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Effects of Transshenoidal Surgery on Patients with Nonfunctioning Pituitary Tumours

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ABSTRACT:

Objective: *Transsphenoidal surgery is the treatment of choice for nonfunctioning pituitary macroadenomas (NFMA). In this study we evaluated the long-term effects of a treatment strategy in which postoperative radiotherapy was not routinely applied to patients with NFMA. The present study was undertaken to assess the effect of surgical removal of adenoma on peripheral adenohypophyseal hormones. In addition, the pituitary hormones have also been measured directly in the adenoma tissue following its surgical removal.*

Materials and Methods: *The present study initially included 22 consecutive patients 18 men and 4 women, of 22-55 (44 ± 2.3) years of age operated for NFMA between 2005 and 2008 at Lahore General Hospital, Lahore. Three of these patients 2 men and 1woman died during the follow-up period and were excluded from the study. Follicle stimulating hormone (FSH), Growth hormone (GH) were determined in serum before and following trans-sphenoidal adenomectomy. The FSH, GH content of the excised adenoma tissue was also measured in male patients. All hormone determinations were carried out using commercially available immunoassay kits (ELISA and IRMA) in duplicate.*

Results: *Radiological imaging revealed a macroadenoma in all patients, with suprasellar extension in 96% and parasellar/infrasellar extension in 32% of cases. Visual field defects were present in 95% of the patients and improved in 84% of cases after surgery (complete recovery 3/19 (15%); partial recovery 13/19 (68%). The results demonstrate that in a subset of 4 of the 16 male patients with NFPAs the presurgical serum FSH values (45.1 ± 0.7 mIU/ml) were markedly and significantly greater than those of the remaining 12 patients (7.9 ± 0.7 mIU/ml) and of control subjects (8.8 ± 0.6 mIU/ml). Following removal of the adenoma in these 4 patients, peripheral serum FSH levels fell within the normal range. In the remaining 12 patients peripheral and mean FSH levels were within the normal range. The individual and mean presurgical serum FSH value in all the three female patients were also higher than those of the control subjects (36.4 ± 6.5 vs 8.4 ± 1.0 mIU/ml, respectively; $P<0.05$). Following removal of the adenoma in 2 female patients serum FSH concentrations showed a marked decline of FSH levels (5.7 mIU/ml and 7.2 mIU/ml) whereas in the remaining one patient, the FSH levels remained relatively high (34.5 mIU/ml). The adenoma tissue FSH content in patients with initial higher serum FSH levels, was also significantly greater than that of the other patients (21.5 ± 2.1 vs 4.4 ± 1.9 IU/g). No significant differences were observed between pre and post-surgical serum GH levels. The GH content of adenoma tissue was either non-detectable or in the low range as compared to the GH content determined in control pooled pituitary tissue.*

Conclusions: *The present study suggests that pituitary tumours diagnosed as NFPAs constitute a heterogenous group of adenomas with regard to their secretory activity of intact adenohypophyseal hormones. Whereas some of these adenomas activity may synthesize one or more pituitary hormones, peripheral concentrations may not be sufficient to produce overt clinical symptoms of hormone hypersecretion. In addition, our study suggests that Transspenoidal surgery without postoperative radiotherapy is an effective and safe treatment strategy for NFMA, without evidence for tumour re-growth in 90% of all subjects, at least for the duration of follow-up presented in this study. However, additional studies are required to exclude higher re-growth and recurrence rates during prolongation of the duration of follow-up.*

Keywords: *Non-secreting pituitary adenomas, Pituitary content, Macroadenomas.*

INTRODUCTION

Pituitary tumours are abnormal growths on the pituitary gland that may secrete excessive amounts of hormones and also in some instances, restrict the pituitary gland resulting in lower peripheral levels of hormone secretion. In most cases, pituitary tumours remain confined to pituitary gland and the associated tissues. Since these tumours do not spread to other parts of the body, therefore, the term adenomas is generally used to designate these growths.[1,2]

