

Ref: Ro J Med Pract. 2020;15(4)  
DOI: 10.37897/RJMP.2020.4.16

# When neurosurgery is not an option...

Ana VALEA<sup>1,2</sup>, Andra MORAR<sup>3</sup>, Eugenia PETROVA<sup>4,5</sup>, Nicoleta DUMITRU<sup>4</sup>, Claudiu TUPEA<sup>4</sup>,  
Mihaela POPESCU<sup>6</sup>, Adina GHEMIGIAN<sup>4,5</sup>, Mara CARSOLE<sup>4,5</sup>

<sup>1</sup> County Clinical Emergency Hospital, Cluj-Napoca, Romania

<sup>2</sup> "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

<sup>3</sup> "Leon Daniello" Clinical Pneumophysiology Hospital, Cluj-Napoca, Romania

<sup>4</sup> "C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania

<sup>5</sup> "C. Davila" University of Medicine and Pharmacy, Bucharest, Romania

<sup>6</sup> University of Medicine and Pharmacy, Craiova, Romania

## ABSTRACT

**Introduction.** As opposed to secreting tumours, non-functioning pituitary adenomas are usually diagnosed at a later stage, when they are large enough to cause symptoms due to mass effect rather than because their associated endocrine dysfunction. We aim to introduce a case report with limited therapy options.

**Case presentation.** We present the case of a 69 year-old male patient with a history of stroke, atrial fibrillation and type 2 diabetes, who was initially admitted to the neurology department three years ago for frontal headaches and visual disturbances. The MRI (magnetic resonance imaging) exam revealed a 15.4/26.7/19.5 mm sellar mass, with suprasellar and parasellar extension, minimal optic chiasm compression and pituitary stalk deviation. Initial pituitary hormone profile showed central hypogonadism and mild hyperprolactinemia. The patient underwent neurosurgery evaluation but at that point transsphenoidal surgery was contraindicated due to severe cardiovascular comorbidities and the patient was referred to the endocrinology department for further follow-up, where he presented a year later, after worsening of symptoms. The MRI revealed tumour enlargement (18.5/28/24.6 mm) and stationary hormonal profile. The diagnosis of nonfunctioning pituitary macroadenoma was once again confirmed, cabergoline was initiated as adjuvant therapy since surgery was still contraindicated because high cardiovascular risk. Stereotactic radiation was not an option due to tumour proximity to the optic chiasm, therefore the patient underwent conventional radiotherapy. Evaluation after 3 months showed stationary clinical picture while MRI scan 3 months revealed a mild tumour growth (4 mm in all diameters). Further cabergoline therapy 2 mg/week was prescribed and the patient needs careful monitorization for worsening of symptoms and hypopituitarism.

**Conclusion.** Surgery is the mainstay of therapy in case of large nonfunctioning pituitary macroadenomas. If contraindicated, the available options include radiotherapy and medical therapy like cabergoline, with varying results, mostly suboptimal.

**Keywords:** pituitary tumour, prolactin, hypophysectomy, radiotherapy

## INTRODUCTION

The vast majority of sellar region masses are represented by pituitary adenomas which are detected

based on endocrine profile, local mass effects or they are incidentally found (1,2,3). Their overall prevalence is difficult to establish, due to the small size of most tumours, with absent or nonspecific symptoms, but au-

Corresponding authors:

Mara Carsote

E-mail: carsote\_m@hotmail.com

topsy and radiologic studies suggest it is around 10 up to 16.7% depending on the study, probably not on an age-related incidence as seen in adrenal non-functioning adenomas (4,5,6).

Approximately 65-70% of pituitary adenomas secrete an excess amount of hormones, such as prolactin (PRL), growth hormone (GH) causing acromegaly, thyroid-stimulating hormone (TSH) or corticotropin (ACTH) causing Cushing's disease, whereas 25 to 35% are clinically nonfunctioning or „silent” (7,8,9). Of these last mentioned, up to 90% are gonadotroph-cell adenomas, as proven by immunocytochemistry, but they are difficult to identify preoperatively due to low/absent clinically manifested secretory profile (10).

