Pituitary adenoma, therapeutic approach and surgical results

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Abstract

Objectives: Pituitary adenoma represents the most frequent tumour encountered in the sellar region. We have proposed to review the principles of diagnosis and treatments and to analyze their standard protocol of approaching pituitary lesions.

Material and method: We have retrospectively analyzed the cases of pituitary adenoma between Jan 2006 and Dec 2010, we studied presenting symptoms, hormonal status, local extension, surgical approach, tumor histology, type of resection, tumor volume, cavernous sinus invasion, surgical corridors, recurrence rate, intra operative and postoperative complications

Results: 72 patients were included in the study, with no significant difference between sexes, the pathology was dominated by pituitary macro adenomas in 47 cases, regarding the hormonal status 51.3% were non secreting pituitary adenomas, the rate of operability in our series was 65.2%, the surgical indication has been given mainly by the hormonal status and involvement of the optic apparatus which in our series was 51%, the invasion of the cavernous sinus has been appreciated according the Knosp criteria (7) and grade 3 and 4 was present in 44% of the cases. The most used surgical approach was the pterional approach in 83% and the remaining 17% by the transsphenoidal approach. The most frequent surgical corridor was represented by the prechiasmatic route in 54%, gross total resection was achieved in 51%. The most frequent postoperative complication encountered in our series was represented from systemic complication the meningitis 13%, as for endocrine complication it was represented by transitory diabetes insipidus in 23.4% and SIADH in 4.2% (2 cases). The follow up at 3 months showed no cases of early recurrence, from the group of patient with STR 6 were sent to radiotherapy. The follow up at 1 year has comprised 3 deaths, 3 cases of hydrocephalus treated with ventriculoperitoneal derivation, 19 cases were with no imagistic or clinical symptoms of tumour and 22 presented with imagistic evidence of stable residual tumour with no clinical symptoms.

Conclusions: The main surgical indication in pituitary adenomas is represented by the secreting hormonal status of the patient (excepting prolactin secreting tumours) and the impairment of the vision. The most frequent surgical approach was represented by the transcranial (pterional) approach due to the large dimensions and invasiveness of the tumours presented in our series but also the

surgical team preference (in the absence of intracranial endoscopy at those times).

Keywords: pituitary adenoma, pituitary apoplexy, prolactinoma, sellar region.

Introduction

Sellar tumours have a large histological variability and represent approximately 10-15% of all intracranial neoplasms, from them pituitary adenomas represent 95% of lesions. Pituitary adenomas can be classified according their size in micro adenomas (<10mm), macro adenomas (>10mm) and giant adenomas (>40mm) (20). According to their functional status pituitary adenomas are classified as non secreting pituitary adenomas (NSPA) or as secreting pituitary adenomas (SPA) with different subtypes depending on the secreted hormone (prolactin/growth hormone etc). At presentation there are three main types of complaints: 1. Symptoms caused by tumor dimension with compression to the adjacent structures (optic chiasm/ diencephalon/cavernous sinus) (24) 2. Symptoms produced by abnormal secretion of hormones insufficiency/hyper secretion (acromegaly/Cushing's disease) 3. Incidental findings – patient explored for some other pathology (6, 8). A particular clinical presentation is represented by pituitary apoplexy with altered level of consciousness, intracranial hypertension signs, blindness caused by sudden expansion of tumor volume secondary to intratumoral hemorrhage/infarction and with clear surgical indication (18, 24). The actual management of those tumors varies from surveillance, medical treatment, surgery or a combined approach; however surgery remains the main therapeutic method (25).

Material and method

We have retrospectively analyzed all cases of pituitary adenomas which were addressed to the 3rd Neurosurgical Department at N. Oblu Hospital between Jan 2006 and Dec 2010, during this period of time eighty three patients were consulted and 72 cases were included in the study, we have excluded the patients younger than eighteen years old, patients with previous surgery for pituitary adenomas and patients who refused the proposed therapeutic method according to our protocol (figure 1 and 2).

