

CLINICAL CASE

SURGICAL APPROACH IN PITUITARY TUMOURS: THE ROLE OF ENDOCRINE PROFILE**Mara Carsote^{1,2}, Simona Elena Albu^{1,3}, Adina Ghemigian^{1,2}, Carmen Georgescu^{4,5}, Ana Valea^{4,5}**¹"Carol Davila" University of Medicine and Pharmacy²"C.I. Parhon" National Institute of Endocrinology, Bucharest, Romania³The University Emergency Hospital, Bucharest, Romania⁴"Iuliu Hatieganu" University of Medicine and Pharmacy⁵Clinical County Hospital, Cluj Napoca, Romania

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Abstract

The surgical approach in the pituitary secreting or non-secreting tumours had a complex development during the last century up to the microscopic transsphenoidal or endoscopic techniques. This is a mini-review of endocrine features in adenomas requiring their remove starting from a case presentation. A 54-year-old female is admitted for endocrine evaluation because of her medical history. At the age of 45 she presented secondary amenorrhea, mild right eye proptosis, and persistent diffuse headache. A pituitary adenoma of 21 by 19 mm was found. Selective transnasal transsphenoidal hypophysectomy was performed. The surgery went well without any incidents. The patient was hospitalised for 14 days. She was released without hypopituitarism, or diabetes insipidus. The immunohistochemistry report showed a weak reaction for GH but the adenoma was considered non-functioning. In 2015 severe headache was progressively seen and it became mostly unresponsive to usual analgesic medication so amitriptylin, and gabapentin were introduced in order to control the pain. MRI showed a right pituitary tumour of 12 by 19 by 13 cm with right cavernous sinus invasion. A second selective pituitary surgery was recommended but the patient still delays it. Hypophysectomy represent the first line of treatment in all the hormonally active pituitary masses (except for the majority of prolactionomas) and in non-secretor macroadenomas. Close endocrine and imagery check-up is indicated at diagnosis and later on even in cases with complete neurosurgical remove, as seen in this case, because the risk of relapse is presented even after a few years. Repeating the surgical procedure is advisable due to compression and local invasion risks, as well as the risk of hypopituitarism.

Keywords: *hypophysectomy, pituitary adenoma, visual field defects***Introduction**

The surgery for pituitary tumours is based on several aspects: the anatomical aspects related to the extension and compression of the surrounding tissues especially regarding the

optic chiasm, the cavernous sinus, the endocrine or non-endocrine features, and the experience of the surgical centre, particularly of the neurosurgeon [1-3]. A baseline endocrine evaluation is essential in every newly diagnosed

pituitary mass but also during long-term follow-up after hypophysectomy.

Materials and methods

A 54-year-old mildly obese female is admitted in 2015 at the Department of Endocrinology from Clinical County Hospital, Cluj-Napoca, Romania for severe headache which is persistent for the last months and not responsive to usual pain management drugs. Her medical history started at the age of 45 years when she presented with secondary amenorrhea, right eye mild proptosis and associated eye pain together with persistent diffuse headache (Figure 1). A pituitary adenoma of 21 by 19 millimetres was found (with a lateral and superior extension).

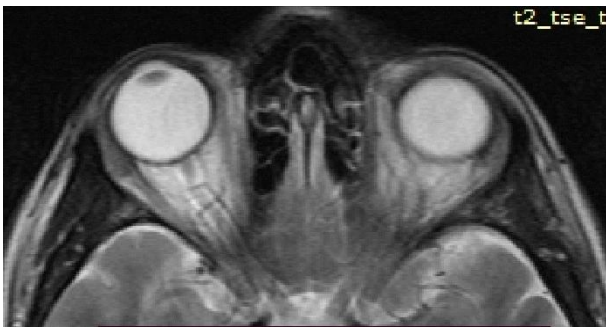


Figure 1 - MRI aspect (transversal plane): symmetrical proptosis (right eye > left eye)

The endocrine profile revealed high Follicle Stimulant Hormone (FSH) of 78.44 mUI/mL (consistent with either menopause or o gonadotropinoma), normal prolactin levels of 20.11 ng/mL, intact thyroid axes, normal suppression dexamethasone test and growth hormone (GH) levels (thus excluding a prolactinoma, Cushing's disease or acromegaly). No visual field defects were found at the moment. The patient did not present pituitary insufficiency. Selective transnasal transsphenoidal hypophysectomy was performed outside the country.

