ORIGINAL ARTICLE

Endocrine Accompaniments in Acromegaly Patients Before and After Surgery

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ABSTRACT

Background and Aim: *The aim of this study was to illustrate the present role of transsphenoidal surgery as primary therapy in GH – secreting adenomas. 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.*

Methods: *The present study is based on 07 patients (04 males and 3 females), 30-50 year of age, diagnosed for Functional Pituitary Adenomas (FPAs) on the basis of clinical and radiological evidence. An equal number of age matched healthy subjects were included as controls. Follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), growth hormone (GH) and prolactin (PRL) were determined in serum before and following trans-sphenoidal adenomectomy. The GH, FSH, TSH and PRL content of the excised adenoma tissue was also measured in male patients. All hormone determinations were carried out using commercially available immuno-assay kits (ELISA and IRMA) in duplicate.*

Results: *The results demonstrate that the mean serum GH levels in the 04 male and 03 female patients with FPAs were found to be significantly higher before surgical removal as compared to those obtained following surgery. Significant differences were observed between pre- and postsurgical serum GH levels in male and female patients with FPA. GH content was also determined in the male adenoma tissue. Following removal of the adenoma in these 4 male and 03 female patients, peripheral serum GH levels fell within the normal range. The adenoma tissue GH content in patients with initial higher serum GH levels was also significantly greater than that of the other patients. The mean serum PRL concentration in male patients before removal of the adenoma and values obtained after surgical removal of the adenoma and those of control subjects were not significantly different. The mean PRL concentration of the adenoma tissue in all the male patients was not significantly different from the control pituitary tissue. However, the presurgical mean serum PRL concentration were significantly higher in 2 of the 3 female patients included in this study as compared to the control values. Following removal of adenoma, normal serum levels were attained in those patients. In the remaining one female patient serum PRL concentration was within the normal range before and following surgical removal of the adenoma. The mean serum FSH levels in the 04 male patients with FPAs were not significantly different before and after surgical removal of adenoma tissue. However, an examination of individual values reveals higher FSH levels in 02 of the male patients and in 01 of the three premenopausal female patients. Following surgical removal of the adenoma, serum FSH concentrations showed a marked decline of FSH levels in those patients. However, the remaining two females showed normal FSH levels before and after surgery. The adenoma FSH content of these patients was not significantly higher than those of the control pituitary tissue. No significant differences were observed between pre and post-surgical serum TSH levels. The TSH content of adenoma tissue was either non-detectable or in the low range as compared to the TSH content determined in control pooled pituitary tissue.*

Conclusion: *Transsphenoidal surgery is thought to be an effective primary treatment for GH-secreting pituitary adenomas according to the most recent criteria of cure. Because the remission rate in cases with cavernous sinus*

invasion is very low, early detection of the tumor before it extends into the cavernous sinus and a long-term endocrinological and radiological follow-up are necessary in order to improve the remission rate of acromegaly.

Keywords: *Acromegaly, Insulin-like growth factor I, Pituitary adenoma, Surgical outcome.*

INTRODUCTION

Acromegaly is a rare but very serious condition usually caused by a growth hormone (GH) – producing pituitary adenoma. Although acromegaly is an uncommon disease, the average incidence rate being reported as 3.1 to 3.8 / million inhabitants / year. The estimated prevalence of the disease is 40 cases / 1000000 population with 3 – 4 new cases / 1000000 population per year. Over 95% of acromegalic patients have GH excess due to a GH – producing pituitary adenoma, and surgical excision of the adenoma has been considered the most reliable therapy to restore GH abnormal response to normal.[1,5]

Ectopic GH or GH-releasing hormone production or a pituitary carcinoma may very infrequently also cause acromegaly. Several retrospective cohort studies suggest that mortality in acromegaly is at least twice of that in the general population.[1–4] The cause of death is most commonly a vascular accident, but significant increases have been reported for both respiratory disorders and malignancies. These studies have also demonstrated that a reduction of GH levels significantly lowered mortality and that mortality rates similar to those of the general population are restored once remission is induced. Partial reduction of GH levels has been proven to be inadequate to restore normal life expectancy.[1,5] Therefore, aggressive management to lower serum GH levels is necessary once the diagnosis has been confirmed. Depot somatostatin analogues are now increasingly being prescribed in acromegaly.