All patients underwent clinical neurological evaluation: significant neurological deficits were notes (3rd nerve palsy, signs of hydrocephalus, altered level of conscious, visual impairments) and the time interval from beginning of symptoms to presentation.

Imagistic evaluation consisted in contrast enhanced MRI with details upon the sellar region. Tumor dimension was recorded and also the invasion into the adjacent structures (3rd ventricle/sphenoid sinus) invasion of the cavernous sinus was assessed according to Knosp classification, routinely the surgical site was analyzed by CT in the first day postoperatively and then by contrast enhanced MRI at 3 and 12 months. Unoperated patients were imagistic followed up using contrast enhanced MRI at 12 months.

Endocrine evaluation consisted in evaluation for free cortisol, ACTH, PRL, GH, TSH, fT4, to assess for endocrine derangements, except 2 cases who presented with pituitary apoplexy.

Ophthalmologic evaluation consisted in visual acuity determination and perimetry.

The patients were assessed for treatment according to the tumor size, endocrine

status and visual disturbance using the following algorithms, treatment options in our series were represented by surveillance, medical treatment and surgery. There were two main surgical techniques: trans sphenoid or trans cranial approach, we have noted the surgical corridors used during intervention, the degree of resection by surgeon intra operative appreciation and on CT scans performed on the 1st day postoperatively, the postoperatively complications (local/systemic).

Results

We have included in our study a number of 72 patients who presented for pituitary adenoma pathology. The cohort was composed of 39 females and 33 males, with a mean age of 50.0 years (ranged 16-75 years). Our series contains a number of 25 cases of micro adenomas from which 6 undergone surgical resection and 47 cases of macro adenomas, with 41 cases operated on. The majority of patients who underwent resection sought medical attention for symptoms related to visual impairment (51%). The remaining patients complained of severe headaches (19%), symptoms related to hormone production (16%) or cranial nerve palsy/epileptic seizures (7% both). 15% of our patients presented with pituitary apoplexy confirmed by the MR imaging and the intra operative aspects.

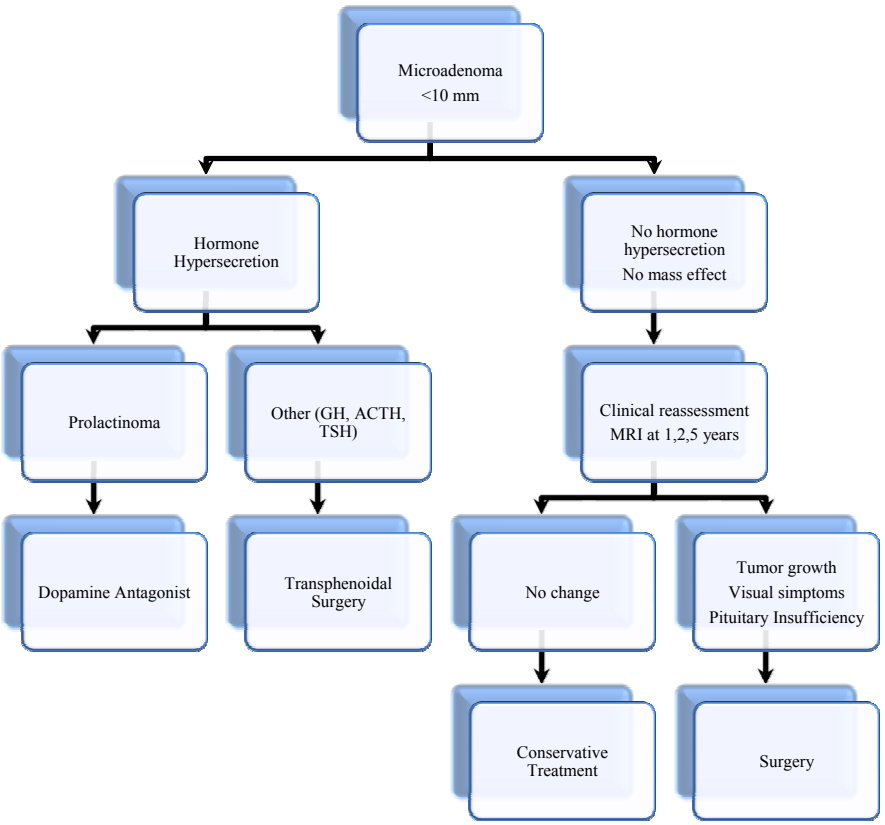


Figure 1 Therapeutic approach in pituitary micro adenomas (<10mm) according to their endocrine functioning status.

