

TREATMENT OUTCOMES OF PITUITARY TUMORS AT THE UNIVERSITY OF SANTO TOMAS HOSPITAL: 2004-2008

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ABSTRACT

Objectives: To describe the outcome of treatment of pituitary tumors at the University of Santo Tomas Hospital (USTH) in 2004-2008 in terms of achieving clinical improvement, hormonal control, and radiological cure and to determine the mortality and morbidity of patients during the immediate postoperative period.

Methodology: This is a retrospective cohort study. Clinical, ophthalmological, hormonal and neuroradiological findings were evaluated at baseline and after treatment. Hormonal control was defined as normalization of excess hormone production while radiological cure was defined as complete eradication of the tumor.

Results: Data of forty one patients (23 males, 18 females; mean age: 42 years, range: 19-68) were reviewed. Majority have clinically non functioning tumors (n=17), followed by prolactinoma (n=12) and acromegaly (n=7). Eighty six percent were macroadenomas. Transphenoidal surgery (TSS) was the main treatment in 70% of patients (n=28) while dopamine agonist was used in another 28% (n=11). Diabetes insipidus occurred in 24% of cases. One patient died of hospital acquired pneumonia. Thirty one patients were evaluated after a mean of 1.4 years (range: 0.25 – 3.9 years). There was a decrease in visual disturbances (73 to 23%), headache (63 to 6%), signs and symptoms of hypogonadism (38 to 19%) and

hypopituitarism (60 to 52%) before and after treatment, respectively. Hormonal control was achieved in 71% while radiological cure was achieved in 35%.

Conclusion: Improvement in clinical parameters and hypopituitarism were achieved after treatment. Hormonal control was achieved in majority of cases despite residual tumors. Surgery was carried out safely in most cases.

Keywords: Pituitary Tumors, Treatment Outcome

INTRODUCTION

Pituitary tumors result in significant morbidity and premature mortality.¹ The medical literature is rich with reports about the clinical profile of Filipino patients with this tumor which showed that the most common presentation were signs and symptoms arising from tumoral mass effect.^{2,3,4,5,6,7} In one series, headache was observed in up to 54% of cases while visual disturbances were observed in 79% in another series.^{2,4} The headache is due to stretching of the dura matter which is innervated by the ophthalmic division of the trigeminal nerve and/or hydrocephalus while visual disturbances results from compression of the optic chiasm or extension of the tumor to the cavernous sinus causing compression of the trochlear nerve.¹ In addition, a large tumor may decrease the availability of hypothalamic stimulatory hormones due to compression of the pituitary stalk or hypothalamic involvement itself or cause compression of normal pituitary tissues all leading to hypopituitarism.⁸ This was found in up to 73% of cases.²

Published data on how we were able to address these problems are still lacking. Moreover, outcome as to achievement of biochemical or hormonal cure and eradication of tumor with the present treatment options available in our setting is still scarce. In our institution, Faller and Gomez have reported a biochemical cure of 32% and radiological cure of 16% among patients treated for pituitary tumors in 1991-2000.² Since then, there have been changes in the management of this disorder with the availability of more sophisticated hormonal and radiological examinations and treatment options. This has

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prompted us to review cases of pituitary tumors treated in our institution during the past four years and to compare our findings with the previous report.

Objectives

This study was undertaken to describe the outcome of treatment of pituitary tumors treated at the University of Santo Tomas Hospital (USTH) in 2004-2008 and to determine the mortality and morbidity during the immediate post operative period. Specifically, outcome was assessed in terms of achieving clinical improvement in headache, visual disturbances, and signs and symptoms of hypogonadism. In addition, biochemical or hormonal control and radiological evidence of cure were determined.

MATERIALS AND METHODS

Patients

We analyzed the records of patients who were treated for pituitary tumor from 2004 to 2008 in our institution. The diagnosis was based on clinical presentation, hormonal evaluation, documented pituitary tumor by cranial magnetic resonance imaging (MRI) and histopathologic examination when available.