Studies have shown them to be both effective and safe with endocrinological remission in up to 60% of cases.[6–9] The newly developed GH receptor antagonist pegvisomant seems to be able to normalise insulin – like growth factor (IGF)-I in up to 97% of patients and may become an important therapeutic option in acromegaly.[10,11] However, the most recent consensus guidelines for the management of acromegaly suggest for the majority of patients surgery as the first – line therapy, either alone or in combination with medical treatment, conventional radiotherapy and / or radiosurgery.[12]

The aim of this study was to update the surgical results in a series of acromegalic patients treated in the Department of Neurosurgery at the Lahore General Hospital, Lahore. We analyzed the surgical outcome by comparing the GH, FSH, TSH and Prolactin level before and after surgery in 07 consecutive acromegalic patients undergoing Transsphenoidal surgery for the treatment of GH – producing adenomas at Lahore General Hospital during 2005 to 2007, in order to reassess the efficacy of transsphenoidal surgery for this disorder.

MATERIALS AND METHODS

The present study initially included 07 patients 04 men and 3 women, of 22 – 55 (44 ± 2.3) years of age with NFPAs. All patients underwent pituitary tumour surgery. The adenoma was removed in all 07 patients through transsphenoidal route. All cases were operated at the Department of Neurosurgery, Lahore General Hospital, Lahore.

The study also included 07 sex and age matched healthy subjects that served as the control group with 22 – 55 years of age. The subjects fulfilling inclusion criteria were enrolled in the study after obtaining his / her written informed consent. The study was approved by the Ethical Committee and the Advanced Studies and Research Board of the University of Health Sciences, Lahore.

Blood samples from patients with pituitary adenomas were obtained prior to surgery and 2 months after removal of the pituitary adenoma. Blood samples were also obtained from an equal number of age and sex matched control subjects for purposes of comparison. Five ml of blood sample were drawn from each patient and blood was centrifuged at 3,000 rpm for 10 – 15 minutes to separate serum and aliquoted in two portions and stored at -30^{o} C until analyzed.

The pituitary adenoma tissue was divided into two parts. One part was fixed in buffered formalin and processed for histological examination, whereas the other half was weighed and homogenized in ice-cold phosphate buffer saline (PBS), at a dilution of approximately 50 mg/ml. The samples were centrifuged for 30 min at 10000 rpm and the supernatant was frozen at -30°C. Pituitary tissue was also obtained from three adult males at the post-mortem examination, pooled and processed identically as the adenoma tissue for extraction. Pituitary tissue from female controls could not be made available.

Following fixation, adenoma tissue was processed for histopathological examinations. Paraffin sections of the tissue were cut at a thickness of 3 – 5 µm and stained routinely with hemotoxylin and counterstained with eosin.

Hormone Determinations

Serum FSH, TSH, GH, PRL were determined by ELISA in duplicate using standard procedures with commercially available assay kits with an automated EIA analyzer. Hormone content of adenoma and pituitary tissue, was measured with a specific radiometric assay in the extract obtained, by commercially available IRMA kits with an automated gamma counter (Perkin Elmer, Turku, Finland).

Statistical Analysis

The significance of differences among different groups was analyzed by one way analysis of variance {ANOVA} followed by Duncan's multiple 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

Growth Hormone

The mean serum GH levels in the 04 male patients with FPAs were found to be significantly higher ($P < 0.05$) before surgical removal as compared to those obtained following surgery (30.2 ± 3.1 vs 4.4 ± 1.5 ng/ml) as shown in (Table 1). However, an examination of individual values reveals that the observed higher mean levels of GH prior to surgery were almost 4 – fold of the control levels (> 7 ng/ml or less) as shown in Tables 1 and 2. Significant differences were observed between pre- and postsurgical serum GH levels in male and female patients with FPA (Tables 7**).** GH content was also determined in the male adenoma tissue. The adenoma tissue content of GH of the male patients is also given in Table 1. As may be noted, the adenoma GH content in patients with the initial higher peripheral concentrations, was also markedly greater ($P<0.05$) than that of the control pituitary tissue.

