.com

### Abstract

*Currently, transcranial hypophysectomy is infrequently used since the trans-sphenoidal approach is very effective and less invasive. Prolactinomas represent one of the rarest indications for pituitary surgery due to the spectacular effects of dopamine agonists as cabergoline. A 66-year-old female presented at age of 52 with headache, low blood pressure. The investigations revealed panhypopituitarism, high prolactin and a large pituitary mass with obstructive hydrocephalus at the left lateral ventricle. Transcranial surgery was performed through a right approach without complications. The pathological report confirmed a pituitary adenoma with intense cellular pleomorphism. A 29-year-old male was admitted at the age of 28 for severe headache, multiple episodes of vomiting, and hypotension. Pituitary insufficiency and hyperprolactinemia were correlated to the presence of an intrasellar tumor of 2/2 cm with extension to the right cavernous sinus, optic chiasm. The pathological report confirmed a pituitary adenoma. Transcranial pituitary surgery represents an option only in selected large macroprolactinomas. After procedure, a good outcome is expected despite the potential secondary eye field defects or pituitary insufficiency which needs medication. Sometime the panhypopituitarism caused first by the tumor itself persists after surgery (as in our first case) or it is corrected (as adrenal insufficiency in the second case). The presence of a residual prolactin producing tumor requires long term specific therapy with dopamine agonists.*

**Keywords:** *transcranial hypophysectomy, prolactinoma, pituitary tumor, cabergoline, transfrontal pituitary surgery*

### Introduction

Currently, transcranial hypophysectomy (TH) represents only an alternative to the otherwise much more common procedure: the trans-sphenoidal pituitary surgery (in association with different techniques regarding

the endoscopic or the microscopic type). [1-4] TH is considered the traditional path to approach the pituitary gland (parasagittal or frontotemporal type) [1-3, 5]. The neurosurgical technique varies with the medical center and neurosurgeon's experience, and generally a dramatic change was registered overtime since

the first procedure was done, the so called "Schloffer's legacy" [1]. The TH risks are related to meningitis, the eye field defects, hypopituitarism, etc [1-3, 6].

The endocrine profile before surgery varies from the non-secretor pattern as seen in large macro-adenomas, craniopharyngiomas or hormonally active tumors as seen in acromegaly, regardless the improvement due to hormonal targeted medication [7-11]. Prolactin producing masses represent one of the rarest indications for pituitary surgery since dopamine agonists as cabergoline or bromocriptine are extremely useful in daily practice [12,13]. However, in this particular situation, large tumors with locally compressive effects may require neurosurgical intervention and transcranial approach is extremely rare done when compared to the transphenoidal procedure [12,13].

We introduce a series of two patients diagnosed with macroprolactinomas and treated with TH, associating a long term medical and surgical follow-up. Their informed written consent was obtained from two different Tertiary University Endocrine Romanian Centers were they are currently under treatment and followed-up.

## Case report 1

### *Medical & surgical history*

A 66-year-old non-smoking female presents with high blood pressure (controlled under medication), hip osteoarthritis, and hyperlipemia. The family history is positive for lung cancer (father). She had secondary amenorrhea since the age of 38.

At the age of 52 she complained of dizziness, headache, bilateral galactorrhea, photophobia, low blood pressure and the endocrine evaluation was consistent for central adrenal insufficiency as well as central hypothyroidism. High levels of prolactin and a large pituitary mass of 2 centimeters (cm) was discovered. After IV contrast computed tomography, actually two connected masses of 1 cm each with homogenous margins in association with obstructive hydrocephalus at the level of left lateral ventricle were discovered. Transcranial approach was recommended and done through a

right approach. The procedure went well without any incidents; IV hydrocortisone was necessary perioperative. No further eye field anomaly was registered except for a prior small spot on the left eye (Figure 1). The pathological report revealed a pituitary adenoma with intense cellular pleomorphism and rare atypical mitosis. She was hospitalized for 28 days. After discharge the subject was given daily 5 miligrams (mg) prednisone and 100 micrograms ( $\mu$ g) of levothyroxine (LT4).

