Original Article

Role of Surgery in Treating Prolactinoma

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ABSTRACT

Background: Prolactin-secreting pituitary adenomas—prolactinomas—account for approximately 30% of all pituitary adenomas and 50 to 60% of functional pituitary tumors. Clinical manifestations are infertility, gonadal and sexual dysfunction in both sexes. In clinical practice, macroprolactinomas are less common than microprolactinomas, and occur more often in men than in women. The objectives for treatment of hyperprolactinemia are to suppress excessive hormone secretion, preserve residual pituitary function, and prevent disease recurrence. Medical therapy with dopamine agonists (DA) is the primary treatment of choice in most cases. Medical therapy is effective in normalizing prolactin levels in more than 90% of patients. Classical surgical indications are intolerance or lack of efficiency of DA, marked visual affection or pituitary apoplexy. Objective: The aim of this study was to analyze outcomes of patients with a prolactinoma treated surgically, to identify factors associated with remission and relapse, and to evaluate if surgical debulking allows for better hormonal control in patients with preoperative resistance to dopamine agonists (DAs). Patients & Methods: This is a retrospective study of thirty cases operated upon for prolactinomas, all their data were reviewed including clinical presentation, preoperative and postoperative prolactin levels, preoperative and postoperative magnetic resonance imaging (MRI), history of medical treatment if present, and indication of surgery in each patient. The outcome either clinical or laboratory was reviewed. Results: Surgery was indicated in patients with severe visual affection, those with apoplexy. In patients who received medical therapy intolerance to the medication was the leading cause then failure of medical therapy. Postoperative remission was obtained in 71.4% of microprolactinomas, 34% of noninvasive macroprolactinomas, and none of the invasive macroprolactinomas. Better remission rate was independently predicted by lower diagnostic prolactin (PRL) levels and by the lack of abnormal postoperative residual tissue. In patients with preoperative DA resistance treated again after surgery, there was a significant reduction in prolactin levels and received a lower DA dose, and about half of the patients had prolactin normalization. Conclusion: Although the high success rates achieved with medical therapy in prolactinoma, surgery still plays role in those with marked visual affection, apoplexy or intolerance to medical therapy, normalization of prolactin can be achieved by surgery and in others who still have high prolactin medication can be used as adjuvant therapy but with lower doses tolerable for the patients.

INTRODUCTION

Prolactinomas are adenomas derived from lactotroph cells in the pituitary gland, and are characterized by hyper secretion of prolactin. Unlike the other anterior pituitary hormones, the hypothalamic control of prolactin production and release is mediated by tonic inhibition by dopamine. Prolactin-secreting adenomas (prolactinomas) account for approximately 30% of pituitary adenomas and 50 to 60% of functional pituitary tumors. They are the most common type of functioning pituitary tumor and are second in frequency to non-functioning adenomas in overall incidence.

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One published estimate of their prevalence is 100 cases per 1 million persons; MR imaging and histological examinations demonstrate that approximately 17% of patients harbor a microadenoma.

Prolactinomas commonly cause reproductive and sexual dysfunction; macroadenomas can cause local mass effect, resulting in visual compromise, cavernous sinus compression, and hypopituitarism. Diagnosis of prolactinoma is based on elevated serum prolactin levels and detection of the adenoma on MRI, after exclusion of other causes of hyperprolactinemia. In general, prolactin levels exceeding 150-200 ng/ml are assumed to be due to prolactinoma, while lower levels in the presence of a pituitary macroadenoma is usually related to stalk effect.

The objectives for treatment of hyperprolactinemia due to prolactinomas are to normalize the hyperprolactinemic state, preserve residual pituitary function, reduce tumor mass, and prevent disease.
reoccurrence. Treatment modalities include medical treatment, surgical resection, and radiation therapy. Indications of surgery for prolactinomas became fewer as a result of the high success rates obtained by medical treatment it may reach up 90% (17-19). Classic indications have been intolerance to medical treatment, cases refractory to medical treatment, and patients preferring surgery. Other indications for surgery include pituitary apoplexy marked visual affection, and females with macroprolactinomas desiring pregnancy.

PATIENTS & METHODS

This study included thirty patients managed for prolactinomas between 2011 and 2014 at the Department of Neurosurgery, Cairo University. There were twelve males and eighteen females, with age ranging from 22 to 67 years. All cases of residual and/or recurrent adenomas previously operated on were excluded.

Patients Evaluation

All thirty patients underwent a comprehensive clinical evaluation that included neurological, ophthalmological, radiological, and medical evaluation.

1-Radiological evaluation:

All patients were examined with contrast-enhanced brain computed tomography (CT) scans as the initial imaging study supplemented by contrast-enhanced magnetic resonance imaging (MRI) to verify tumor location and its relationship to the carotid circulation and optic chiasm. According to tumor size on preoperative MRI, tumors were classified as microadenomas < 1cm, macroadenomas > 1cm, and giant adenomas with maximum diameter > 4 cm. Invasion of the surrounding compartments particularly the cavernous sinus was determined from the MRI. Cavernous sinus invasion was defined as a tumor Grade III or IV according to the classification system of Knosp, et al, and tumors were assigned as invasive or non-invasive (Fig. 1).