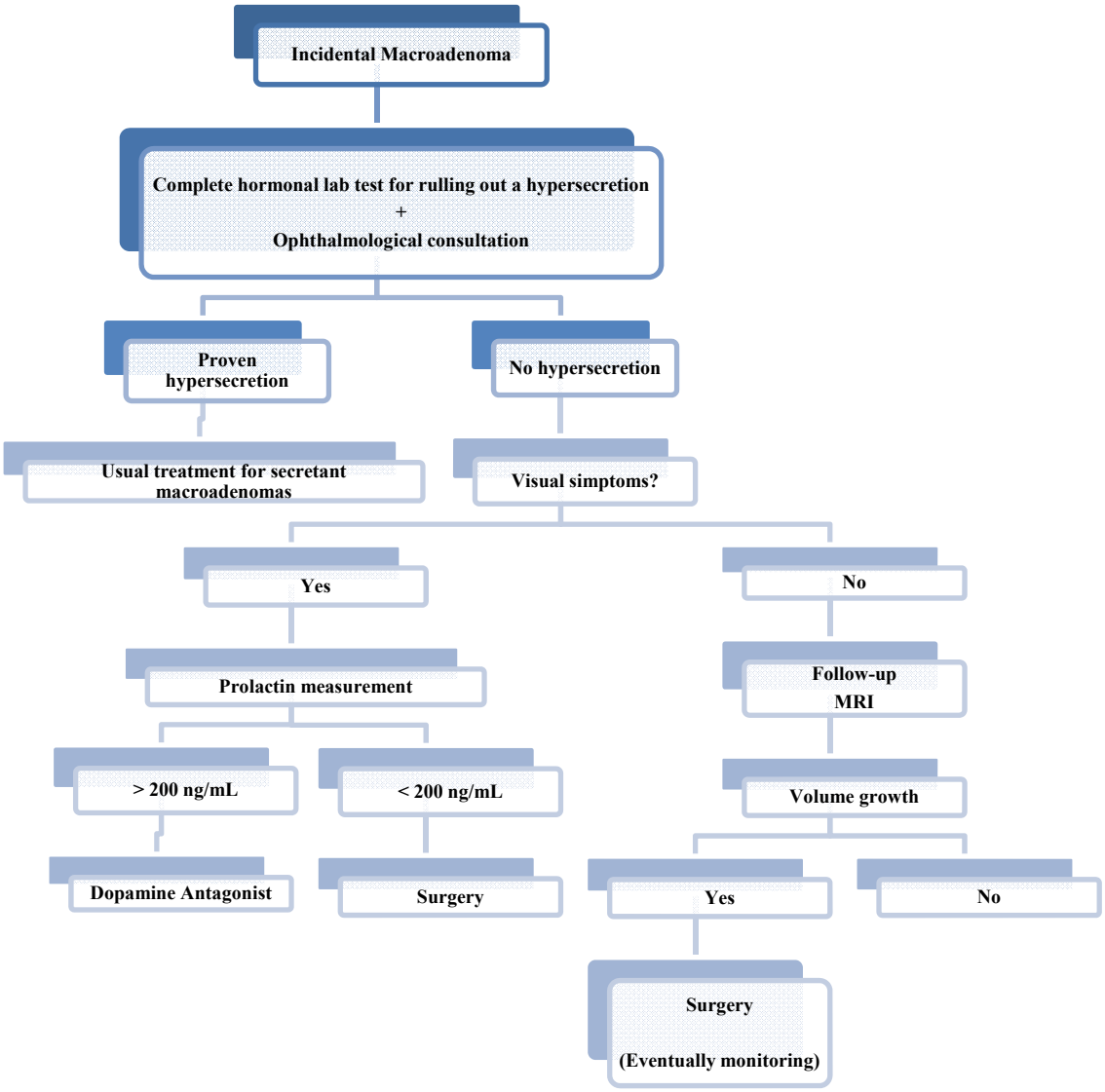


Figure 2 Therapeutic approach in pituitary macro adenoma (>10mm) according to their functional endocrine status and their effect upon intracranial optic structures

