CLINCAL CASE

COMPLICATIONS OF NONFUNCTIONING PITUITARY MACROADENOMA REQUIRING SURGERY

B. Socea[1,2], Roxana Turturea[3], Andra Morar[4], Cristina Moldovan[3], Alexandra Bolocan[2,5], Oana Botezan[3], Alexandra Ene[3], Mara Carsote[7], Ana Valea[3,7]

[1]Clinical Emergency Hospital "Sf. Pantelimon", Bucharest, Romania
[2]The University of Medicine and Pharmacy Carol Davila, Bucharest, Romania
[3]County Clinical Hospital, Cluj-Napoca, Romania
[4]Clinical Hospital of Infectious Diseases, Cluj-Napoca, Romania
[5]Emergency University Hospital of Bucharest, Romania
[6]C.I. Parhon National Institute of Endocrinology, Bucharest, Romania
[7]I. Hatieganu University of Medicine and Pharmacy &County Clinical Hospital, Cluj-Napoca, Romania

Corresponding author: Mara Carsote
E-mail: carsote_m@hotmail.com

Abstract

Hypopituitarism is the main complication of nonfunctioning pituitary macroadenomas. A 64-year-old patient was admitted for marked asthenia, generalized muscle contractions, acroparesthesia and lumbar pain. Clinical examination revealed grade I obesity, discrete eyelid edema, negative Chwosteckand Trousseau signs. Hormonal profile showed the presence of somathotropic pituitary insufficiency, low testosterone levels (of 1.3 ng/mL, normal: 1.68-7.58ng/mL), gonadotropin and prolactin levels within the normal range, normal values for TSH (Thyroid Stimulated Hormone) and FT4 (Free Thyroxine). On admission, low serum and urinary cortisol values were obtained, with an appropriate response after the Synacthen test. The MRI (Magnetic Resonance Investigation) examination revealed a pituitary macroadenoma of 20/21/21 mm, compressing the optic chiasm and thalamus, with bilateral 180-degree involvement of the internal carotid artery. The ophthalmological examination described a lower scotoma in the left eye, without amputation of the visual field. Thyroid and glucocorticoid hormone replacement therapy was recommended, along with neurosurgical intervention. In pituitary macroadenomas, the close proximity to the optic chiasm and carotid arteries limits the curative therapeutic potential and increases the risk of postoperative complications.

Keywords*: macroadenoma, pituitary, hypopituitarism.*

Introduction

In the majority of cases, nonfunctioning pituitary adenomas (NFPA) are benign tumors of the endocrine system [1,2].

Approximately 25-33 % of pituitary gland tumors are represented by NFPAs, making them the most common of these tumors [3,4]. By the time they are diagnosed, most NFPAs are larger than 1 cm and require treatment because of the high probability of causing mass effect and hypopituitarism [3-5]. If there are visual field defects, mass effects or hypopituitarism, current guidelines recommend surgical intervention as first-line treatment, with an endoscopic resection of the tumour, using the transsphenoidal approach [2,6].

Case presentation

A 64-year-old non-smoking male patient was admitted eight months ago for marked asthenia, generalized muscle contractions, acroparesthesia and lumbar pain. His medical history mentioned primary hypothyroidism, high blood pressure, aseptic necrosis of the femoral head, renal microlithiasis and hypertriglyceridemia.

Clinical examination revealed grade I obesity with a BMI (body mass index) of 32.65 kg/m2, moderately high blood pressure of 145/85 mmHg.heart rate of 72bpm, discrete eyelid edema, negative Chwosteck and Trousseau signs.

Parameter	Value	Normal limits	Units
IGF-1	60.1	75-212	ng/mL
Plasma Cortisol	0.72	6-23	µg/dL
Urinary Cortisol	28	50-190	⌈g/24h
TSH	*1.02	0.4-4	⌈UI/mL
FT4	*0.76	0.61-1.35	ng/dL
PRL	5.20	2.64-13.2	ng/mL
FSH	5.73	1.27-19.3	UI/mL
LH	1.81	1.24-8.62	UI/mL
Testosterone	1.30	1.68-7.58	ng/mL
Glycemia	85	74-106	mg/dL
Cholesterol	245	<200	mg/dL
Triglycerides	243	<150	mg/dL
Creatine phosphokinase	200	<171	U/L
Iron	63	70-180	µg/dL
Hemoglobin	12.4	13-17	g/dL
Hematocrit	34.8	40-54	%

Table 1 - The preoperative endocrine and biochemical parameters of a 64-year-old man diagnosed with pituitary macroadenoma. IGF-1=Insulin-like Growth Factor 1; TSH=Thyroid Stimulating Hormone; FT4=Free Thyroxine ; PRL= prolactin; FSH=Follicle-Stimulating Hormone; LH=Luteinizing Hormone; * 75 µg/day Levothyroxine therapy.