Nonfunctioning pituitary adenomas account for approximately 30% of pituitary tumors[3]. The tumors are usually seen in the fourth and fifth decades and are more common in males than females. Most of these arise from gonadotroph cells and are monoclonal and usually chromphobic.[4,5] It had been thought that these tumors did not produce hormone subunits. Recently, however, improved immunoperoxidase staining techniques reveal that some nonfunctioning adenomas actually secrete one or more of the glycoprotein hormones follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid stimulating hormone (TSH) and/or their alpha and beta subunits. Alpha subunit production has been found more commonly than beta subunit production.[6-8]

The clinical presentations for Non-functioning Pituitary Adenomas include visual symptoms, headache or symptoms and signs of hypopituitarism. Visual symptoms are found in 60-70% of cases and may be in the form of visual blurring, a loss of temporal field in one or both eyes, and loss of visual acuity. Headache is found in about 40% of patients and is often nonspecific dull ache over vertex that does not vary with position or time of the day.[9,10]

These nonfunctioning tumors invariably contain cytoplasmic secretory granules, suggesting that they do produce specific substances, unidentified hormones, biologically inactive precursors, or hormone fragments. Some of these hormonally silent tumors are revealed by immunohistochemistry to contain hormones, but they appear to be incapable of discharging these hormones in sufficient quantities to disturb endocrine equilibrium.[11,12]

Advances in radioimmunoassay, immunocytochemical and molecular biology techniques have allowed for detailed characterization of these tumors. In vitro studies have shown that majority of clinically nonfunctioning adenomas synthesize intact glycoprotein hormones and/ or their free alpha and beta-subunits. The glycoprotein hormones include LH, FSH, and TSH and consist of a common alpha subunit and a unique beta subunit which confers both immunologic and biologic specificity. Secretion of gonadotropin and free subunits occurs commonly in cultured pituitary tumor cells, with only a minority of tumors showing evidence of TSH secretion. Therefore, the majority of these tumors are presumably of gonadotroph origin.[13]

Nonfunctioning pituitary macroadenomas (NFMAs) are the most prevalent macroadenomas.[14] The main presenting symptoms of NFMAs are visual field defects and hypopituitarism due to mass effects. Transsheniodal surgery is the treatment of choice because medical treatment in general is not effective in reducing the size of NFMAs. However, during long-term follow-up after transsphenoidal surgery, there is tumour growth in 12-46% of the patents.[15] Therefore, some centers provide postoperative radiotherapy in a selection of the patients to prevent tumour re-growth.[15,16] Nonetheless, even after postoperative radiotherapy, tumour re-growth was reported in 2-36% of the radiated patients. In addition, radiotherapy induces a higher incidence of hypopituitarism during long-term follow-up[16-18] and is associated with rare, complications such as secondary brain tumours. Therefore, a restrictive indication for postoperative radiotherapy seems appropriate.

Prospective trials evaluating the effect of postoperative radiotherapy on re-growth rates of NFMAs have not been published. Retrospective studies, involving homogeneous cohorts of transsphenoidal operated NFMAs with a long follow-up period, are scarce.[19] Only two studies[20,21] have been published in consecutive NFMA patients with a wait- and –see policy after transsphenoidal surgery. These studies, comprising 71 and 51 patients, respectively, report tumour growth in 21 and 26% during long-term follow-up. However, these reports do not propose a wait- and –see policy for all NFMA patients.

Few studies have been carried out to systematically assess the effect of removal of nonfunctional pituitary adenoma on peripheral adenohypophyseal hormones and the correlation of the serum levels with the hormone content of the adenoma tissue. The present study was, therefore, undertaken to determine serum gonadotropin FSH, TSH, GH and PRL concentration in patients before and following removal of pituitary adenomas diagnosed presurgically, as nonfunctional. In addition we have measured hormones content of the adenoma tissues for a possible correlation with serum levels of these hormones.

CONCLUSIONS

Few studies have been carried out to systematically assess the effect of removal of nonfunctional pituitary adenoma on peripheral adenohypophyseal hormones and the correlation of the serum levels with the hormone content of the adenoma tissue.