Preoperative imaging revealed micro adenomas in 34.7% and macro adenomas (diameter large than 10 mm) in 65.3%. Invasion of the cavernous sinus was appreciated using the Knosp criteria (7) and was grade 2 in 35%, grade 3 in 27% and grade 4 in 17 %, the suprasellar tumor extension was detected in 58.3%.

In our cohort none of the patients had undergone previous resection. Regarding the hormonal status our series contains 51.3% cases of nonfunctioning adenomas, 37.5 % presented with secreting adenomas from which 55.5% (15 cases) of GH secreting adenomas and 37,7% prolactinomas (10 cases).

Surgical results

In our series 47 patients (65.2%) underwent surgical resection, from them 39

operations (83%) were performed using a transcranial route (pterional approach), the rest of the operated patients (8 cases) had a sublabial transsphenoidal approach. The unoperated patients (25 cases) 34.8% beneficiated from conservatory treatment (dopaminergic agonists) in 12 cases (48%), imagistic surveillance in 11 patients, and 2 patients were sent to gamma knife according to their preference. The mean time for surgical intervention was 3h30' with no clear difference between the transcranial and transsphenoidal approaches. The degree of resection in our series was noted according to the subjective intraoperative appreciation and objectively sustained on the 1st day CT scan, as result we have obtained gross total resection (GTR) in 51% of operated cases.

The most frequent surgical corridor used was represented by the pre chiasmatic route in 54 % and opticocarotidian route in 24%, the transsphenoidal route was used in 12 % of the cases while the translaminaterminalis and carotidooculomotor route were used in 6% and 4% respectively The surgical complications were divided into systemic complications and were represented by meningitis in 6 cases, as for local surgical complications we had 16 cases of hematomas in the surgical bed from them only 1 necessitating evacuation and 2 cases of CSF leak 1 spontaneous closed.

The postoperative status was assessed and revealed no endocrine deficiency in 60 % cases, transitory diabetes insipidus in 23.4 %, 4.2% had SIADH and 6% had panhypopituitarism.

The outcome of patients operated on for pituitary adenomas consisted in 2 per operative deaths (death in the first 30 days after surgery – 1 case of pulmonary embolism and another of severe water electrolytes imbalance), 4 cases had no amelioration of visual symptoms, and 1 patient had a new neurological deficit (left hemiparesis); the rest of the patients had a good surgical outcome.

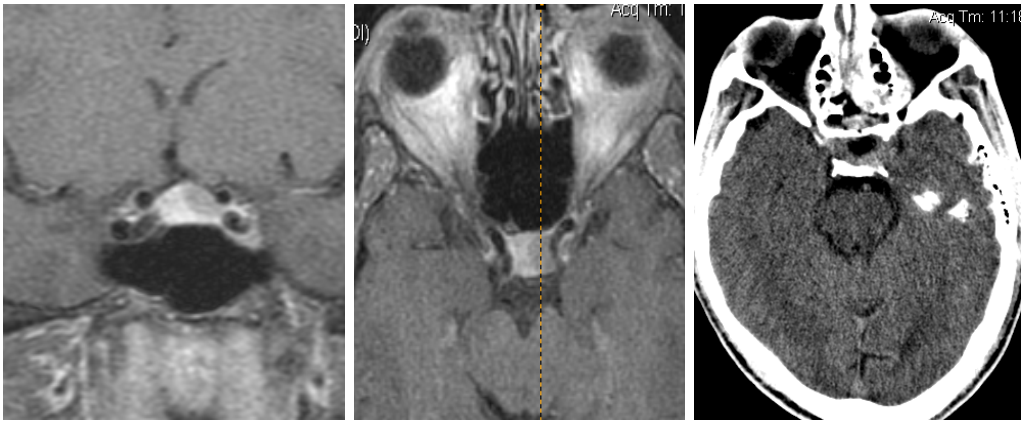
At three months follow up we had one early recurrence (AP: adenocarcinoma), 22 patients had no imagistic evidence of intracranial tumor, from the group of patients with residual tumor 6 were sent to radiotherapy and the rest were symptom free and kept under surveillance.