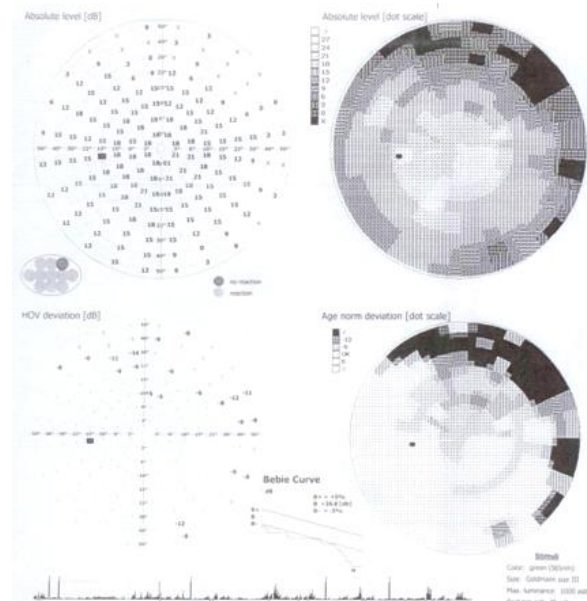


Figure 1 - Left eye field assessment after transcranial pituitary surgery for a large prolactin-producing mass in a 52-year-old female patient: a small superior scotoma

### *Follow-up*

For the next decade, she was followed-up only based on the clinical exam, blood ionogram and some hormonal tests. The values of free Levothyroxine (FT4) were normal 1.4 ng/dL with normal adequate limits between 0.8 and 2 ng/dl, under LT4 substitution while the prolactin was constantly high (of 470 ng/mL, repeated of 538 ng/mL, with normal ranges between 6 and 29.9 ng/mL) but no further therapy was added. She also received the diagnosis of osteoporosis and treatment with different oral bisphosphonates was introduced over the years.

13 years after initial TH, the patient was admitted for a detailed endocrine assessment at a Tertiary Romanian Center of Endocrinology. The subject complained of arterial pressure variations, chronic asthenia, dry skin, unspecific

muscle and joints pain. Panhypopituitarism was confirmed by low Insulin-like Growth Hormone 1 (IGF1), decreased Follicle Stimulant Hormone (FSH), suppressed Adrenocorticotropic Hormone (ACTH) and morning plasma cortisol, inadequately low Thyroid Stimulant Hormone (TSH) for low-normal FT4 under T4 therapy (consistent with sinus bradycardia) (Table 1, Figure 2). The eye exam was status quo. The contrast computed tomography (CT) revealed a cerebral mass defect on the right side after the transcranial approach, triventricular hydrocephalus, and three tumors: one at the intrasellar level of 1.2 by 1 cm; the others are suprasellar in contact with the third ventricle and Willis polygon, and optic chiasm (associating micro-calcifications) of 1.6 by 1.2 cm (on the right) and of 1.5 by 1.4 cm (on the left) (Figure 3,4). Elevated levels of prolactin were highly suggestive for a prolactinoma and cabergoline was started (twice a week) with progressively increased dose (up to 2 mg per week) in association with prior mentioned medication except for the increase of LT4 to 125 µg per day. 2 months later the prolactin dramatically decreased above the lower normal limit (to 49 µUI/mL, normal between 127 and 637 µUI/mL), respective to 32 µUI/mL, after 8 months (when pituitary imagery scan revealed a few millimeters decrease of the pituitary masses). Close neurosurgical, endocrine, and imagery check-up is recommended.

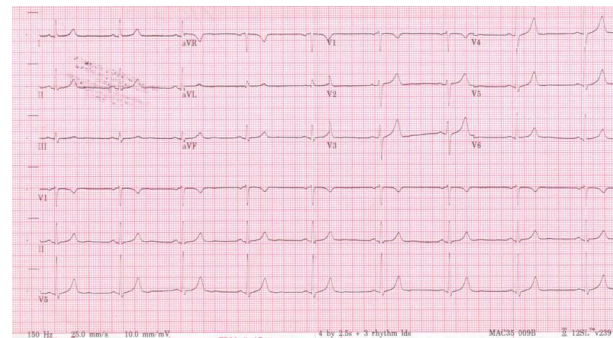


Figure 2 - Electrocardiogram of a female aged 65: sinus bradycardia is suggestive for mild central hypothyroidism due to transfrontal pituitary surgery for a macroprolactinoma (ventricular rate of 52 bpm, PR interval of 144 ms, QRS duration of 90 ms, QT/QTc of 428/398 ms)



Figure 3 - Coronal Plane: Intrasellar mass of 1.2 by 1 cm, and two suprasellar masses in contact with the third ventricle and Willis polygon, and optic chiasma, associating micro-calcifications of 1.6 by 1.2 cm (on the right) and of 1.5 by 1.4 cm (on the left)