2- Hormonal evaluation

Diagnosis of prolactinoma was based on elevated serum prolactin above 150 ng/ml and detection of adenoma on magnetic resonance imaging (MRI), with other causes of hyperprolactinemia being excluded including the cases of stalk effect for pituitary adenomas. All patients were subjected to complete laboratory investigations that included, blood chemistry, hematology and neuroendocrine profile including; prolactin, growth hormone, thyroid stimulating hormone, lutetizing hormone, follicular stimulating hormone, T3 and T4. Initial remission was defined as a fasting morning basal PRL level 500 mU/ml (23.6 ng/ml) without dopaminergic therapy for at least 4 weeks before surgery on day 7 after surgery. Follow-up remission was defined as a morning fasting basal PRL level 500 mU/ml without dopaminergic therapy for at least 3 months at the latest follow-up.

3-Clinical evaluation:

Clinical manifestations were classified as manifestations of hyperprolactinemia (galactorrhea, amenorrhea, infertility, and impotence). Male hypogonadism was defined by clinical manifestations, a testosterone level 2.8 ng/ml and subnormal levels of gonadotropin. Manifestations due to mass effect (headache, diminution of vision, field defects, and diplopia), and manifestations due to apoplexy (sudden deterioration of vision, acute development of ptosis or diplopia). Failure of medical treatment was not considered except after at least 6 months of treatment, patients with visual acuity in one or both eyes less than 1/60 and/or with more than 50% field defect in one or both eyes, were considered to have marked visual affection. The indication of surgery in each patient was reviewed, and whether surgery was primary or secondary line of treatment, the surgical approach used in each patient was documented and any intraoperative complication was documented.

4-Follow up:

Follow up period ranged from 3 months to 2 years, with postoperative serum prolactin measured within the first postoperative week to detect the remission rate and to be repeated after 3 months then on individual basis. Postoperative MRI (performed within 3 months after surgery) was reviewed and extent of resection in each case was documented. Postoperative adjuvant therapy whether medical treatment or radiosurgery was recorded.

RESULTS

This study consisted of eighteen female and twelve male patients. The mean age of the patients was 36 years (median age 32 years) with a range from 12 to 69 years. Seven patients (23.33%) harbored microadenomas, sixteen patients (43.33%) had macroadenomas, and seven patients had giant adenomas. This study showed also sex difference.
comparing microadenoma and macroadenoma, as in microadenoma the seven cases were all females, in macroadenoma there were nine females and seven males with female predominance (56.25%), in giant adenoma there were two females and five males which shows male predominance of (71.4%). According to pre-operative prolactin, patients were classified into three groups; group 1 which included seventeen (56.67%) patients and prolactin ranged from 200-500 ng/ml. Group 2 in which prolactin ranged from 500-1000 ng/ml included four (13.33%) and the third group with nine (30%) cases and their prolactin was higher than 1000 ng/ml. In this study headache was the presenting symptom in seventeen patients (56.6%), amenorrhea & galactorrhea was the presenting symptom in thirteen cases (43.33%) which were female loss of libido and impotence was found in four male cases (13.33%), while infertility was found in five female cases (16.67%). Visual abnormality occurred in four male cases (56.67%), apoplexy was present in four cases (13.33%), 3rd nerve palsy was found in one case, and 6th nerve palsy was found in one case. Spontaneous csf leak was found also in one patient after medical therapy. Retrospective analysis of indications for the operative treatment of prolactinomas in our study revealed several patient subgroups. Subgroup 1 consisted of five patients with intolerable side effects due to dopaminergic therapy. Additionally, there were non-responders to DA therapy with regard to normalization of hyperprolactinemia (subgroup 2); which included ten cases, or inadequate tumor shrinkage (subgroup 3); and it included two patients (Fig. 2).

There were a further nine patients presenting either with cranial nerve palsies due to involvement of the cavernous sinus, CSF fistulas after therapy with DA or signs of an acute space-occupying tumor, hemorrhage on MRI with or without previous medical therapy. These patients were excluded from the surgical indications analysis because they all represented surgical emergency cases independent from the time periods and the type of dopaminergic drug. Thus, we finally defined three ‘classical’ indication subgroups for operative treatment of prolactinomas. By contrast the retrospective analysis revealed two subgroups of patients that we defined as ‘modern’ indications for transsphenoidal surgery for prolactinomas consisting of two patients who individually decided on a primary surgical treatment (subgroup 4) and patients with cystic tumors (80% of tumor volume according to the preoperative MRI T2-sequences) that are unlikely to shrink sufficiently under dopamine agonist (subgroup 5) which included two cases.