The surgery went well without any incidents. The patient was hospitalised for 14 days. Neither diabetes insipidus, no pituitary insufficiency were diagnosed after tumour remove. The immunohistochemistry report showed a weak reaction for GH but the adenoma was considered non-functioning. For

the next 6 years she was followed-up in different medical centres.

The background disease seemed controlled (including the headaches) for a few years without any signs of tumour relapse at imagery. In 2013 the MRI showed no tumour but in 2014 a small mass at the level of right cavernous sinus was detected. In 2015 severe headache was progressively seen and it became mostly unresponsive to usual analgesic medication so amitriptylin, and gabapentin were introduced in order to control the pain. MRI showed a right pituitary tumour of 12 by 19 by 13 millimetres with right cavernous sinus invasion and compression to optic chiasm (Figure 2,3). The endocrine tests showed once again a non-functioning profile. A second selective pituitary surgery was recommended but the patient still delays it.

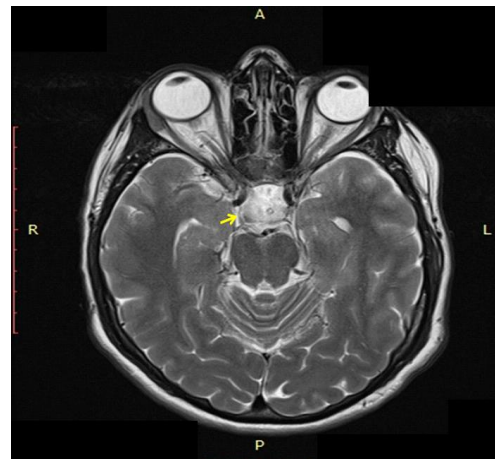


Figure 2 - MRI aspect pituitary: macroadenoma with right cavernous sinus invasion - transversal plane

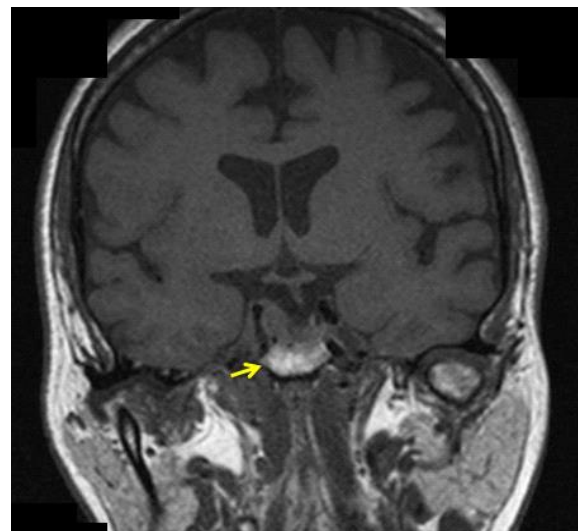


Figure 3 - MRI aspect pituitary: macroadenoma with right cavernous sinus invasion - coronal plane

Discussions

The surgery of the pituitary tumours has a history of more than a century. Transcranial approach of hypophyseal masses was first reported in 1889 by Horsley [4-6]. The first transsphenoidal transnasal procedure for a pituitary adenoma was performed by Hermann Schloffer in 1907. [4-6] Despite the fact that his patient died soon after surgery this represented an open door to a very dynamic and spectacular field of surgery involving both neurosurgeons and otolaryngologists. Three years later Oskar Hirsch introduced the endonasal technique which he finally simplified it [4-6]. Harvey Cushing improved the procedure thus helping to decrease the mortality rate. Since 1950 the use of antibiotics considerably helped the peri-operative mortality reduction as seen in other types of general surgery [4-7]. Different type of approaches by nose, ear or throat were tried [6-8]. Since 1960 the introduction of microscope during a pituitary tumour remove enhanced the precision of resection and Jules Hardy is one of the pioneers in this field by using the binocular microscope during a selective procedure in order to preserve the normal gland [6-8].