Hormonal profile revealed the presence of pituitary insufficiency: IGF1 (Insulin-like Growth Factor 1) of 60.1 ng/mL (normal: 75-212ng/mL), low testosterone (of 1.3 ng/mL, normal: 1.68-7.58ng/mL), normal levels of gonadotropins and prolactin, low serum and urinary cortisol (Table 1). The Synacthen test was performed, confirming the central origin of glucocorticoid deficiency by showing a more than 4-fold increase of the basal value of serum cortisol (5.09µg/dL 45 min after Synacthen injection versus a basal cortisol level of 0.72µg/dL). Thyroid function tests revealed normal TSH and FT4levels under levothyroxine replacement therapy (75µg per day). Biochemical workup showed iron deficiency anaemia, high cholesterol, triglycerides and creatine phosphokinase levels (Table 1). The MRI examination revealed a pituitary macroadenoma of 20/21/21 mm, compressing the optic chiasm and thalamus, with bilateral 180-degree involvement of the internal carotid artery (Figure 1).

The ophthalmologic examination described a lower scotoma in the left eye, without amputation of the visual field. Neurosurgical intervention was recommended along with thyroid and glucocorticoid hormone replacement therapy, as well as specific therapy for associated conditions.

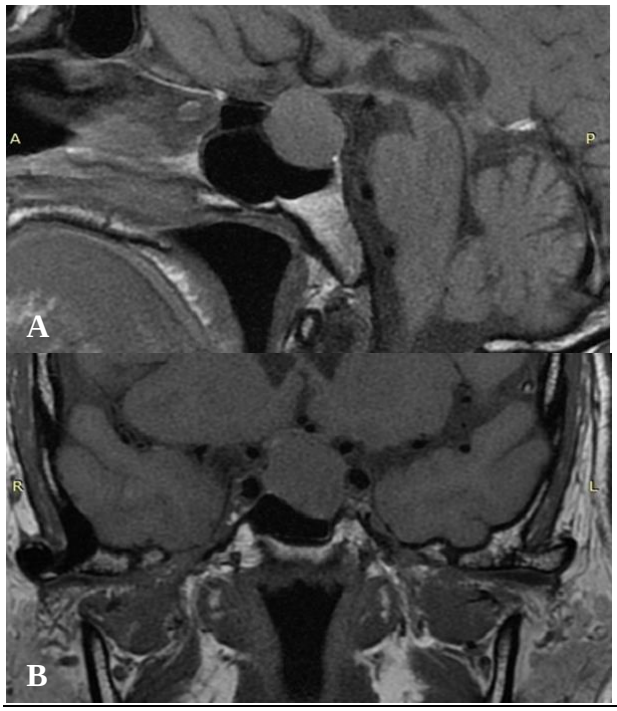

Figure 1 - Preoperative contrast-enhanced pituitary MRI of a 64-year-old man: pituitary macroadenoma of 20/21/21mm. A: Sagital plane, B: Coronal plane.

Discussions

In clinical practice, NFPAs comprise about 80 % of all pituitary macroadenomas [3]. Because of the lack of an identifiable syndrome

of pituitary hormone hypersecretion, it can be hard to diagnose a nonfunctioning adenoma, allowing it to grow over the years and become amacroadenoma [5].

Overall, at least one pituitary hormone insufficiency can be found in these patients' history [6].

Immunohistochemistry results nowadays show that in the majority of cases clinically nonfunctioning adenomas consist of cells staining positive for pituitary hormones, whereas 20–40%of adenoma cells are immunohistochemically negative [3,4,5]. Up to 65% of clinically nonfunctioning adenomas are positive for gonadotropins and about 10% stain positive for corticotroph cells. Positive imunohistochemistry is rare for somatotroph, thyrotroph and lactotrophe cells [7,8,9]. In our patient's casewe do not have information about the histological type of the tumor because surgery has not been performed yet.

The positive diagnosis of a pituitary adenoma should differentiate it from other brain or intracranial tumours such as cranio-pharyngioma, meningioma, glioma, bilateral tilted disc syndrome, optic nerve coloboma, nasal retinoschisis, nasal retinitis pigmentosa and masquerade syndromes (chronic retrobulbar optic neuritis, nutritional amblyopia, uncorrected refractive error, normal tension glaucoma and age‐related maculopathy) [10]. In this case the information provided by the hormonal profile, the ophthalmologic examination and the MRI examination allowed the diagnosis of nonfunctioning pituitary macroadenoma.