Duration of follow-up was determined from the initiation of first treatment to the last date of follow-up in the clinic. The patient's most recent clinical state and results of biochemical and radiological evaluations were the outcomes described. Patients were included if at least three months had elapsed since the time of initial treatment to ensure a minimum of 3 months of follow-up.

Clinical Parameters

Improvement in clinical parameters namely headache, visual disturbances and signs and symptoms of hypogonadism was assessed by reviewing prospectively filled up pituitary tumor evaluation form of the Section of Endocrinology and Metabolism of the USTH seen by endocrinology fellows at the clinical division and private wards and the charts of patients seen at private clinics.

Visual disturbances include visual field cuts, optic atrophy and cranial nerves III, IV and VI palsies accounted for by pituitary tumor extension to the optic chiasm and cavernous sinus where cranial

nerves IV and VI are located. Basic ophthalmological examination and assessment of visual acuity and visual fields by confrontation test and perimetry were done.

Signs and symptoms consistent with hypogonadism include amenorrhea, decreased libido, erectile dysfunction and infertility.

Endocrine Evaluation

Assessment of anterior pituitary function was made by measuring serum levels of growth hormone (GH), insulin-like growth factor-1 (IGF-1), prolactin (PRL), follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, testosterone, adrenocorticotrophic hormone (ACTH), 8AM cortisol, thyroid stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3).

The presence of hypopituitarism was defined as biochemical deficiency in at least one endocrine axis. Secondary hypogonadism or FSH/LH deficiency was diagnosed when estradiol or testosterone levels were low in the presence of inappropriately normal or low FSH and/or LH levels. In two postmenopausal women, this was diagnosed when LH or FSH was below the normal postmenopausal range. Secondary hypothyroidism or TSH deficiency was diagnosed by a low free thyroxine (fT4) with low or normal thyrotropin (TSH). Secondary adrenal insufficiency or ACTH deficiency was diagnosed by early morning serum cortisol of <3.0 ug/dL or below the lower limit of normal values accompanied by other signs and symptoms of adrenal insufficiency as assessed by the attending physician. The normal range of serum cortisol in our laboratory is 8.7 to 22.4 µg/dl.

Secondary or concurrent hyperprolactinemia was defined as serum prolactin that is less than 5-fold elevated in a patient not diagnosed to have prolactinoma.

Resolution of hypopituitarism was based on biochemical evidence of normalization of a previously documented deficiency. Biochemical control of prolactinoma was defined as normalization of prolactin levels while that of acromegaly was defined as normalized insulin-like growth factor-I (IGF-I) for age and sex and a glucose-suppressed GH value less than or equal to 2 mg/dl. In Cushing's disease, a suppression to <1.8 ug/dl of early morning serum cortisol after an overnight 1mg-dexamethasone was used to assess cure.

Neuroradiological Evaluation

Based on cranial MRI, pituitary adenomas with greatest diameter less than 10 mm were considered microadenomas while those greater than 10 mm were labelled as macroadenomas. Tumor extension was classified as suprasellar, parasellar, infrasellar, or combined suprasellar and parasellar, infrasellar extension. Radiographic cure was defined as absence of visualized tumor on repeat cranial MRI. Tumor regrowth was defined as increase in size of residual tumor.

RESULTS

Forty one patients were included for analysis out of 53 patients who consulted with pituitary tumors during the study period. Pituitary adenomas constitute the majority of cases while other pituitary tumors were craniopharyngioma, and Rathke's cleft cyst. The histological confirmation of pituitary adenoma was obtained in 30 out of 36 patients. Immunohistochemical stain was not available in the majority. There were 23 males and 18 females ranging in age between 19 and 68 years (mean: 42).