Today, more than 100 years later from the first step, the minimally invasive pituitary surgery is targeted to the pathological mass seeking for best conservative way regarding the stalk, the optic chiasm, and, of course, the hypophysis. The technique of hypophysectomy varies from: open to microscopic transsphenoidal (as seen in our case) or endoscopic approach [1-3]. The anatomical issues are primarily considered based on the tumour dimensions, forms, and invasion.

The indication of surgery is established before the surgery by a multidisciplinary team including endocrine and eye profile. Pituitary adenomas (regardless of their nature, secretor or not), Rathke cleft cysts and craniopharyngiomas are the most common findings in endocrine evaluations regarding a hypophyseal mass [1-3]. During the last years the endonasal approach has been used in most situations while only some extremely aggressive tumours with high dimensions needed craniotomy [1-3]. Today many centres are actually targeting to use the endoscopic route.

The endocrine profile (if the tumour is hormonally active) is important in order to treat the co-morbidities like cardiovascular associated diseases and diabetes mellitus (as seen in cortico- and somato-tropinomas), pituitary insufficiency diagnosed prior to surgery in order to have a better clinical outcome [3,4,9]. Otherwise the neurosurgical technique itself (not the post-operative protocol) is minimally based on the endocrine overproduction or deficiency [9,10]. Opposite to this aspect, the endocrine features and complications become a challenge to the anaesthesiologist [9,10].

The endocrine type of tumours introduces the entire hormone panel of complex diseases including metabolic and bone complications. For instance, the GH overproduction means acromegaly, the adrenocorticotrop hormone (ACTH) excess means Cushing's disease, etc [9-11]. Each of these disorders has specific indications of neurosurgery. All the hormonally active pituitary masses associate as first line therapy the indication of surgery except for majority of prolactionomas [10-12]. The risks after minimally invasive pituitary surgery are bleeding, cerebrospinal fluid rhinorrhea and associated potential of meningitis; diabetes insipidus (including a triphase pattern), the syndrome of inappropriate antidiuretic hormone secretion, pituitary insufficiency; smell and visual field defects [12-14]. Many cases depending of tumours' characteristics and neurosurgeons' skills are persistent or recurrent after surgery [11,12,15].

The GH producing tumour or somatotropinoma has an indication of selective hypophysectomy if the tumour is active, especially if eye field defects, pituitary apoplexy or others compression effects are seen [16,17]. The contraindications include the patients with general surgical and anaesthesias risks as advanced age or severe cardiac and respiratory conditions [16-18]. Even when total resection is not achieved, the partial procedure is useful because it lowers the hormonal level and improves the clinical outcome as high blood pressure, diabetes mellitus, hyperlipemia, cardiomegaly [18,19]. Acromegaly benefits from specific medication as somatostatin analogues and GH receptors blockers [17,19,20]. Histopathological As seen in others tumours, the

pituitary radiotherapy is necessary in selective non-responsive cases [19,20]. It takes at least one year to see its effects and in order to apply the least traumatic procedure of irradiation (gamma knife radio-surgery) a specific anatomic condition is necessary (at least 5 millimetres from the tumour to optic chiasm are required) [19,20]. In our case a silent somatotropinoma has been suggested based on GH mild reaction antibodies after surgery but the endocrine dynamic tests that were repeated at different moments were negative. The surgical rate of success in acromegaly varies from 70 to 90% in microadenomas and from 50 to 60% in tumours larger than 1 cm [16,19,20]. For years it has been a debate whether to pre-treat with somatostatin analogues before surgery or to have first the hypophysectomy since the evidence based medicine brought arguments for both sides [19-21].