Table 1: *Mean ± SEM serum GH levels and GH content of adenoma tissue, in male and female patients with FPA and in normal subjects.*

Group	Serum GH (ng/ml)	Adenoma tissue GH (ng/ml)
Males Control Subjects (n = 04)	0.4 ± 0.1	
Patients with pituitary adenoma (n = 04)		17939
Presurgical	30.2 ± 3.1*	
Postsurgical	4.4 ± 1.5	
Pooled pituitary tissue		102.9
Females Control Subjects (n = 03)	0.2 ± 0.06	
Patients with pituitary adenoma (03)		
Presurgical	38.9 ± 10.3*	
Postsurgical	5.7 ± 4.8	

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

Table 2: *Serum GH levels in male patients with FPA and in age-matched control subjects.*

	Patients with FPA				Control subjects		
	Patient ID	Age (y)	GH (ng/ml)		Patient ID	Age (y)	Serum Control GH (ng/ml)
			Presurgical	Postsurgical			
Males	PA1	40	31.3	1.4	C1	35	0.09
	PA2	42	22.2	3.5	C2	42	0.2
	PA3	35	37.5	8.6	C3	35	0.4
	PA4	32	29.8	4.3	C4	32	0.9

Table 3: *Serum GH levels in female patients with FPA and in age-matched control subjects.*

Patients with FPA					Control subjects		
	Patient ID	Age (y)	GH (ng/ml)		Patient ID	Age (y)	Serum Control GH (ng/ml)
			Presurgical	Postsurgical			
Females							
	PA5	23	33.6	15.3	C5	23	0.1
	PA6	35	58.7	0.8	C6	35	0.2
	PA7	50	24.2	0.9	C7	50	0.2

Prolactin

The mean serum PRL concentration in male patients before removal of the adenoma and values obtained after surgical removal of the adenoma and those of control subjects were not significantly different (Table 4 and 5). The patients serum PRL concentrations were within the normal limit of circulating PRL levels (<17.0 ng/ml). The individual and mean serum PRL levels in the male patients were in normal range before and after surgery. The mean PRL concentration of the adenoma tissue in all the male patients was not significantly different from the control pituitary tissue.

However, the presurgical mean serum PRL concentration were significantly higher in 2 of the 3 female patients included in this study as compared to the control values. Following removal of adenoma,

Table 4: *Mean ± SEM serum PRL levels and PRL content of adenoma tissue, in male and female patients with FPA and normal subjects.*

Group	Serum PRL (ng/ml)	Adenoma tissue PRL Content (ng/g)
Males Control Subjects (n = 04)	5.5 ± 0.5	
Patients with pituitary adenoma		11.4
Presurgical	10.9 ± 2.7	
Postsurgical	7.5 ± 2.2	
Pooled pituitary tissue		1.8
Females Control Subjects (n = 03)	5.7 ± 0.2	
Patients with pituitary adenoma (n = 03)		
Presurgical	32.8 ± 6.9*	
Postsurgical	15.1 ± 1.7	

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

Table 5: *Serum PRL levels in male patients with FPA and in age-matched control subjects.*

Patients with FPA					Control subjects		
	Patient ID	Age (y)	PRL (ng/ml)		Patient ID	Age (y)	Serum Control PRL (ng/ml)
			Presurgical	Postsurgical			
Males	PA1	40	18.4	10.2	C1	35	6.7
	PA2	42	6.1	3.4	C2	42	6.1
	PA3	35	11.5	12.6	C3	35	4.3
	PA4	32	7.8	4.0	C4	32	5.0

Table 6: *Serum PRL levels in female patients with FPA and in age-matched control subjects.*

	Patients with NFPA				Control subjects		
	Patient ID	Age (y)	PRL (ng/ml)		Patient ID	Age (y)	Serum Control PRL (ng/ml)
			Presurgical	Postsurgical			
Females	PA5	23	26.9	6.4	C5	23	5.2
	PA6	35	61.4	10.1	C6	35	5.7
	PA7	50	10.1	4.3	C7	50	6.1

normal serum levels were attained (Table 6). In the remaining one female patient serum PRL concentration was within the normal range before and following surgical removal of the adenoma.