Parameter	Patient's value	Normal limits	Units
TSH	0.085*	0.5-4.5	µUI/mL
FT4	14	10.2-22.4	pmol/L
T3	52.8	80-200	ng/dL
TPO	10	0-35	UI/mL
FSH	0.38	16.74-114**	mUI/mL
ACTH	4.55***	3-66	pg/mL
Morning plasma cortisol	1.1***	6.2-19.4	µg/dL
IGF1	24	29-204	ng/mL
Prl	201****	2.74-10.64	ng/mL
GH****	0.05	< 1	ng/mL

\*Under daily morning 100µg of Levothyroxine therapy;  
 \*\* Consistent with physiological menopause (according to the patient's age) \*\*\* 3 days after stopping daily therapy with prednisone 5 mg \*\*\*\* Nadir of GH during OGTT (75 g Oral Glucose Tolerance Test)

Table 1 - The endocrine parameters 13 years after transcranial hypophysectomy in a 65-year-old female with prolactinoma

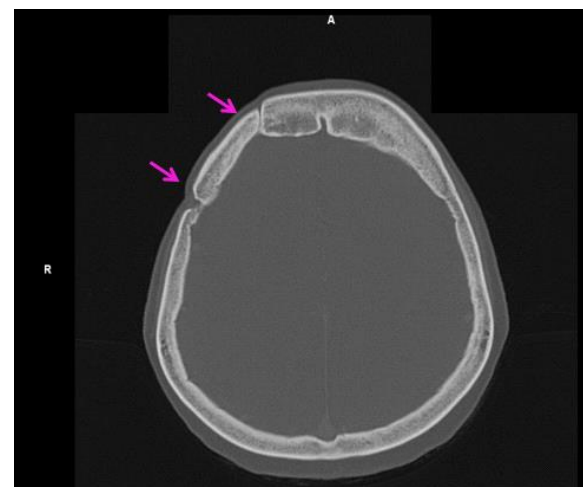


Figure 4 - IV Contrast MRI performed preoperatively on a 28-year-old male: Intrasellar tumor of 2 by 2 cm with extension to the right cavernous sinus, contacting with the optic chiasma.

## Case report 2

### *Medical and surgical history*

A 29-year-old non-smoking male, with irrelevant medical family history, is known with chronic B hepatitis under antiviral therapy.

At the age of 28 he was admitted in a Romanian Neurosurgery Center for severe frontal and occipital headache, dizziness, photophobia, multiple episodes of vomiting, and low blood pressure. The endocrine evaluation revealed high levels of prolactin, central adrenal insufficiency, and also central hypothyroidism (Table 2). CT scan performed in emergency revealed a tumor mass at the level of sella turcica with a possible intra-lesion hemorrhagic area. Analgesic, antiemetic drugs, volume depletion treatment, and IV hydrocortisone were administered. In addition, Magnetic Resonance Imagery (MRI) with IV contrast was performed and an intrasellar tumor mass of 2 by 2 cm with extension to the right cavernous sinus, optic chiasm, and pituitary stalk was discovered (Figure 5,6). The transcranial approach was performed through a right approach. No complications were reported intra or postoperatively. IV hydrocortisone which was initiated preoperatively was continued during and after the procedure.

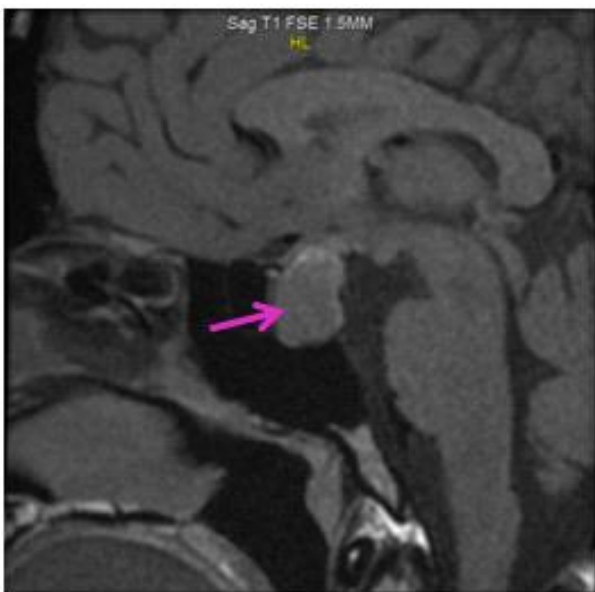


Figure 5 - IV Contrast MRI performed preoperatively on a 28-year-old male: Intrasellar tumor of 2 by 2 cm with extension to the right cavernous sinus, contacting with the optic chiasma - Sagittal Plane

The pathological report revealed a pituitary adenoma with intense cellular pleomorphism, eosinophilic cytoplasm, clear cell limits, and rare atypical mitosis, consistent with a macroprolactinoma in association with hormonal panel. The subjects was hospitalized for 12 days and, after discharge, he was treated with daily 10 mg prednisone, 50 µg of daily LT4 and 1 mg of cabergoline twice per week.