The present study was, therefore, undertaken to evaluate the long-term effects of transsphenoidal surgery in an unselected patients operated for NFPA and to determine serum FSH and GH concentration in patients before and following removal of pituitary adenomas diagnosed presurgically, as nonfunctional. In addition we have measured hormone content of the adenoma tissues for a possible correlation with serum levels of these hormone.

MATERIALS AND METHODS

The present study initially included 22 patients 18 men and 4 women, of 22-55 (44 ± 2.3) years of age with NFPAs. Three of these patients 2 men and 1woman died during the follow-up period and were excluded from the study. All patients underwent pituitary tumour surgery. Between 2005-2008, all patients were operated by transshenoidal surgery for NFMA (diameter > 1 cm) at the Department of Neurosurgery, Lahore General Hospital, Lahore. Patients were assessed at presentation before surgery, within the first 2 months after surgery. Clinical characteristics, visual field defects, pituitary function and magnetic resonance imaging (MRI) images were assessed. Pre- and postsurgical data were available for all 19 patients. In 19 patients at least three postsurgical MRI scans were available, enabling the evaluation of radiological tumour re-growth or recurrence. The duration of follow-up in each patient was determined by the interval between the date of transsphenoidal surgery and the date of the last MRI scan. In five patients, postoperative radiotherapy was applied. Patients receiving prophylactic radiotherapy were treated with conventional external radiotherapy.

Patients with NFPAs were diagnosed on the basis of the following criteria:

a) Presence of a sellar mass with or without extrasellar extension detected by magnetic resonance imaging (MRI) or high resolution computed topographic (CT) scans.
b) Absence of signs or symptoms of pituitary hyperfunction.
c) Patients presenting signs and symptoms of a sellar mass such as headache and visual problems.
d) Histological confirmation by light microscopy of pituitary tumour in the excised adenoma tissue.

The study also included 22 sex and age matched healthy subjects that served as the control group with 22-55 years of age. Subjects included in the control group had no medical history of any chronic disease and endocrinopathies, and were not on current or past medication of steroids, antipsychotropic and other medications known to affect pituitary hormone secretion. The subjects fulfilling inclusion criteria were enrolled in the study after obtaining his/her written informed consent.

The pituitary tumours were assessed by MRI scanning. Tumour extension was classified as suprasellar, parasellar / infrasellar, or combined suprasellar and parasellar/ infrasellar extension. MRI imaging was performed in all patients within 6 months after transsphenoidal surgery, for the second time 1 year later. Patients were classified according to the postoperative MRI as having residual tumour or not having residual tumour. Tumour re-growth was defined as an increase in size of residual tumour. Recurrence was defined as appearance of tumour mass in a patient without residual tumour mass on postoperative MRI.

Opthalmological evaluation include assessment of visual acuity and visual fields, performed by Humphery or Goldmann perimeter before and a few weeks after surgery. Patients who had persistent visual field deficits after surgery or noticed visual disturbances any time during prolonged follow-up were reassessed by the opthamologists.

Statistical Analysis

The significance of differences among different groups was analyzed by one way analysis of variance {ANOVA} with Duncan's t- test. P value of <0.05 was considered statistically significant. All calculations were carried out with the SPSS version 12 (SPSS Inc, Chicago, IL, USA).

RESULTS

Preoperative Patient Chatacteristics

The most prevalent presenting symptoms were visual field defects (94.7%) and headache (84.2%). Radiological imaging by MRI revealed a macroadenoma in all patients, with suprasellar extension in 96% and parasellar / infrasellar extension in 31.57% of cases.

Table 1: *Characteristics of the patients before surgery.*

Characteristics	Value %
No of patients	19
Mean age (yrs)	44
Male	16
Female	3
Clinical presentation:	
Visual field defects	18/19 (94.7%)
Headache	16/19 (84.2%)
Cranial nerve defects	2 (9%)
Radiology:	
Suprasellar extension	16/19 (96%)
Parasellar/infrasellar extension	6/19 (31.57%)

Surgical Treatment

All patients were treated by transshenoidal surgery. One patient died of subarachnoidal bleeding 2 days after surgery, resulting in a perioperative mortality rate of 4.5%.