The baseline characteristics of patients per tumor type were presented in table I while outcome of treatment was summarized in table II. There were 17 cases of clinically non-functioning tumors (CNFT). Of these, 12 were males and 5 were females aged 19-67 years (mean: 46). All were macroadenomas ranging in size between 12 to 48 mm. All patients underwent adenectomy via transphenoidal approach as primary treatment. Three patients were lost to follow-up. Radiological evidence of cure was achieved in 3 patients while 11 other patients had residual tumors. Of the latter, 5 received radiotherapy and 6 were observed. During a 10-42 months range of follow up, tumor regrowth was observed in one patient who subsequently underwent repeat TSS followed by RT. Visual disturbances resolved in 10 patients while headache totally resolved in all patients. Signs and symptoms of hypogonadism resolved in only one of 3 patients. Biochemically, hypopituitarism was persistent in 11 patients. No new case of hypopituitarism was identified so far.

Twelve patients (4 males and 8 females, mean age: 34, range: 19-51) were treated for prolactinoma. Baseline serum prolactin levels ranged from 114 to 257,100 ng/ml. Ten patients have macroadenomas (range: 17-71 mm), three of whom have cystic components while four were giant and invasive which measured more than 40 mm with varying extensions

to the frontal lobe, midbrain, pons, cerebellum and third ventricle producing obstructive hydrocephalus. Three of these tumors have mixed solid and cystic components. Two patients have microadenomas (range: 1.7-8.5 mm). Bromocriptine at a dose of 2.5 to 15mg/day was the initial treatment for 11 patients. Of these, two patients were lost to follow up while 2 other patients achieved both hormonal control and radiological evidence of cure. Seven patients eventually underwent TSS due to the following indications: failure to normalize PRL after 3 months of being at 15mg/day of bromocriptine (n=1), growth of tumor (n=2) and pituitary apoplexy (n=2) while on treatment. Two other patients preferred surgical over medical treatment. Residual tumor was present after surgery in all of these patients thus, bromocriptine was continued which afforded hormonal control in four patients. Two patients underwent radiotherapy. During follow-up of 3 to 36 months, tumor regrowth was seen in one patient. Another patient who presented with a large and invasive cystic tumor but the serum prolactin was only 114 ng/ml even after 1:100 dilution underwent open craniotomy as initial treatment. Immunohistochemical stain of tissues obtained turned out positive for PRL. Due to residual tumor, bromocriptine was commenced postoperatively. Serum prolactin was still elevated as of last follow-up. Four patients have improvement in visual disturbances, headache and signs and symptoms of hypogonadism. Biochemically, hypopituitarism was persistent in four patients after treatment.

There were seven patients treated for acromegaly (4 males and 3 females, mean age: 41 years, range: 26-53). Two patients have microadenomas (range: 4-9mm) while 5 patients have macroadenomas (range: 15-32cm). The basal GH values were 10-36 ug/L. All patients underwent TSS. Hormonal control and radiological evidence of cure were achieved in 5 patients. Residual tumor was present in 2 patients, one of whom underwent RT. Visual disturbances and headache resolved in all patients. However, signs and symptoms of hypogonadism specifically amenorrhea, infertility, and erectile dysfunction were still persistent in 4 patients. This was despite improvement in anterior pituitary function in biochemical improvement in 2 patients.

Other types of tumors treated were Cushing's disease (n=1), Rathke's cleft cyst (n=1) and craniopharyngioma (n=3). A microadenoma in a 52-year old female with clinical and biochemical profile consistent with Cushing's disease was

successfully removed after TSS. Serum cortisol was also suppressible with a 1-mg dexamethasone test postoperatively. Rathke's cleft cyst was successfully removed after surgery but patient was lost to follow-up after a month. Surgery was the main treatment for patients with craniopharyngioma (n=3). Of two patients who followed-up, complete tumor removal was achieved in one patient but symptoms of headache, visual disturbances and signs and symptoms of hypogonadism resolved in both patients. Hypopituitarism was persistent in one patient with residual tumor.

Transphenoidal surgery (n=29, 71%) was the main treatment for the majority of our patients. Open craniotomy was performed in three patients (one with invasive macroprolactinoma and 2 patients who initially underwent TSS but required evacuation of hematoma formation postoperatively). Radiotherapy (RT) and ventriculoperitoneal (VP) shunt were used as adjunct therapies. At the completion of this paper, 2 more patients with CNFT and acromegaly were still for RT due to the same indication. VP shunt was done in 4 patients (CNFT, n=1; prolactinoma, n=1; craniopharyngioma (n=2) due to hydrocephalus. One patient required a repeat TSS after having undergone TSS and radiotherapy.