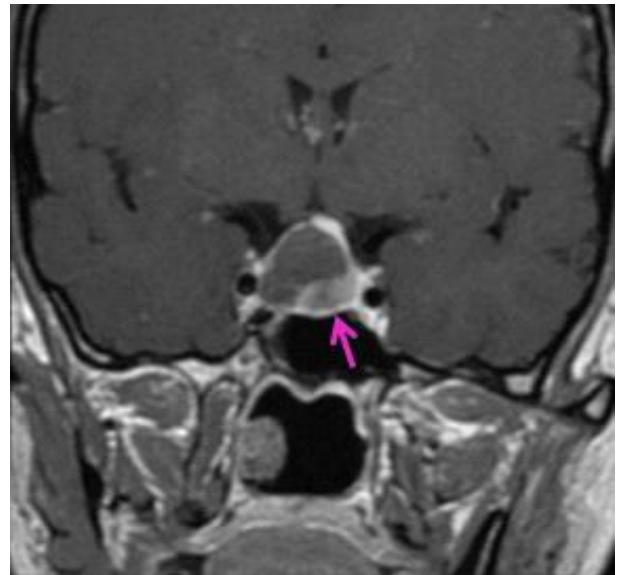


Figure 6 - Coronal Plane



Figura 7 - IV Contrast MRI performed 3 months after transfrontal pituitary surgery: area of bleeding at the site of transcranial incision.

Follow-up

After surgery, the first hormonal tests were performed after 3 months and they revealed normal levels of cortisol and prolactin of 11.8ng/mL (normal adequate limits between 1.8-17 ng/mL) with low FT4 under adrenal and thyroid substitution together with dopamine agonist. Therefore the same dose of cabergoline was maintained, and levothyroxine was increased to 75 µg daily while prednisone was changed to hydrocortisone 10 mg per day. MRI performed at that time revealed a small area of bleeding at the site of the transcranial incision which remitted within weeks (Figure 7). 6 months after surgery the clinical exam, blood ionogram, and hormonal profile showed adequate control of thyroid and adrenal function, and normal serum prolactin. Central hypogonadism has been ruled out by registering normal testosterone and FSH under cabergoline (Table 2). The eye exam showed left hemianopsia which was similar with the aspect immediately after the surgical procedure (Figure 8). Cerebral MRI contrast was performed and a cystic sellar lesion of 1.5 by 0.9 by 0.8 cm was revealed without any residual solid tumor mass (consistent with tumor necrosis) (Figure 9, 10).

of the adrenal insufficiency hydrocortisone therapy was discontinued and the patient was further treated with 75 µg of daily LT4 and 1 mg cabergoline twice per week. 12 months after the pituitary surgery, normal prolactin and freeT4 were registered under therapy as well as the other pituitary hormones. Further close surveillance is recommended.

Parameter	Pre-operative	Months after surgery			Normal limits	Units
		3	6	12		
<b>Prl</b>	165	11.8 *	10.6 *	8.82 *	1.8-17	ng/mL
<b>TSH</b>	0.29	0.37 **	0.789 **	0.18 **	0.4-4	µUI/mL
<b>FT4</b>	0.86 **	0.88 **	1.16 **	1.70 **	0.89-1.76	ng/dL
<b>Morning plasma cortisol</b>	0.80	10.6	11.8	12	5-25	µg/dL
<b>Testosterone</b>	NA ***	4.6	6.76	7.4	1.8-9	ng/mL
<b>FSH</b>	NA ***	4.3	7.8	6.8	1-11.5	U/L
<b>LH</b>	NA ***	3.4	4.5	5	0.8-7.6	U/L

\*under oral cabergoline; \*\*under daily levothyroxine; \*\*\*not available

Table 2 - The endocrine parameters of a male patient diagnosed (at the age of 28) and treated for macroprolactinoma: before and after transfrontal pituitary surgery