POSTSURGICAL EVALUATION:

Visual field defects

Visual field deficits improved in 84% of cases after surgery (complete recovery 3/19 (15%); partial recovery 13/19 (68%).

HORMONES DETERMINATIONS:

Follicle Stimulating Hormone (FSH)

Males

The mean serum FSH levels in the 16 male patients with NFPAs were found to be significantly higher ($P<0.05$) before surgical removal as compared to those obtained following surgery (17.2 ± 4.2 vs 8.5 ± 1.2 mIU/ml) (Table 2 and Fig 1). However, an examination of individual values revealed that the observed higher mean levels of FSH prior to surgery, were mainly due to the inclusion of 4 patients (PA10, 26, 29 and 30; Table 2) in which serum FSH levels were almost 4-fold of the control levels (> 40 mIU/ml) as shown in Tables 2 and Fig. 1. In these subjects serum FSH concentrations returned to the normal range following removal of the adenoma. The adenoma tissue content of FSH of these two subsets of patients is given in Table 2. We observed that the adenoma FSH content in patients with the initial higher peripheral concentrations, was also markedly greater ($P< 0.05$) than that of the patients with normal or low serum FSH levels and the control pituitary tissue. In the remaining 12 patients the difference in mean serum

Table 2: *Mean ± SEM serum FSH levels and FSH content of adenoma tissue, in male patients with NFPA and normal subjects.*

Group	Serum FSH (mIU/ml)	Adenoma tissue FSH content (IU/g)
Males		
Control Subjects (n= 16)	8.8 ± 0.6	
Patients with pituitary adenoma		
(a) Subset I-with low or normal FSH levels (n=12)	4.4 ± 1.9	
Presurgical	7.9 ± 0.7	
Postsurgical	6.5 ± 0.4	
(b) Subset II-with elevated FSH levels (n=4)	21.5 ± 2.1	
Presurgical	45.1 ± 0.7*	
Postsurgical	14.6 ± 3.8	
Pooled pituitary tissue		15.5
Females		
Control Subjects (n= 03)	8.4 ± 1.0	
Patients with pituitary adenoma (03)		
Presurgical	36.4 ± 6.5*	
Postsurgical	15.8 ± 9.3	

*Significantly different from postsurgical and control value ($P< 0.05$; ANOVA followed by Duncan's t- test).

FSH concentrations between presurgical and postsurgical serum values, was not significant (Table 2).

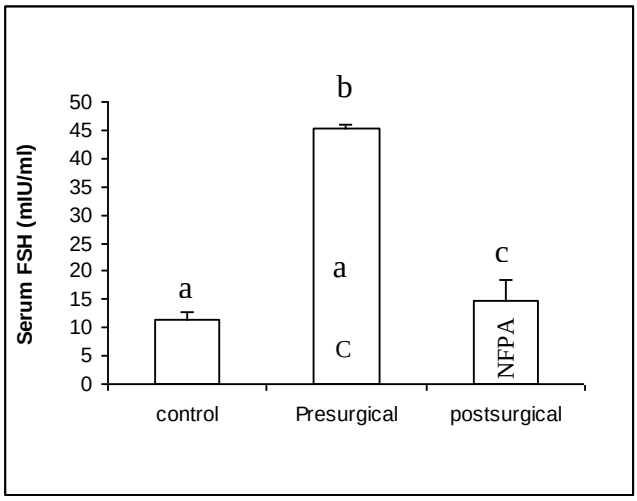

Figure 1: *Mean ± SEM serum concentration of FSH (mIU/ml) in subset of 4 male patients with high presurgical serum FSH levels and age-matched control subjects. The values with different superscripts (a,b) are different from each other (P< 0.05; ANOVA followed by Duncan's t- test).*

Table 3: *Mean ± SEM serum FSH levels in female patients with NFPA and normal subjects.*

Group	Serum FSH (mIU/ml)
Females	
Control Subjects (n= 03)	8.4± 1.0
Patients with pituitary adenoma (03)	
Presurgical	36.4 ± 6.5*
Postsurgical	15.8 ± 9.3

*Significantly different from postsurgical and control values (P< 0.05; ANOVA followed by Duncan's t- test).