As opposed to secreting tumours, which are usually diagnosed earlier due to specific clinical syndromes mostly related to hormone excess, nonfunctioning pituitary adenomas (NFPAs) are typically diagnosed incidentally or at a later stage, when they are large enough to cause symptoms due to mass effect (central deficiency, not pituitary hormones excess) (2,3,11). The most common presentations include neurologic symptoms (such as visual impairment and headaches), hypopituitarism due to compression of the normal pituitary tissue, as well as the discovery of an incidental sellar mass on a head MRI (magnetic resonance) or CT (computed tomography) scan performed for unrelated pathologies (4,12,13).

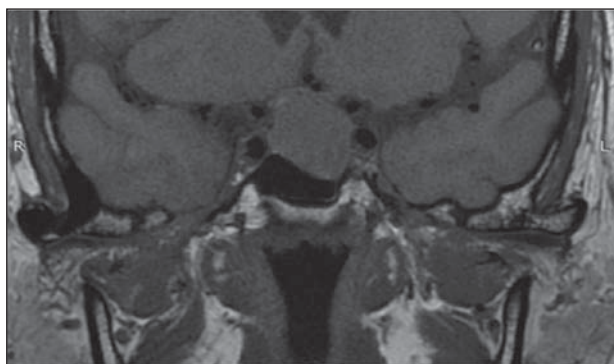
Treatment options and outcome depend on the type and size of the adenoma, as well as the stage in which it is diagnosed but also it depends on general health status of the patient, if a surgical procedure is feasible considering the patient's comorbidities (3,13). For nonfunctioning macroadenomas with mass effect, transsphenoidal surgery remains the first-line treatment as well as for corticotropinoma and somatotropinoma (2,14). Other options include radiotherapy and, to an extent, medical therapy like cabergoline in NFPA, Cushing's disease, acromegaly as seen in prolactinomas but with less efficient effects (15-17).

We aim to present the case of a patient with an invasive, nonfunctioning pituitary macroadenoma, with limited therapeutic options. The patient agreed for anonymously introduce his medical data.

## CASE PRESENTATION

A 67 year-old male patient was initially admitted to the Neurology Department three years ago for frontal headaches accompanied by blurred vision and dizziness. His medical history revealed a stroke with left spastic hemiparesis, type 2 diabetes mellitus, and atrial fibrillation, arterial hypertension with very high cardiovascular risk, bilateral cataracts, psoriasis and total right coxofemoral prosthesis. The head MRI exam re-

vealed a 15.4/26.7/19.5 mm sellar mass, with invasion of the left cavernous sinus, suprasellar extension in the sphenoid sinus, minimal optic chiasm compression and pituitary stalk deviation (Figure 1).



**FIGURE 1.** Magnetic resonance imaging: a 15.4/26.7/19.5 mm pituitary mass, with suprasellar and parasellar extension on a 69 year-old male patient

Initial laboratory tests showed central hypogonadism and mild hyperprolactinemia, with normal IGF-1 (insulin-like growth factor), TSH, FT4 (free thyroxine) and plasma morning cortisol levels. The diagnosis of NFPA was established, but transsphenoidal surgery was contraindicated due to the severe cardiovascular comorbidities, therefore he was referred to the endocrinologist for medical treatment and follow-up. The patient postponed endocrine evaluation one more year, when he was admitted in the Endocrinology Department with progressive worsening of headaches, visual disturbances, asthenia and fatigue. Clinical examination revealed a slightly overweight patient with a BMI (body mass index) of 25.1 kg/m<sup>2</sup>, normal blood pressure) of 110/70 mmHg and heart rate of 72 beats per minute, pale skin, left spastic hemiparesis. The hormonal profile showed persistent mild hyperprolactinemia (of 19.06 ng/ml, normal levels: 2.64-13.2 ng/ml), central hypogonadism (low total testosterone of less than 0.1 ng/mL, normal ranges: 1.68-7.58 ng/ml, FSH (follicle stimulating hormone) of 6.83 mUI/ml, normal levels between 1.27 and 19.3 mUI/ml, LH (luteinizing hormone) of 1.37 U/l, normal: 1.24-8.62 U/l), central hypothyroidism (low FT4 levels of 0.57 ng/dl, normal: 0.61-1.35 ng/dl, with TSH of 2.59 mUI/ml, normal: 0.4-4 mUI/ml), negative anti-thyroid peroxidase and anti-thyroglobulin antibodies, growth hormone deficiency with low IGF-1 levels of 63.3 ng/ml (normal: 69-200 ng/ml) and normal plasma morning cortisol (Table 1).