No re-intervention was considered by the neurosurgical examination. Since the remission

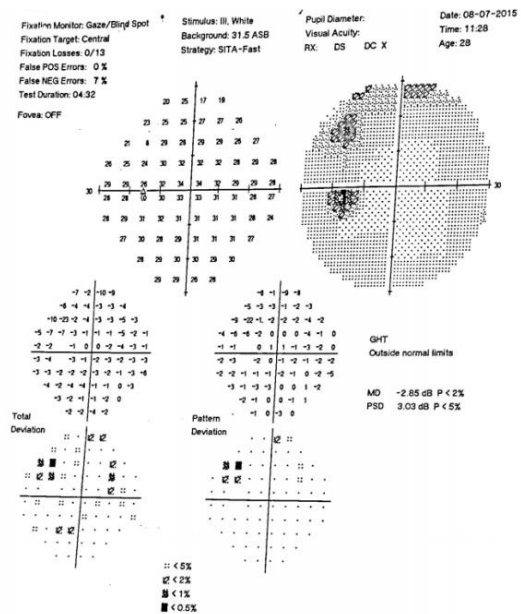


Figure 8 - Eye field assessment 6 months after transcranial pituitary surgery for a large prolactin-producing mass in a 28-year-old male patient: left hemianopsia



Figure 9 - Cerebral MRI contrast performed 6 months after pituitary surgery for a large prolactin-producing mass on a 28-year-old male patient: intrasellar cystic lesion of 1.5 by 0.9 by 0.8 cm without any residual tumor mass - Sagittal Plane

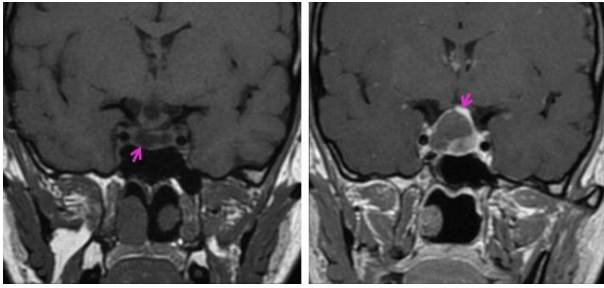


Figure 10 - Coronal Plane

## Discussions

The female case presents the data we obtained after more than a decade since the transcranial pituitary surgery. The male case has a medical and surgical history of more than 1 year. Generally, the macroprolactinomas have a good prognosis despite surgery and the need of lifelong medication as dopamine agonists.

The first case introduces the idea that the diagnosis of prolactinoma was missed prior to surgery and also for the first 13 years after surgery despite sustained high values of prolactin. At first admission, surgery was necessary as a first line option because of the anatomical profile and not because of the endocrine secretor pattern. Also, the second case needs surgery due to local compression.

Currently, the female subject has imagery of the pituitary-hypothalamic area with rather bizarre aspects pointing 3 tumors of around 1 cm. The skull anomalies due to the transfrontal procedure are still seen as pointed on figure 3.

Generally, a pituitary mass may associate a high prolactin due to direct production by a prolactinoma (as seen in both cases) or a somatotropinoma and due to the stalk effects and consecutive inhibition of dopamine (5,13). Secondary amenorrhea was registered at the age of 38; it is difficult to establish the correlation with the tumor but this is possible. Extremely elevated levels of prolactin need to be correlated with different confounding factors as seen in the hook effect or macro-prolactinemia (and prolactin assay after Polyethylen Glycol or PEG is used to avoid this in daily practice) (14,15).

The complete cystic transformation due to necrosis (as seen on the second case) may be caused entirely by cabergoline but some effects of the surgical approach might actually be registered.

## Conclusions

Transcranial pituitary surgery represents an option in selected cases displaying large prolactin producing tumors. After surgery, a good outcome is expected despite secondary eye field defects or pituitary insufficiency which needs medication. The presence of a residual tumor requires long term specific therapy with dopamine agonists.

## List of abbreviations

cm = centimeter  
 IV=intravenous  
 mg = miligrams  
 FT4 = free Levothyroxine  
 LT4 = levothyroxine  
 IGF1 = Insulin-like Growth Hormone -1  
 FSH = Follicle Stimulant Hormone  
 TSH = Thyroid Stimulating Hormone  
 CT = computed tomography  
 MRI = Magnetic Resonance Imagery  
 µg = micrograms

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