With the main cause of symptomatology being the mass effect on surrounding elements, the main complaints are visual field defects with or without decreased visual acuity, unspecified headache and the consequences of hypopituitarism [11-14]. In the present case, the absence of headache and opto-chiasmatic syndrome explains the delayed diagnosis, in the pituitary insufficiency stage.

The pituitary surgery is not required in majority of pituitary tumours since they are incidentalomas or prolactinomas but neoplasia with a larger diameter than 1 cm usually are referred to neurosurgery [15]. Incidental findings in endocrine glands especially pituitary gland and adrenals are usually harmless unless rare situations as the present case when they are large masses with local effects, of either solid, cystic or mix consistence [15]. Currently the diagnosis of incidental finding including in endocrinology is more frequent due to the large access to imaging scans like ultrasound, computed tomography or magnetic resonance imagery [15]. For practitioners in endocrinology field an incidentaloma must be non-secretor, not only accidentally detected [15]. The classical incidentalomas of hypophysis and adrenal glands are actually less frequent than thyroid incidentaloma but the preferred term is thyroid nodule [15,16].

On the other hand, pituitary surgery for non-functioning macroadenomas represents a challenge as seen here since irreversible neurological and endocrine complications are pre-operatory detected [17-20]. Unfortunately, in these cases with negative secretor profile the adjuvant medical therapy for tumour growth is lacking opposite to secretor adenomas as seen in acromegaly or Cushing's disease where endocrine specific therapy is still an option, even not the first line of approach which is still neurosurgery [21,22]. The medical therapy associated to these mentioned conditions is based on somatostatin analogues like octreotide, lanreotide or pasireotide or growth hormone blockers like pegvisomant for acromegaly [21,22]. There still a medical therapy with a low rate of response in acromegaly or even in Cushing' s disease (up to 25% rate of response) which also been used in non-functioning pituitary macroadenoma like dopamine agonists bromocriptine or cabergoline (which is actually the specific first line therapy in prolactinomas) [23-26]. However, the use of cabergoline in non-functioning tumours is limited to certain cases with relapse of the tumour but associating a mild clinical picture which does not indicate re-intervention since only 10-25% of cases display some level of response to cabergoline [23-26].

Conclusion

In pituitary macroadenomas, the close anatomical relationship with the optic chiasm and carotid arteries limits the curative therapeutic potential and increases the risk of postoperative complications. Some of the possible complications may resolve in time, but there are

complications that can persist and will need lifelong treatment and surveillance.

Acknowledgements: There in no conflict of interest. We thank the patient for his consent.