Diabetes insipidus was excluded. Thyroid ultrasound showed diffuse goitre, with normal echogenicity. Pituitary MRI revealed an enlarged tumour of 28/18.5/24.6 mm, with grade 4 invasion of the left cavernous sinus, grade 1 invasion of the sphenoid sinus and compression of the optic chiasm. The diagnosis of

**TABLE 1.** The endocrine and biochemical parameters of a 69 year-old male patient with nonfunctioning pituitary macroadenoma before radiation therapy

Parameter	Value	Normal range	Units
Testosterone	< 0.1	1.68-7.58	ng/ml
FSH	6.83	1.27-19.3	mU/ml
LH	1.37	1.24-8.62	U/l
PRL	19.06	2.64-13.2	ng/ml
TSH	2.59	0.4-4	mIU/ml
FT4	0.57	0.61-1.35	ng/dl
Morning plasma cortisol	8.37	6-23	mg/dl
IGF-1	63.3	69-200	ng/ml
Anti-TPO	0.65	< 10	U/ml
Anti-TG	< 1	< 4	U/ml
Na <sup>+</sup>	137	136-146	mmol/l
K <sup>+</sup>	4.6	3.5-5.1	mmol/l
Creatinine	0.81	0.67-1.17	mg/dl
Urea	28	17-43	mg/dl
Glycaemia	98	74-106	mg/dl
AST	29	< 50	U/l
ALT	24	< 50	U/l
Serum total calcium	9.61	8.8-10.6	mg/dl
Total cholesterol	172	< 200	mg/dl
Triglycerides	121	< 150	mg/dl
Haemoglobin	14.1	13-17	g/dl

FSH = follicle-stimulating hormone; LH = luteinizing hormone; PRL = prolactin; TSH = thyroid stimulating hormone; FT4 = free thyroxine; IGF-1 = insulin-like growth factor 1; Anti-TPO = anti-thyroid peroxidase antibodies; Anti-TG = anti-thyroglobulin antibodies; Na<sup>+</sup> = blood sodium; K<sup>+</sup> = blood potassium; UD = urinary density; ALT = alanine aminotransferase; AST = aspartate aminotransferase

NFPA with suprasellar and parasellar extension was confirmed, as well as hypopituitarism on multiple lines - somatotropin, gonadotropin and thyrotropin deficiency in addition to functional hyperprolactinemia and diffuse goitre. Since surgical contraindications were maintained based on cardiology and anaesthesiology assessment, radiation therapy was recommended and the patient was prescribed hormone replacement therapy with levothyroxine 25 mg/day (he refused testosterone therapy), as well as cabergoline 0.5 mg/week initially, increased to 2 mg/week for adjuvant shrinkage effect. Due to tumour proximity to the optic chiasm, the patient underwent conventional fractionated radiotherapy, with a total dose of 50.4 Gy administered in 28 fractions within 39 days. Endocrine follow-up at 3 months after ending the radiotherapy procedures showed adequate levothyroxine replacement while the pituitary MRI showed tumour expansion of about 4 mm in all diameters. Cabergoline therapy was re-started gradually increasing the dose to 2 mg/week, with the goal of preventing further tumour growth. The MRI performed 14 months after radiotherapy showed a significant reduction in tumour size of

18.5/16/12.3 mm, lower grade parasellar and suprasellar invasion, without optic chiasm compression. Clinical symptoms also improved and there was no worsening of hypopituitarism. The patient continued levothyroxine therapy and cabergoline 2 mg/week with periodic monitoring.