The follow up at 1 year comprised contrast enhanced MRI evaluation and clinical neurological examination, 19 patients had no imagistic or clinical evidence of residual tumor, in 21 patients the imagistic evaluation detected residual tumour but without clinical symptoms, this category of patients being kept under imagistic and endocrine surveillance, we had three recurrences and the treatment was represented by surgery. The mortality in our group at 1 year was 6.3% (3 patients), as late complications we had 3 cases of hydrocephalus 2 in the group of GTR an 1 in the group of STG – all treated with ventriculoperitoneal derivation.

TABLE 1

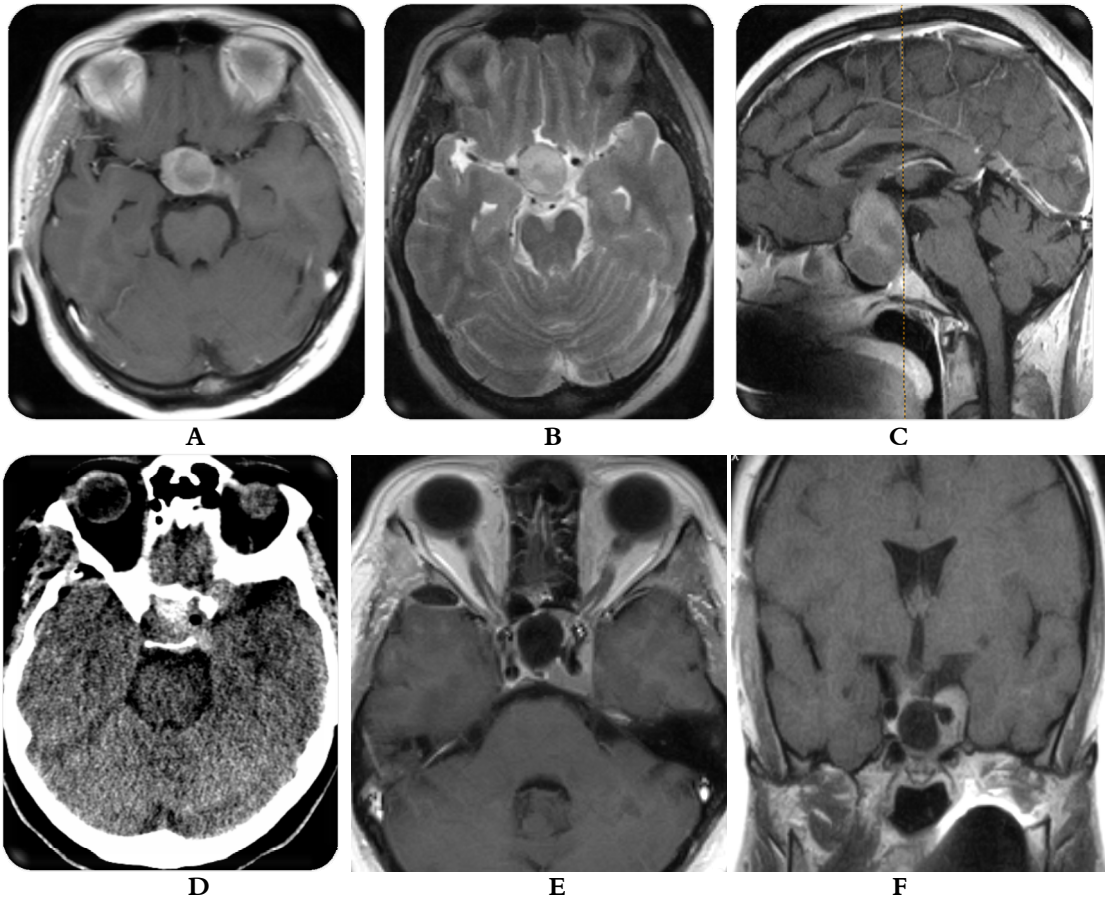
Early complications in 47 patients operated for pituitary adenoma