Dopamine agonists as cabergoline or bromocriptine represent a medical alternative with a weak potential in acromegaly but the first option in the management of prolactinomas which are the most frequent functioning hypophyseal adenomas [22,23]. Surgery in these cases is extremely rare necessary if there is no answer to medication (resistant or malignant behaviour of the tumours) or severe side effects to oral drugs are seen, as well as optic compression or pituitary apoplexy [22-24]. A few patients prefer neurosurgery to long-term medication [24,25]. In cases of tumour-related hyperprolactinemia confirmation the technique decision is similar to others pituitary adenomas (functioning or non-functioning tumours). In very rare cases the gamma knife radiosurgery is indicated if medication and/or surgery are not efficient thus the control of prolactin excess is obtained but unfortunately it causes hypopituitarism in most of the cases [22-25]. Due to prolactin excess a functional component of amenorrhea is registered mimicking menopause in some cases [26]. In our patient, after the exclusion of a gonadotropinoma, the secondary amenorrhea was most probably related to premature menopause and the menses did not resume after surgery.

An ACTH producing pituitary adenoma is a small tumour of less than 5 millimetres in more than half of cases, so the success of surgery may be limited [27-29]. Unfortunately Cushing's

disease has a high rate of morbidity and mortality because of arterial hypertension, pro-coagulation status, risk of cardiac ischemia, dyslipidemia, etc [27,28]. All these need to be medically treated before surgery, in order to reduce the peri-operative complications [29,30]. After successful surgery, secondary adrenal insufficiency is found and this is a potentially life threatening situation [29,30]. The risk of recurrence is 3 up to 47% of cases, so close endocrine follow-up is necessary [29,30]. In order to obtain the metabolic and cardiovascular control of the disease before surgery or in cases of unsuccessful pituitary surgery pasireotide, a newly introduced somatostatin analogue, might help [31]. Bilateral adrenalectomy is reserved for severe cases, as well as radiotherapy [32].

Thyrotropin-secreting adenomas are rare masses (less than of 1% of all pituitary adenomas) and they usually are large, aggressive neoplasia and hypophysectomy is required in majority of cases [33-35]. Pre-operative thyroid hormones excess control is necessary, and ocreotide therapy is useful as adjuvant before and after neurosurgery. If tumour removal does not control the disease, pituitary radiotherapy might help [33-35]. The gonadotroph secreting adenomas are the rarest secretor hypophyseal adenomas, usually with diameters larger than 1 centimetre [36,37]. Hypophysectomy is necessary to control the disease and to confirm the diagnosis based on pathological and immunochemistry examination [36,37]. The differential diagnosis in a women with a pituitary macroadenoma and secondary amenorrhea is established with non-secreting tumours overlapped with physiological menopause as found in our case.

In cases when the endocrine panel of investigations does not identify a clear hormonal excess (so called non functioning adenomas) the surgery is mainly based on tumours dimensions and their complications [38-40]. If the pituitary mass is less than 1 centimetre and the follow-up does not indicate a growth (this is the case of pituitary incidentalomas) the neurosurgical approach is not necessary opposite to macroadenomas [38-40]. These may associate hypopituitarism at onset or after surgery, as well as visual fields defects [38-40]. Their aggressive profile sometimes needs radiotherapy or re-surgery. In any case

regardless of the initial size, long-term follow-up is essential [38-40].

The presented case is a non-secretor macroadenoma that initially went well after selective endonasal hypophysectomy but relapsed after almost 7 years. Generally, adjuvant pituitary irradiation after initial successful neurosurgery is not indicated but the risk of tumour re-growth is up to 13% if there is no tumour on MRI and up to 40% if the tumour begins to be identified at MRI (as our case was for the last two years) [41,42]. This explains close imagery scans in order to identify the growth rate and the need for serial endocrine testing [43-45]. If the patient continues to delay the procedure, cabergoline might have a small effect and radiotherapy is indicated with small benefits considering the tumour anatomy. None of these two options will correct the visual fields effects [43-45].

Conclusions

Selective hypophysectomy is indicated in most of the pituitary adenomas with endocrine overproduction (except for prolactin producing adenomas) as well as in non-functioning tumours larger than 1 centimetre. The hormonal evaluation is essential at baseline and during follow-up regardless of the fact that surgery was successful or not because, as seen in this adult female case, the risk of relapse is presented despite no tumour was identified at MRI for a long time after endonasal hypophysectomy. Re-surgery is indicated because the risk of growth and associated compression such as visual field defects may appear.

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