## DISCUSSIONS

Transsphenoidal surgery is the first-line treatment in case of NFPA that cause neurological symptoms (1). It has been shown to improve vision in 80% of cases, but complete removal of the tumour is only achieved in about 20% of patients in cases with macroadenomas (18,19). In patients with large tumour remnants, neurosurgery is usually followed by radiation therapy since recurrence rates are high (1,18,19). The main goal of radiation therapy is to prevent further tumour growth, but studies have shown partial shrinkage and, rarely, complete resolution, in up to two thirds of cases over time (20,21). Radiation therapy is not a first-line treatment option, because effects occur gradually, within months to years (18,20). In our patient's case, due to surgical contraindications, primary radiation therapy was employed and partial resolution of neurological symptoms as well as tumour shrinkage occurred within first 14 months. Stereotactic radiation is the main choice, unless contraindicated, due to fewer side effects (1,18,19). These include occurrence or worsening of hypopituitarism, and more rarely optic pathway or cranial nerve injury, secondary tumours or stroke (1,18,19). Because of tumour localization, conventional fractionated radiotherapy was the only option for our patient but without further complications after 14 months. Some studies also report a small increase in tumor size in the first 6 months after radiotherapy, probably due to cytotoxic effect, that usually resolves during follow-up (22). This also occurred in our patient's case.

To date no medication has been shown to consistently and significantly reduce the size of NFPA except for dopamine agonists to some extent (23). Many studies focused on cabergoline, since most NFPA express dopamine receptors, mainly dopamine receptor 2 (23,24). Greenman et al. found that dopamine agonist treatment, especially with cabergoline, is associated with decreased prevalence of residual tumour enlargement after transsphenoidal surgery (25). In our patient's case, cabergoline was added after conventional radiation therapy and the combined treatment led to significant tumour shrinkage after 14 months. Other aspects of the present case include the large panel of severe cardiovascular and metabolic complications that did not allow the neurosurgical procedure like type 2 complicated diabetes mellitus, arterial hyper-

tension, history of stroke and chronic atrial fibrillation. High blood pressure may be caused by endocrine condition like thyrotoxicosis but also by adrenal and pituitary tumours at any age, but not necessarily NFPA (26,27). Unsubstituted hypogonadism may also cause osteoporosis (we did not have the circumstances that led to previous hip prosthesis) in association with diabetes mellitus (28-30). NFPA causes bone loss due to pituitary hormones deficiencies while secretor tumours at the same level causes increased fracture risk because of hormone excess like prolactinoma, acromegaly, Cushing's disease (31-33).

## CONCLUSIONS

Surgery is the mainstay of therapy in case of non-functioning pituitary macroadenomas causing neurological symptoms or pituitary hormones deficiency, with the best therapeutic results. It is often followed by adjuvant stereotactic radiation therapy. In some cases, patient characteristics and comorbidities preclude from choosing the first-line therapy, and the challenge lies in combining second-line options such as conventional radiation and medical therapy like cabergoline in order to obtain an optimal outcome.