The immediate complications of surgery were shown in table III with transient diabetes insipidus as the most common in 17% of cases. None of the patients developed permanent diabetes insipidus. This was followed by cerebrospinal fluid (CSF) rhinorrhea in 4 patients. Two patients developed transient worsening of vision at the second and 30th day after TSS. Repeat imaging showed hematoma requiring open craniotomy. One patient with craniopharyngioma died 7 days post op due to hospital/ventilator acquired pneumonia.

DISCUSSION

In this study, we reported the outcome of treatment in patients having large pituitary tumors. Transphenoidal surgery was the most frequent mode of treatment since this is the treatment of choice in the majority of tumors treated such as CNFT, acromegaly, craniopharyngioma, Cushing's disease and Rathke's cleft cyst. Although medical is the treatment of choice for prolactinoma, and was indeed the initial treatment in all but one patient in our series, 63% of them eventually underwent surgery.

Majority of cases came from the clinical division of our hospital. Immediate postoperative mortality occurred in only one patient due to hospital acquired pneumonia. Transient diabetes insipidus was the most common complication but has declined in incidence from 45% in our previous series.² Moreover, none of our patients developed permanent diabetes insipidus.

Overall, hormonal control was achieved in 71% (n=12 out of 17) of hypersecreting tumors while radiological cure was achieved in 37% of cases (n=12 out of 32). Compared with the previous report of Faller and Gomez, there was improvement in the outcome in terms of achievement of hormonal control and radiological evidence of cure.

We compared the baseline characteristics of our patients who have their tumors completely removed and those who have residual tumors after surgery in table IV. As shown, microadenomas (acromegaly 2, Cushing's disease 1) were completely removed after surgery. Two patients with microprolactinomas also achieved radiological evidence of cure with bromocriptine therapy alone. Only 12% (n=4) of macroadenomas were completely removed after surgery showing that complete tumor eradication is not always possible in patients with large tumors.⁹ This goal is also difficult to achieve in invasive tumors especially those encasing major blood vessels as seen in tumors with cavernous sinus extension (n=6). Indeed, tumor size is a relevant prognostic marker for the success of any treatment with surgical and medical outcome being better in patients with microadenomas compared with macroadenomas. For instance, success of TSS in GH-secreting microadenomas was reported to be 65% versus 52% in macroadenomas.¹⁰ Medical treatment using low dose bromocriptine for prolactinoma was able to normalize PRL levels, restore gonadal function, and cause tumor shrinkage in up to 80 to 90% of patients with microprolactinomas while only 70% with macroadenomas.¹¹ Gillam *et al* summarized surgical outcome for prolactinoma in 50 studies and found out that TSS normalized PRL in 38 to 100% of microprolactinoma (n=2,137) and 6.7 to 80% of macroprolactinoma (n=2,226). Overall long-term surgical cure rate for microadenomas (using a normal PRL as criterion) is 61.1% while that for macroadenomas is 26.2%.¹² Remission rates for Cushing's disease presenting as microadenoma are in the range of 65-90% and less than 65% in macroadenomas.⁹