References

[1]The pituitary society. Viewed April 27, 2015. http://www.pituitarysociety.org.
[2]M.H. Murad, M.M. Fernández-Balsells, A. Barwise, J.F. Gallegos-Orozco, A. Paul, M.A. Lane, et al. Outcomes of surgical treatment for nonfunctioning pituitary adenomas: a systematic review and meta-analysis, ClinEndicrinol (Oxf) 2010;73:777–91.
[3]S. Saunders, J.P. Vora. Endocrine evaluation of pituitary tumours, Br J Neurosurg 2008;22(4):602–8.
[4]Y. Chen, C.D. Wang, Z.P. Su, Y.X. Chen, L. Cai, Q.C. Zhuge, Z.B. Wu. Natural history of postoperative nonfunctioning pituitary adenomas: a systematic review and meta-analysis, Neuroendocrinology 2012;96:333–42.
[5]C.A. Jaffe. Clinically non-functioning pituitary adenoma, Pituitary 2006;9:317–21.
[6]O.M. Dekkers, A.M. Pereira, J.A. Romijn. Treatment and follow-up of clinically nonfunctioning pituitary macroadenomas, J ClinEndocrinolMetab 2008;93(10):3717–26.
[7]D. Zhao, Y. Tomono, K. Tsuboi, T. Nose. Immunohistochemical and ultrastructural study of clinically nonfunctioning pituitary adenomas, Neurol Med Chir (Tokyo) 2000: 40453-456.
[8]R. Loch Batista, E. Barbosa Trarbach, M. Diniz Marques, V. Angelo Cescato, G. Ochmanda Silva, G. Clarissa,et al. Nonfunctioning Pituitary Adenoma Recurrence and Its Relationship with Sex, Size, and Hormonal Immunohistochemical Profile, World Neurosurgery 2018: e241-e246.
[9]S. Yamada, K. Ohyama, M. Taguchi, A. Takeshita, K. Morita, K. Takano, T. Sano. A study of the correlation between morphological findings and biological activities in clinically nonfunctioning pituitary adenomas, Neurosurgery 2007;61:580 –584.
[10]J.J. Kanski. Clinical Ophthalmology 6thed. London, UK: Butterworth Heinemann, 2007: 811.
[11]B.M. Arafah, M.P. Nasrallah. Pituitary tumors: pathophysiology, clinical manifestations and management, EndocrRel Cancer 200; 8: 287–305.
[12]D.J. Baruffi, K.R. Thompson. Radiologic presentation of pituitary adenoma, Optom Vis Sci 2012; 89: e56–e64.
[13]G.S. Kosmorsky, W.J. Dupps, R.L. Drake. Non‐uniform pressure generation in the optic chiasm may explain bitemporalhemianopsia, Ophthalmology 2008; 115: 560‐565.
[14]A. Prete, M.C. Salvatore, R. Salvatori, Current best practice in the management of patients after pituitary surgery, TherAdvEndocrinolMetab 2017 Mar; 8(3): 33–48.
[15]Poiana C, Chirita C, Carsote M, Hortopan D, Goldstein A. Galactocele and prolactinoma--a pathogenic association?Maturitas. 2009 Jan 20;62(1):98-102. doi: 10.1016/j.maturitas.2008.10.015. Epub 2008 Dec 24.
[16]Dumitru N, Ghemigian A, Carsote M, Albu SE, Terzea D, Valea A. Thyroid nodules after initial evaluation by primary health care practitioners: an ultrasound pictorial essay. Archives of the Balkan Medical Union 2016; 51 (3), 434-438
[17]R.F. Dallapiazza , J.A. Jane Jr. Outcomes of endoscopic transsphenoidal pituitary surgery. Endocrinol Metab Clin North Am. 2015 Mar;44(1):105-15.
[18]M.K. Jang , C.G. Park , S. Jang , E.H. Kim . Prevalence and Impact of Postoperative Headaches in Nonfunctioning Pituitary Macroadenoma Patients: A Longitudinal Cohort Study. World Neurosurg. 2019 Oct 8. pii: S1878-8750(19)32565-3. doi: 10.1016/j.wneu.2019.09.123.
[19]T. Ogiwara , A. Nagm , T. Nakamura , T. Mbadugha , T. Horiuchi , K. Hongo . Significance and Indications of Surgery for Asymptomatic Nonfunctioning Pituitary Adenomas. World Neurosurg. 2019 May 8. pii: S1878-8750(19)31257-4. doi: 10.1016/j.wneu.2019.04.250.
[20] M. Harary , A.C. DiRisio , H.Y. Dawood , J. Kim, N. Lamba , C.H. Cho , T.R. Smith , H.A. Zaidi, E.R. Laws . Endocrine function and gland volume after endoscopic transsphenoidal surgery for nonfunctional pituitary macroadenomas. J Neurosurg. 2018 Nov 1:1-10. doi: 10.3171/2018.5.JNS181054.
[21]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 Med. 2015;88(3):310-3. doi: 10.15386/cjmed-435.
[22]M.E Molitch. . Diagnosis and Treatment of Pituitary Adenomas: A Review. JAMA. 2017 Feb 7;317(5):516-524. doi: 10.1001/jama.2016.19699.
[23]G. Iván , N. Szigeti-Csúcs , M. Oláh , G.M. Nagy , M.I. Góth . Treatment of pituitary tumors: dopamine agonists. Endocrine. 2005 Oct;28(1):101-10
[24]E. Kuhn , P. Chanson . Cabergoline in acromegaly. Pituitary. 2017 Feb;20(1):121-128. doi: 10.1007/s11102-016-0782-6.
[25]R.S. Auriemma , R. Pivonello , L. Ferreri , P. Priscitelli , A. Colao . Cabergoline use for pituitary tumors and valvular disorders. Endocrinol Metab

Clin North Am. 2015 Mar;44(1):89-97. doi: 10.1016/j.ecl.2014.10.007.
[26]R. Palui , J. Sahoo , S. Kamalanathan , S.S. Kar , S. Selvarajan , H. Durgia . Effect of cabergoline monotherapy in Cushing's disease: an individual participant data meta-analysis. J Endocrinol Invest. 2018 Dec;41(12):1445-1455. doi: 10.1007/s40618-018-0936-7.