## REFERENCES

- Saeger W, Lüdecke DK, Buchfelder M, Fahlbusch R, Quabbe HJ, Petersenn S. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. *Eur J Endocrinol.* 2007;156(2):203-216.
- Gheorghisan-Galateanu AA, Carsote C, Valea A. Incidentaloma: from general practice to specific endocrine frame. *JPMA. The Journal of the Pakistan Medical Association.* 2017; 67(6):917-922.
- Carsote M, Chirita C, Dumitrascu A, Hortopan D, Fica S, Poiana C. Pituitary incidentalomas-how often is too often?. *Journal of Medicine and Life.* 2009; 2(1):92-97.
- Ezzat S, Asa S, Couldwell W, Barr C, Dodge W, Vance ML, McCutcheon IE. The prevalence of pituitary adenomas: a systematic review. *Cancer.* 2004; 101(3):613-619.
- Gheorghiu ML, Hortopan D, Dumitrascu A, Carageorghieopol A, Stefanescu A, Trifanescu R, Niculescu D, Baciuc I, Carsote M, Poiana C, Badiu C, Coculescu M. Age-related endocrine tumors: Non-functioning adrenal tumors as compared to pituitary adenomas. *Acta Endocrinologica (Bucharest).* 2009;5(3):371-383.
- Valea A, Carsote M, Ghemigian A, Dumitrache C. Pituitary macroadenoma and thyroid autoimmunity: cross-sectional observations in adult population. *Current Health Sciences Journal.* 2016; 42(S5):50-53.
- Valea A, Carsote M, Ghervan C, Georgescu C. Glycemic profile in patients with acromegaly treated with somatostatin analogue. *Journal of Medicine and Life.* 2015;8(Spec Issue):82-6.
- Valea A, Ghervan C, Carsote M, Morar A, Iacob I, Tomesc F, Pop DD, Georgescu C. Effects of combination therapy: somatostatin analogues and dopamine agonists on GH and IGF1 levels in acromegaly. *Clujul Medical.* 2015;88(3):310-17.
- Valea A, Ghervan C, Carsote M, Albu SE, Georgescu CE. Different surgical options in Cushing's disease. *Journal of Surgical Sciences.* 2016;3(1):39-40.
- Chaidarun SS, Klibanski A. Gonadotropinomas. *Semin Reprod Med.* 2002; 20(4):339-348.
- Poiana C, Chirita C, Carsote M, Hortopan H, Ioachim D, Corneci CM, Stanescu B. Adrenal and pituitary incidentalomas in a case of Cushing's syndrome. *Chirurgia (Bucharest).* 2013;1990:108(6):886-891.
- Molitch ME. Nonfunctioning pituitary tumors and pituitary incidentalomas. *Endocrinol Metab Clin North Am.* 2008; 37(1):151-171.
- Valea A, Morar A, Dumitru DP, Carsote M, Ghemigian A, Dumitrache C. Infertility as the onset of Cushing's disease: is pasireotide a treatment option? *Ars Medica Tomitana.* 2015;21(3):128-31.
- Valea A, Carsote M, Terzea D, Ghemigian A. Timing of surgical approach on patients with somatotropinoma and differentiated thyroid cancer. *Journal of Surgical Sciences* 2016;3(3):148-52.
- Ghemigian A, Carsote M, Ghervan C, Dumitrascu A, Albu SE, Georgescu CE, Valea A. Long-term follow-up after transcranial hypophysectomy in macroprolactinomas. *Journal of Surgical Sciences.* 2016;3(1):44-50.
- Giraldi EA, Ioachimescu AG. The Role of Dopamine Agonists in Pituitary Adenomas. *Endocrinol Metab Clin North Am.* 2020; 49(3):453-474.
- Poiana C, Chirita C, Carsote M, Hortopan D, Goldstein A. Galactoceles and prolactinoma – A pathogenic association? *Maturitas.* 2009; 62(1):98-102.
- Dekkers OM, Pereira AM, Romijn JA. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas. *J Clin Endocrinol Metab.* 2008; 93(10):3717-3726.
- Murad MH, Fernández-Balsells MM, Barwise A, Gallegos-Orozco JF, Paul A, Lane MA, Lampropoulos JF, Natividad I, Perestelo-Pérez L, Ponce de León-Lovatón PG, Albuquerque FN, Carey J, Erwin PJ, Montori VM. Outcomes of surgical treatment for nonfunctioning pituitary adenomas: a systematic review and meta-analysis. *Clin Endocrinol (Oxf).* 2010;73(6):777-91.
- Pollock BE, Cochran J, Natt N, Brown PD, Erickson D, Link MJ, Garces YI, Foote RL, Stafford SL, Schomberg PJ. Gamma knife radiosurgery for patients with nonfunctioning pituitary adenomas: results from a 15-year experience. *Int J Radiat Oncol Biol Phys.* 2008;70(5):1325-1329.
- Mingione V, Chun PY, Vance ML, Steiner M, Sheehan J, Laws ER, Steiner L. Gamma surgery in the treatment of nonsecretory pituitary macroadenoma. *J Neurosurg.* 2006;104(6):876-883.
- Tung GA, Noren G, Rogg JM, Jackson IMD. MR imaging of pituitary adenomas after gamma knife stereotactic radiosurgery. *Am Roentgen Ray Soc.* 2001;177(4):919-924.
- Pivonello R, Matrone C, Filippella M, Cavallo LM, Di Somma C, Cappabianca P, Colao A, Annunziato L, Lombardi G. Dopamine receptor expression and function in clinically nonfunctioning pituitary tumors: comparison with the effectiveness of cabergoline treatment. *Clin Endocrinol Metab.* 2004; 89(4):1674-83.
- Gabalec F, Beranek M, Netuka D, Masopust V, Nahlovsky J, Cesak T, Marek J, Cap J. Dopamine 2 receptor expression in various pathological types of clinically non-functioning pituitary adenomas. *Pituitary.* 2012;15:222-226.
- Greenman Y, Cooper O, Yaish I, Robenshtok E, Sagiv N, Jonas-Kimchi T, Yuan X, Gertych A, Shimon I, Ram Z, Melmed S, Stern N. Treatment of clinically nonfunctioning pituitary adenomas with dopamine agonists. *Eur J Endocrinol.* 2016;175(1):63-72.
- Carsote M, Ghemigian A, Terzea D, Gheorghisan-Galateanu AA, Valea A. Cystic adrenal lesions: focus on pediatric population (a review). *Clujul Medical.* 2017;90(1):5-12.
- Trifanescu R, Danculescu Miulescu R, Carsote M, Poiana C. Hypokalemic periodic paralysis as first sign of thyrotoxicosis. *J Med Life.* 2013;15:6(1):72-75.