Table I. Baseline Characteristics of Patients According to Pituitary Tumor Type

	CNFNT	PROLACTINOMA	ACROMEGALY	CUSHING'S DISEASE	RATHKE'S CLEFT CYST	CRANIO-PHARYNGIOMA	ALL CASES (%)
n	17	12	7	1	1	3	40
Mean age (range)	46 (19-67)	34 (19-51)	41 (26-53)	52	61	35 (22-42)	41 (19-67)
Male	12	4	4	0	1	2	22 (55)
Clinical Presentation							
Visual disturbances	16	9	3	0	1	1	29 (73)
Headache	12	8	3	0	1	2	25 (63)
Hypogonadism	2	9	4	0	0	0	15 (38)
Endocrine Evaluation							
LH and/or FSH deficiency	5/8	0/4	3/5	ND	ND	ND	8/17 (47)
TSH deficiency	13/16	5/12	4/7	0/1	1/1	2/3	24/40 (60)
ACTH deficiency	9/16	5/12	1/7	NA	0/1	1/3	13/26 (50)
Secondary hyperprolactinemia	10/16	NA	2/6	ND	1/1	1/3	13/26 (50)
Neuroradiological Evaluation							
Macroadenoma	17	10	5	0	NA	NA	31/36 (86)
Tumor extension							
Suprasellar	16	10	5	NA	1	2	33/40 (82)
Cavernous sinus	4	7	1	NA	–	1	13/40 (33)
Sphenoid sinus	6	5	2	NA	–	2	15/40 (38)
Combined	5	9	2	NA	–	2	18/40 (45)
Hydrocephalus	2	2	0	0	0	2	6/40 (15)
Treatment							
Main treatment, n							
TSS	17	1	7	1	1	2	28 (70)
Medical	–	11*	–	–	NA	NA	11 (28)
Adjunct treatment, n							
RT	5	1	1	–	–	2	9 (23)
VP shunt	1	1	–	–	–	2	4 (10)
Medical	–	NA	–	1	–	NA	1 (2)
Open Craniotomy	1	1	–	–	–	1	3 (7)

CNFNT – Clinically Nonfunctioning Tumors; NA – not applicable; ND – not done; TSS – transphenoidal surgery; RT – radiotherapy; VP – ventriculoperitoneal.

Endocrine evaluation per tumor type was expressed as number of cases with positive result/cases tested.

* Nine patients subsequently underwent transphenoidal

Table II. Follow-Up of Patients after Treatment

	CNFNT	PROLACTINOMA	ACROMEGALY	CUSHING'S DISEASE	CRANIOPHARYNGIOMA	ALL CASES (%)
n	14	9	7	1	2	31
Duration, months	10-42	3-36	3-47	14	4-24	3-47
Clinical Presentation						
Visual disturbances	4	3	0	0	0	7 (22)
Headache	0	2	0	0	0	2 (6)
Hypogonadism	2	3	1	0	0	6 (19)
Endocrine Evaluation						
LH/FSH deficiency	4/7	0/2	1/3	ND	ND	5/12 (42)
TSH deficiency	11/14	4/9	2/7	ND	0/2	16/32 (50)
ACTH deficiency	4/14	1/9	1/7	0/1	0/2	6/32 (19)
Biochemical control						
	NA	6/9	5/7	1/1	NA	12/17 (71)
Radiological cure						
	3/14	2/9	5/7	1/1	1/2	12/32 (37)

CNFNT – Clinically Nonfunctioning Tumors; NA – not applicable; ND – not done

Endocrine evaluation per tumor type was expressed as number of cases with positive result/cases tested.

Biochemical and radiological cure was expressed as cured/number of cases.

Table III. Immediate Postoperative Complications of Transphenoidal Surgery and Open Craniotomy

Complications	Frequency (%)
Transient Diabetes Insipidus	7 (17)
CSF leak	4 (9)
Hemorrhage	2 (4)
Transient worsening of vision	2 (4)
Death	1 (2)

CSF – cerebrospinal fluid

Table IV. Characteristics of Patients Who Achieved Complete Tumor Removal

	Tumor Completely Removed n (%)	Tumor Incompletely Removed n (%)
Size of tumor		
Microadenoma	3 (100)	0
Macroadenoma	4 (12)	22 (84)
Tumor extension		
Suprasellar	4 (12)	22 (84)
Cavernous sinus	0	6 (100)
Sphenoid sinus	6 (54)	5 (46)
Combined	5 (50)	5 (50)
Tumor type		
CNFT	2 (12)	11 (84)
Prolactinoma	--	7 (100)
Acromegaly	5 (71)	2 (29)
Cushing's disease	1 (100)	0
Craniopharyngioma	1 (50)	1 (50)