Type of Complication	No. of patients %	Treatment
Meningitis	6 (13)	Antibiotics
Blood collection	16 (34)	Evacuation (1)
CSF leak	2 (4.2)	Surgical closure (1)
Transitory DI	11 (23.4)	Desmopresin
SIADH	2 (4.2)	Water restriction
Panhypopituitarism	3 (6.3)	Hormone replacement



A B C

Figure 3 T1 contrast enhanced IRM coronal **A** and axial
B sections showing a hypo intense, non enhancing lesion, in the left pituitary gland
C CT scan in the 1st day after transsphenoidal surgery in a 60 y o female with acromegaly and GH 47.8μg/L



A B C

D E F

Figure 4 MRI examination T1 with contrast enhancement axial (A)/sagital (C) and T2 axial showing a sellar and suprasellar mass hyperintense in T1 and axial T2 (B) with inhomogeneous contrast enhancement suggestive for pituitary apoplexy, (D) CT scan on 1st day postoperatively (transcranian) in the same 50y old F patient in treatment with Dostinex® for a known prolactinoma who presented with visual loss and impaired consciousness. (E) and (F) T1 contrast enhanced MRI at 3 months showing a residual tumor in the left cavernous sinus.

Discussion

Our experience has brought us to the conclusion that the treatment of pituitary adenomas should be multidisciplinary, namely, endocrinological, surgical and radiotherapeutical. The order in which treatment is applied is dependent on the tumour size, hormonal status of the patient and the clinical condition of the patient.

The goals of surgery are to remove the tumor, relieve the mass effect, improve visual abnormalities, reduce hormone hypersecretion to normal levels, and preserve normal pituitary function (16), surgery is the first-line treatment in pituitary adenomas with compression upon optic structures and visual impairment and in all actively secreting adenomas except prolactinomas (16). Either transcranial or transsphenoidal approaches can be adopted in the surgical treatment of pituitary adenomas, in our cohort the most used surgical approach was transcranial (pterional) due to the preference of the operative team and due to the complexity of the cases (CS invasion Knosp 3 and 4 in 40%) in our series cavernous sinus invasion was directly correlated with STR, safe complete resection of tumor lateral to the carotid artery remaining nearly impossible with no regards to the surgical corridor used (3, 22, 23), also the suprasellar extension of the tumor (58.3% in our series), recommend considering the transcranial approach as the natural choice unless the tumour suspected to be hemorrhagic (1, 4). In reality, surgery is very effective in relieving the mass effect; however, most patients harboring a large lesion will require additional treatment to produce hormonal remission and prevent regrowth of residual tumor, and many will require hormone replacement therapy to reestablish a normal hormonal balance (3, 8, 27).

Radiation treatment (conventional, stereotactic, or proton- beam) of the pituitary is most commonly used as an adjunctive treatment after incomplete tumor resection (19). Radiotherapy reduces the risk of residual tumor enlargement and offers the chance of permanent control of hormone hyper secretion, in our series 6 patients of 23 with incomplete resection were treated using stereotactic radiation therapy. In our cohort the rate of gross total resection was achieved in only 51% of the cases that is lower than literature data (1, 23).

Surgical indication is also guided by the functional status of the pituitary adenoma, all secreting pituitary adenomas have surgical indication except prolactinomas, in which the first line of treatment is oral administration of a dopamine agonist, such as cabergoline, bromocriptine, or pergolide (8, 16) (more than 90% of patients respond to this treatment with reduction in the serum PRL level and with tumor shrinkage).