28. Radu L, Carsote M, Gheorghisan-Galateanu AA, Preda SA, Calborean V, Stanescu R, Gheorman V, Albulescu DM. Blood Parathyrin and Mineral Metabolism Dynamics A clinical analyze. *Rev Chim. (Bucharest)*. 2018;69(10):2754-8.
29. Carsote M, Radoi V, Geleriu A, Mihai A, Ferechide S, Opris D, Paun D, Poiana C. The serotonin and the bone assessment. *Journal of Medicine and Life*. 2013; 6(2):151-155.
30. Carsote M, Preda SA, Mitroi M, Camen A, Radu L. Serum Osteocalcin, P1NP, Alkaline Phosphase, and CrossLaps in Humans: the relationship with body mass index. *Rev Chim. (Bucharest)*. 2019;70(5):1615-1618.
31. Valea A, Turturea R, Botezan O, Carsote M, Ghemigian A, Georgescu CE. Management of recrent postoperative Cushing's disease. *Journal of Surgical Sciences*. 2018; 5(3):170-174.
32. Ghemigian A, Cocolos A, Neagu P, Petrova E, Dumitru N, Albu SE, Carsote M. Cushing's disease – same condition, different scenarios. *Archives of the Balkan Medical Union*. 2018;53(1):135-139.
33. Carsote M, Ghemigian A, Valea A, Dumitrascu A. Acromegaly – related osteoporosis. *Romanian Journal of Clinical Research*. 2018;1(1):27-30.