Follicle Stimulating Hormone

The mean serum FSH levels in the 04 male patients with FPAs were not significantly different before and after surgical removal of adenoma tissue (Table 7). However, an examination of individual values reveals higher FSH levels in 02 of the male patients. In these subjects serum FSH concentrations returned to the normal range following removal of the adenoma as shown in Tables 8. The adenoma FSH content of these patients was not significantly higher than those of the control pituitary tissue.

In 01 of the three premenopausal female patients included in the study,

Table 7: *Mean ± SEM serum FSH levels and FSH content of adenoma tissue, in male and female patients with FPA and normal subjects.*

Group	Serum FSH (mIU/ml)	Adenoma tissue FSH Content (IU/g)
Males Control Subjects (n = 04)	8.09 ± 0.8	
Patients with pituitary adenoma		2.5
Presurgical	10.57 ± 3.08	
Postsurgical	16.4 ± 9.61	
Pooled pituitary tissue		10.6
Females Control Subjects (n = 03)	8.4 ± 1.7	
Patients with pituitary adenoma (03)		
Presurgical	16.3 ± 9.3*	
Postsurgical	7.9 ± 1.6	

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

Table 8: *Serum FSH levels in male patients with FPA and in age – matched control subjects.*

	Patients with FPA				Control subjects		
	Patient ID	Age (y)	FSH (mIU/ml)		Patient ID	Age (y)	Serum Control FSH (mIU/ml)
			Presurgical	Postsurgical			
Males	PA1	40	5.4	4.9	C19	35	07
	PA2	42	19.5	8.6	C17	42	6.3
	PA3	35	8.4	9.05	C18	35	8.9
	PA4	32	19.2	8.2	C19	32	10.0

Table 9: *Serum FSH levels in female patients with FPA and in age-matched control subjects.*

Patients with NFPA					Control subjects		
	Patient ID	Age (y)	FSH (mIU/ml)		Patient ID	Age (y)	Serum Control FSH (mIU/ml)
			Presurgical	Postsurgical			
Females	PA5	23	7.8	6.4	C17	23	7.07
	PA6	35	6.05	6.2	C18	35	11.8
	PA7	50	35.02	11.2	C19	50	6.3

the serum FSH was significantly higher than of the control as shown in Table 9. Following surgical removal of the adenoma, serum FSH concentrations showed a marked decline of FSH levels in that patient. However, the remaining two females showed normal FSH levels before and after surgery.

Thyroid Stimulating Hormone

The presurgical mean serum TSH concentrations in male and female patients with pituitary adenoma were mostly in the lower range and were not significantly different from levels following removal of the adenoma and of the control subjects. The TSH content of male adenoma tissue was either in the non-detectable range of the assay or comparable to the control pituitary tissue (Table 10).

Table 10: *Mean ± SEM serum TSH levels and TSH content in adenoma tissue, in male and female patients with FPA and normal subjects.*

Group	Serum TSH (µIU/ml)	Adenoma tissue TSH Content (µIU/ml)
Males Control Subjects (n = 04)	1.7 ± 1.4	
Patients with pituitary adenoma (n = 04)		1.4
Presurgical	0.3 ± 0.1	
Postsurgical	0.4 ± 0.1	
Pooled pituitary tissue		14.5
Females Control Subjects (n = 03)	0.3 ± 0.1	
Patients with pituitary adenoma (03)		
Presurgical	1.2 ± 0.8	
Postsurgical	0.6 ± 0.4	

Table 11: *Serum TSH levels in male patients with FPA and in age-matched control subjects.*

Patients with FPA					Control subjects		
	Patient ID	Age (y)	TSH (µIU/ml)		Patient ID	Age (y)	Serum Control TSH (µIU/ml)
			Presurgical	Postsurgical			
Males	PA1	40	0.2	0.1	C19	35	6.0
	PA2	42	0.3	0.9	C17	42	0.1
	PA3	35	0.1	0.2	C18	35	0.1
	PA4	32	0.6	0.4	C19	32	0.6

Table 12: *Serum TSH levels in female patients with FPA and in age-matched control subjects.*