All patients underwent transsphenoidal surgery, except three cases of those with giant adenomas who received trans-cranial operative procedure. Overall initial remission after selective adenomectomy with the dopaminergic therapy aborted at least 4 weeks before surgery was achieved in fifteen out of thirty patients (50%), also including giant prolactinomas. The seven cases of microadenoma showed complete normalization of prolactin while eight cases (34.7%) of non invasive macroadenoma showed normalization of prolactin. The other fifteen cases who showed only reduction in serum prolactin they started to receive medical treatment with small doses, five of them showed normalization over months post operatively. Two cases of invasive adenoma received radio surgery. Visual manifestation improved in thirteen patients out of seventeen (76.4%). Gross total excision was obtained in fifteen patients out of thirty and partial excision in the remaining (Fig. 3), the gross excision was achieved in all the cases of microadenoma (Fig. 4) and seven cases of macroadenoma (23.33%). Post-operatives leak occurred in three patients, one case was treated by lumbar drain insertion for 5 days the other two cases needed surgical repair. Diabetes insipidus occurred in four patients being transient in three cases and permanent in one patient.
Fig. 4a-c: A 25-year-old woman, with microprolactinoma presented with amenorrhea and galactorrhea. The patient’s initial serum prolactin level was 47.7 ng/ml. She underwent a complete transsphenoidal resection of the tumor. The morning fasting serum prolactin level obtained on postoperative day 1 was 1 ng/ml, which was suggestive of a biochemical cure. a: pre-operative coronal without contrast. b: post-operative coronal without contrast. c: post-operative coronal with contrast.

DISCUSSION

The therapy of prolactinomas is aimed at: (1) reduction of prolactin concentrations and its clinical consequences, such as gonadal dysfunction, infertility, and osteoporosis; (2) reduction of tumor mass, thereby relieving visual field defects and hypopituitarism; (3) preservation of residual pituitary function; (4) prevention of continuing growth of tumour mass, and (5) improvement of quality of life. Treatment goals are similar for micro- and macroprolactinomas, although in the case of macroprolactinomas more emphasis of the therapy is focused on control of tumor size. Medical treatment with bromocriptine and later by cabergoline has been considered the first line of treatment in most of the patients with prolactinomas, being successful in achieving biochemical cure in up to 90% of cases in addition to deceasing tumor size (Fig. 5).

Disadvantages of bromocriptine treatment are the frequent occurrence of side effects, leading to interruption of therapy in 12% of the patients. Tumor regrowth after discontinuation has been reported. Surgery has been considered as a second line therapy in patients with prolactinoma. The international Pituitary Congress in San Diego in 2005 finalized that non-responders to dopaminergic therapy, patients with intolerable adverse effects of DA therapy, patients with CSF fistulas under DA, or patients with rapidly progressive neurological deficits are candidates for a surgical intervention. These patients also represent the ‘classical’ indication subgroups in this paper. One of the main surgical indications in this study was failure of medical treatment to normalize the prolactin level (ten cases) and/or control tumor growth, and this included (two cases), following surgery patients with these indications achieved normalization of prolactin in (three cases) while the rest of the patients had lower postoperative prolactin levels but no cure. All of non-cured patients were given lower doses of medications which were more tolerated, a finding reported by Amar and his colleagues. Furthermore, cure was achieved with the postoperative medical treatment in four of these patients, as tumor cytoreduction improves the response to medical treatment and decreases the needed doses. Five patients were operated upon due to intolerance to medical treatment (three on bromocriptine and two on cabergoline), three of these patients were cured, while the other two patients were given cabergoline in lower dose and achieved cure. The series included only two patient who preferred surgery as initial treatment to avoid long-term medical therapy, an indication reported by Thomson, and one patient was cured. Pituitary apoplexy has been considered as an indication for surgery by many authors; however other authors reported successful treatment with dopamine agonists in cases with apoplexy.

The four patients operated upon for apoplexy have not been on medical treatment previously, and biochemical cure was achieved in one of them. Marked visual deterioration was the indication of surgery in 56.67% of patients, and it was considered as a surgical indication.
CONCLUSION

Prolactinomas account for approximately 40% of all pituitary adenomas. Medical therapy with dopamine agonists is highly effective in the majority of cases and represents the mainstay of therapy. Surgery is a valuable second line of treatment in cases of failure of medical treatment or intolerance. Relative indications of surgery include patients presenting with marked diminution of vision and patients with apoplexy. New indications in those having microadenoma with cystic component and are likely not to respond to medical treatment, the biochemical cure can be achieved in microadenoma. Biochemical cure is rarely achieved following surgery in patients with giant and/or invasive adenomas. Complicated situations, such as those encountered in resistance to dopamine agonists, pregnancy, and giant or malignant prolactinomas, may require multimodal therapy.

Disclosure:
The authors have no personal, financial or institutional interest in any of the drugs, materials, or devices described in this article.

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