It is known that approximately 60% of patients with a GH-producing tumor are found to harbor a macro adenoma that is often invasive, making its complete removal unlikely - this is the reason we prefer to operate GH secreting pituitary adenomas at moment of diagnosis, without previously use of somatostatin analog (attitude that is still a controversy in the literature) (8, 16). On the other hand there is a clear surgical indication for ACTH secreting adenomas, in which there is no effective medical therapy to reduce ACTH production or decrease tumor size, surgical removal of the lesion being the first choice of therapy. If the surgery is not successful, pituitary

irradiation should be considered and medical therapy with ketoconazole. As for non functional adenomas, there is no effective medical treatment, surgery being the primary therapeutic option according to their volume and clinical symptoms (15).

Another clear surgical indication, given by the clinical status of the patient, is represented by pituitary apoplexy – surgical emergency (comprises visual deficits, ophthalmoplegy, hypopituitarism, altered levels of consciousness) the apoplexy rate in our group was 15%, greater than data in the literature (10%) (1, 12), the apoplexy was encountered only in macro adenomas in our series from which 13 were non functional macro adenomas and 2 were GH secreting adenomas. In the literature there are several theories concerning the precipitating factors in apoplexy, Biousse et al. divide this factors in: 1) factors associated with reduced blood flow, 2) acute increase in blood flow, 3) stimulation of the pituitary gland, and 4) the anticoagulated state (2, 12) however in our series we did not managed to identify precipitating factors such as (surgical intervention, postpartum status, radiotherapy, head injury) (2, 12, 18).

Regarding the postoperative complications, the most frequent was represented by meningitis 13%, the rate of CSF leaks was encountered in only 2 cases both after transsphenoid surgery from which one was closed spontaneously. One particularity of our operated pituitary adenoma is represented by the packaging of the pituitary fosa after tumor removal with pure alcohol for 3 minutes in order to destroy the remnant of any neoplasic cells; also all of our patients beneficiated from glucocorticoid therapy (prednisone acetate) administrated pre operatively 25mg/day in a fractionated fashion and continued in the post operatively with progressively decreasing doses. This attitude is due to the fact that patients undergoing pituitary adenoma surgery may be prone to hypocortisolic states due to pre-existing or newly developed hypothalamic-pituitary-adrenal axis impairment, in order to avoid potentially life threatening hypocortisolic states which may appear in patients with HPA impairment, adequate corticoid replacement therapy is considered mandatory (5, 10). Of course in the literature there is no consensus regarding these attitude because some authors administer peri-operative corticoid replacement medication regardless of the pre-operative HPA integrity while others limit peri-operative corticoid substitution to patients with impaired HPA. Also, the reported dosages of corticoids administered per operatively differ (5, 10, 17).

Postoperatively endocrine status showed transitory diabetes insipidus in 23.4% from which 4.2% developed the second phase of diabetes insipidus, SIADH, it is very important to make the difference between these two conditions with similar clinic manifestations because the treatment is completely different. None of our patients developed the third phase of diabetes insipidus, the permanent phase. There are several theories regarding the post operative fluid balance disorders such as: mobilization of previously third space soft-tissue fluid especially in patients harboring GH secreting tumors, baseline elevations in the levels of renin, angiotensin, atrial natriuretic peptide, and arginine vasopressin in patients with acromegaly have been implicated in this phenomenon, and their reduction after surgery likely contributes to

the diuresis experienced by patients via a reduction in sodium retention (26).