Females

In all the three premenopausal female patients included in the study, the individual presurgical serum FSH levels were greater than those following surgery (Table 3). The mean value was significantly higher than of the controls (36.4 ± 6.5 vs 8.4 ± 1.1 mIU/ml, respectively). As shown in Table 3 and Fig 2. These values exceeded the normal serum FSH concentrations described for healthy women (3.0-22.0 mIU/ml). Following surgical removal of the adenoma, serum FSH concentrations showed a marked decline of FSH levels in 2 patients (PA4 and PA16) whereas in the remaining one patient (PA19), the FSH levels remained relatively high (34.5 mIU/ml) even after removal of the adenoma.

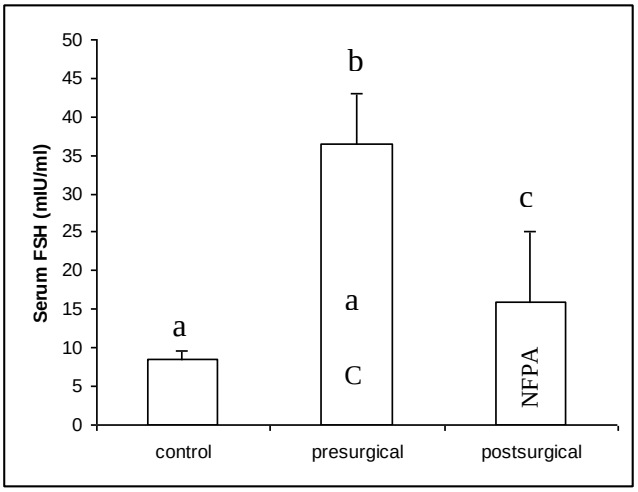

Figure 2: Mean ± SEM serum concentration of FSH (mIU/ml) in female patients with NFPA and age-matched control subjects. The values with different superscripts (a,b,c) are different from each other (P<0.05; ANOVA followed by Duncan's t- test).

Table 4: *Mean ± SEM serum GH levels of male patients with NFPA and in normal subjects.*

Group	Serum GH (ng/ml)	Adenoma tissue GH content (ng/g)
Males		
Control Subjects (n= 16)	0.5 ± 0.1	
Patients with pituitary adenoma (n=16)	697 ± 339	
Presurgical	1.3 ± 0.5	
Postsurgical	1.5 ± 0.2	
Pooled pituitary tissue	780	

Growth Hormone (GH)

Males

No significant differences were observed between pre- and postsurgical serum GH levels in male patients with NFPA (Tables 4 and Fig 3) although mean serum GH concentrations were slightly but discernibly higher in patients as compared to controls (1.1 ± 0.4 vs 0.5 ± 0.1**).** After surgical treatment 6 patients (36.8%) were GH deficient. The GH content was also comparable to the control pituitary tissue (Table 4).

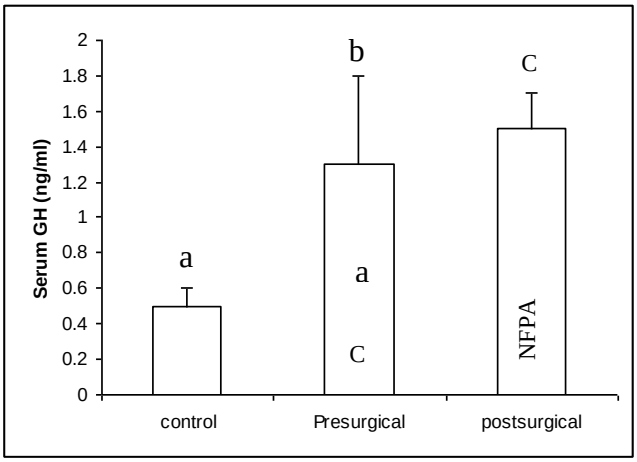

Figure 3: *Mean ± SEM serum concentration of GH (ng/ml) in male patients with NFPA and age-matched control subjects.*

Females

The mean serum GH concentrations of the 3 female patients before surgery were within the normal range described for healthy women (≤7 ng/ml) as shown in Table 5.