	Patients with NFPA				Control subjects		
	Patient ID	Age (y)	TSH (µIU/ml)		Patient ID	Age (y)	Serum Control TSH (µIU/ml)
			Presurgical	Postsurgical			
Females	PA5	23	0.3	0.2	C17	23	0.5
	PA6	35	0.5	0.3	C18	35	0.3
	PA7	50	2.8	1.4	C19	50	0.1

DISCUSSION

In the present study, we have attempted to assess the hormonal contribution of the pituitary adenomas diagnosed as functioning, by measuring pituitary hormones in serum before and after surgical removal of the tumour, and in the excised adenoma tissue. Our results indicate that the production and release of GH, occurs in all acromegalic patients. In the present study a hypersecretion of GH was evident in 4 male and 3 female patients. These observations are further supported by the finding that the GH content of the adenoma tissue of these patients was significantly higher than those of the control pituitary tissue. In this study, we observed a significant positive correlation between post-surgical GH levels after transsphenoidal surgery (TSS), suggesting that lower GH levels in the early postoperative period are a good predictive marker. These findings are consistent with previous reports.[5,6]

In some previous studies, FPAs have been shown to secrete adenohypophysial hormones, most commonly PRL.[21,25] In our study, we have observed normal PRL levels in male patients before and after surgical removal of the adenoma. However, the presurgical mean serum PRL concentration were significantly higher in 2 of the 3 female patients included in this study as compared to the control values. Following removal of adenoma, normal serum levels were attained. These observations are supported by the finding that the adenoma PRL content in patients with the initial higher peripheral concentrations, was also markedly greater ($P < 0.05$) than that of the patients with normal serum PRL levels and the control pituitary tissue.

Similarly, higher FSH levels were found in 02 of the male patients and 01of the three premenopausal female patients included in the study, the mean value was significantly higher than of the control. Following surgical removal of the adenoma, serum FSH concentrations showed a marked decline of FSH levels in those patients. FSH content of the adenoma tissue of these patients was not significantly higher than those of the control pituitary tissue. Other studies have reported a low incidence of elevated gonadotropins in patients with FPAs and these results are generally consistent with our findings.[4,7-11]

In our study, the presurgical mean serum TSH 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 TSH levels before and following removal of the adenoma. Other studies have also reported low or normal TSH levels in patients with FPAs and are generally consistent with our findings.[13,14]

In our study, we have analyzed the surgical results of TSS for acromegaly focusing on patients with biochemical and clinical follow-up data. Preoperative data such as age and sex distribution, tumor, preoperative GH concentration were comparable with those from other studies.[1,3,14,21]

An endocrinological "cure" for acromegaly, as defined by the stringent criteria of biochemical remission,[10,21] was achieved in 100% of patients, similar to that reported in the most recent series.[16,19-21,25] TSS remains an effective treatment for acromegaly, whereas medical treatment and / or radiotherapy should be reserved for patients with persistent GH / IGF-I hypersecretion after surgery.[4]

TSS of GH – secreting pituitary adenoma continues to be a safe and effective method for dealing with a large number of patients with acromegaly. The goal of overall management should be to provide the patient with the most effective means of long term control of this benign but potentially disabling disease.

The limitation of this study is being short study duration in small number of patients. Therefore, a prospective study in more patients will be necessary to further evaluate the factors affecting the remission rate

of acromegaly. It is hoped that with advances in pharmacotherapy, surgical treatment may become even more focused, more precise and more effective over time.

CONCLUSION

This article gives an insight on the treatment of acromegaly, especially on adenomas invading the cavernous sinus. On the basis of recent remission criteria, our series demonstrate the good efficacy of TSS for acromegalic patients with microadenomas and non-invasive macroadenomas. In patients with larger tumors, cavernous sinus invasion or high preoperative GH levels, the remission rate is lower. Therefore, early detection of the tumor and a long-term endocrinological and radiological follow-up may improve the remission rate of acromegaly. However, this study only investigated changes in GH, PRL, FSH and TSH serum levels and over a short postoperative period. Long – term observation is needed to confirm whether the current criteria can predict long – term disease activity accurately in patients with acromegaly.

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