CNFT – Clinically Nonfunctioning Tumors

The major benefit of surgery in patients with large sellar tumors is the amelioration of signs and symptoms secondary to mass effect and possibly, hypopituitarism without compromising function of normal pituitary tissues and adjacent vital structures.⁹ Debulking also decreases tumor burden which may lead to a more successful use of radiation or pharmacologic therapy, or a combination of both as adjunct therapies.¹ Thus, despite the low radiological cure rate, much benefit was observed in providing relief of visual disturbances and headache among our patients. Dekkers *et al* reviewed 8 articles on the effects of transphenoidal surgery in clinically non-functioning macroadenoma and showed that visual field defects improved in 31 up to 87% of cases. Moreover, full recovery from headache was achieved in the majority of cases.¹³ Losa *et al* also showed that resolution of headache among those with prolactinomas occurred to the same extent in both radiologically cured and not-cured patients.¹⁴ In our series, headache was persistent in those who have significant tumors left while persistent visual

disorders was found among those who already have optic atrophy at baseline.

Although surgery was effective in providing relief from headache and visual disorders, hypopituitarism was persistent in almost half of our patients with secondary hypothyroidism in 50%, followed by secondary hypogonadism and adrenal insufficiency in 42% and 19% of patients, respectively. The lack of complete work-up especially test for growth hormone deficiency may underestimate the actual rate of hypopituitarism in our patients. Other series have shown that pituitary insufficiency that manifests preoperatively from tumor compression of the normal gland may or may not diminish with surgical debulking.⁸ Using pooled data from 6 studies, a significant proportion of patients have not recovered from hypopituitarism with GH deficiency found in about 83% of cases, followed by LH/FSH then TSH and ACTH deficiency in 60% and 30% of cases, respectively.⁸

The effects of pituitary tumor and its treatment to the gonadal function of our patients was included in this report because most of them were in the reproductive age group and that signs and symptoms of hypogonadism were actually the reasons for consult in some of them. In pituitary tumors, hypogonadism may result from LH/FSH deficiency or the antagonistic effect of hyperprolactinemia to their pulsatility.^{1,12,15} Interestingly, clinical and biochemical evidence of hypogonadism do not always go hand in hand. For instance, 4 male patients denied of any symptoms despite low serum testosterone with inappropriately normal LH and FSH. In addition, 2 of our patients (one with acromegaly and another with prolactinoma) still have amenorrhea despite normalized PRL and suppressible GH. These probably reflect the complex nature that regulates a normal function of the hypothalamic-pituitary-gonadal axis.

There were clear indications for the use of other treatment options in some of our patients such as cabergoline in prolactinomas who failed to respond with bromocriptine or somatostatin analogues as adjuncts to residual GH-producing tumors. Unfortunately, these are not yet available in our setting. As soon as they are, outcome is expected to improve making the result of this study a baseline from which future outcomes can be compared with.

To our knowledge, this is the first local study to focus on the outcome of treatment of pituitary tumors. We have not only provided baseline data but have added information to existing knowledge that a large tumor at diagnosis portends poor outcome in terms of morbidity from hypopituitarism, need for adjuvant treatment for residual tumor, and lifelong hormone replacement and follow-up. Previous local studies have demonstrated the predominance of macroadenomas across different types of tumors.^{2,4,5,6,7} Since these partially reflect late diagnosis, recognition of signs and symptoms is of paramount importance. In addition, the results of this study have also opened avenues for further research to look at the aggressive characteristics of these tumors. Although the mean follow-up period of our patients was relatively short, 3 patients already have tumor regrowth (2 CNFT, 1 prolactinoma). In CNFT, Dekkers *et al* observed tumor regrowth in 9 and recurrence in 1 out of 97 patients after a mean follow-up of 6 years after TSS.⁸

CONCLUSION

With a follow-up of 0.25 to 3.9 years, most patients in our series have residual tumors but majority of hypersecreting tumors achieved biochemical or hormonal

control. Our outcome has improved when compared with previous report. Transphenoidal surgery was the most common mode of treatment and was carried out safely in our series. Transient diabetes insipidus was the most complication.

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