There is well known the triphasic response of the diabetes insipidus,1) the first phase of diabetes insipidus is initiated by a partial or complete pituitary stalk section, which severs the connections between the cell bodies of AVP-secreting neurons in the hypothalamus and their nerve terminals in the posterior pituitary gland, which prevents AVP secretion this phase is usually treated with single doses of parenteral desmopressin in order to decrease polyuria and minimize the occurrence of hyponatremia due to overtreatment, 2) the second phase is dominated by the inappropriate antidiuresis, which is caused by uncontrolled release of AVP from either degenerating posterior pituitary tissue, or from the remaining magnocellular neurons whose axons have been severed, 3) the third phase develops if >80-90% of the AVP-secreting neuronal cell bodies in the hypothalamus have degenerated and which results in permanent diabetes insipidus ; these patients being best managed with long-term administration of intranasal or oral desmopressin (9)

In our protocol we follow up clinical and imagistic the operated patients at 3 months, in order to avoid IRM artifacts after per operative administration of corticosteroids (used to avoid pituitary insufficiency).

Results at 3 months showed one early recurrence (with tumor regrowth and significantly clinical symptoms - the patient was re operated and the histology showed pituitary adenocarcinoma KI 67 18% (21)), 22 patients had no imagistic evidence of intracranial tumor, from the group of patients with residual tumor 6 were sent to radiotherapy and the rest were symptom free and kept under surveillance. Gamma Knife surgery is a commonly used adjunctive treatment for patients with a residual or recurrent adenoma, or in patients with persistent hormone hypersecretion. Decreasing the adenoma volume by resection and temporarily withholding pituitary suppressive medications seem to be prudent approaches prior to radiosurgery (13, 14). We have sent to radiotherapy only the cases with significant mass lesions and especially non functional pituitary adenomas (3) in which is known the lack of medical treatment. The endocrine status at three months was represented by the presence of panhypopituitarism in 6% (treated with hormonal substitution) of the cases with no other endocrine deficits. The visual symptoms had no improvement in 4 patients (16.6% of patients who were operated on and presented with visual impairment) but with no cases of worsened vision. In a recent paper Schramm and coworkers published the results of visual outcome in patients with pituitary adenomas and preoperative chiasma syndrome, according to them the syndrome completely regressed in 42.9%, improved in 38.3%, remained unchanged in 11.2% and worsened in 7.4% of the patients postoperatively (11)

It is also believed that visual acuity improvement is significant during the first two postoperative weeks, with no further significant improvement after this period while visual field defects significantly improve during the first two weeks postoperatively and continue to improve for the first three months but no later than that; this affirmation given the idea that maximum visual improvement after

pituitary surgery is at three months postoperatively (11).

Results after 1 year follow up showed 19 patients with no imagistic or clinical evidence of residual tumor, in 20 patients the imagistic evaluation detected minimal residual tumour but without clinical symptoms, this category of patients being kept under imagistic and endocrine surveillance, we had three recurrences and the treatment was represented by surgery, the mortality in our group at 1 year was 6.3% (3 patients - 2 per operatively deaths first month following surgery and 1 after 6 months with no relation to the surgery). Late complications in our series were represented by the appearance of hydrocephalus, we had three cases of hydrocephalus at 1 year follow up who presented with Hakim-Adams syndrome and without any imagistic sign of obstruction, all of them being treated with ventriculoperitoneal derivation 1 case presented with hydrocephalus at the time of diagnostic and the condition did not remitted after surgery but the other two cases developed the hydrocephalus post operatively.

Conclusions

In our series the main surgical approach was the transcranial (pterional) route due to the complexity of the cases (large tumors with extension into the suprasellar region and into the cavernous sinus) and the preference and experience of the operating team. The packaging of the sella with pure alcohol after protecting the optic structures seems to be a safe procedure with no contribution to visual deterioration, the rate of pituitary apoplexy is greater than the rate cited in the literature with no predisposing factors identified that should represent a signal of alarm because pituitary apoplexy represent a life threatening condition that must be recognized and needs adequate urgent treatment.

Pituitary adenoma remains a pathology with lot of controversies and in which further randomized studies are need in order to clarify them although usually the operation is not the end of the problem, given the potential need for hormone treatment before and after surgery, additional treatment such as pituitary radiation therapy, and the risk for recurrence. Patients with pituitary lesions require lifelong follow up by all physicians (endocrinologist, neurosurgeon, and radiation oncologist) involved in their care. A coordinated, multidisciplinary approach to the care of these patients should result in successful care and optimal outcomes.

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