Table 5: *Mean ± SEM serum GH levels of female patients with NFPA and in normal subjects.*

Group	Serum GH (ng/ml)
Females	
Control Subjects (n= 03)	0.5 ± 0.2
Patients with pituitary adenoma (03)	
Presurgical	2.0 ± 0.6
Postsurgical	0.4 ± 0.2

DISCUSSION

This study demonstrates that transsphenoidal surgery without postoperative radiotherapy is an effective and safe treatment strategy for NFPAs, at least for the duration of follow-up presented in this study. In the present study, we have attempted to assess the hormonal contribution of the pituitary adenomas diagnosed as nonfunctioning, by measuring pituitary hormones in serum before and after surgical removal of the tumour. Previous literature indicates that NFPAs are morphologically heterogeneous and can be separated into two main categories based on immunohistochemical and electron microscopic appearances.[7,8] According to this classification one category of NFPAs 'null cell adenomas', includes tumours lacking characteristics of normal adenohypophyseal cells and possessing neither morphological nor immunohistochemical markers indicating their cytogenesis or direction of differentiation. The second group generally termed as 'silent adenomas', includes tumours exhibiting immunohistochemical and ultrastructural features of some of the recognizable adenohypophyseal cells but without any sign of hormone secretion. Our results indicate that the production and release of intact glycoprotein hormones such as FSH, occurs only in a small proportion of patients with NFPAs. In the present study a hypersecretion of FSH was evident in 4 male and 3 female patients (37%) with NFPAs and in 6 of these patients (4 males and 2 female patients) increased FSH levels reverted to normal serum concentrations.

Daneshdoost et al[22] in their study found a higher proportion of patients (10 of 38) with NFPAs who had a supranormal serum concentration of intact FSH and LH, 6 men had supranormal α-subunit concentrations and 6 men had supranormal LH β concentrations. Other studies have reported a low incidence (4-17%) of elevated gonadotropins in patients with NFPAs and these results are generally consistent with our findings.[9,11,23]

The foregoing observations suggest that a large proportion of NFPAs are derived from proliferation of gonadotrope cells and have led to their proposed reclassification as gonadotropinomas.[23,24] In one third of such tumours the quantity of FSH β-subunit mRNA is reported to be in excess of the level of α-subunit mRNA.[24] This is not observed in normal pituitary cells where α-subunit production predominates and assembly of the β-subunit is regarded as the rate-limiting step in hormone production. Whereas evidence for increased gonadotrophin synthesis by NFPAs is commonly seen *in vitro*, excess hormone production is much less observed *in vivo*.[8,19,24]

In our study, the presurgical mean serum GH concentrations in patients with pituitary adenoma were mostly in the lower range and were not significantly different from the control. No significant differences were observed in GH levels before and following removal of the adenoma. The GH content of adenoma tissue was comparable to the GH content of the control pituitary tissue. These results indicate that in cases included in this study the synthesis of GH by the adenoma tissue was negligible. Other studies have also reported low or normal and GH levels in patients with

NFPAs and are generally consistent with our findings.[10,22,25]

Perioperative mortality was minimal in our series (4.5%) and comparable with those reported in other studies.[6,20,22] Visual field defects improved in more than 84% of the patients, which is comparable with other studies in which improvement of visual field defects has been reported in 75-100%.[25-26]

Taken together, the present data suggests that a significant proportion of NFPAs may actively synthesize and secrete pituitary hormone such as FSH, in amounts that may not be sufficient to produce any overt clinical signs of hormone hypersecretion. The study also indicates the need of monitoring of hormone profile of patients with NFPAs before and after surgery, on an individual basis, for efficient case management.

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