ORIGINAL ARTICLE

Endoscopic Transsphenoidal Surgery for Acromegaly

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ABSTRACT

Objective: *The aim of this study was to determine the preoperative predictors of the extent of resection and endocrinological remission following endonasal endoscopic removal of growth hormone (GH) – secreting pituitary adenomas. Trans-sphenoidal surgery is the preferred treatment modality for growth hormone (GH) – secreting pituitary adenomas. In many series, the reported postoperative remission is based mainly on achievement of GH levels less than 2 ng/ml. Strict criteria for insulin – like growth factor I normalization and even lower GH levels (< 1 ng/ml) are now suggested to define cure of acromegaly, but the evidence does not yet support such low GH levels in epidemiological follow-up. We analyzed our postoperative results in a sample of local population with acromegaly.*

Methods: *Seven patients harboring GH – secreting adenomas (07 macroadenomas) underwent transsphenoidal surgery between 2005 and 2007 in Lahore General Hospital. The patient group included 03 women and 04 men of 23 – 50 years of age. All the patients were operated for the first time. Biochemical remission was defined as a repeated fasting or glucose – suppressed GH level of 2 ng/ml or less, and a normal insulin – like growth factor I level.*

Results: *The majority of acromegalic patients (83%) had macroadenomas > 1 cm in maximum diameter. Gross – total resection was achieved in 05 (71%) of 07 patients. Notably, endoscopic transsphenoidal surgery allowed complete resection of all lesions without cavernous sinus invasion, regardless of the suprasellar extent. Biochemical remission was achieved in 06 (85%) of 07 patients. A postoperative reduction in GH serum levels were associated with a higher rate of biochemical cure ($p < 0.05$). Significant differences were observed between pre- and postsurgical serum GH levels in male patients with Acromegalic tumors. Although mean serum GH concentrations were discernibly higher in patients as compared to controls (30.2 ± 3.1 vs 0.4 ± 0.1). In all the three premenopausal female patients included in the study, the individual presurgical serum GH levels were greater than those following surgery. The mean value was significantly higher than of the controls (38.9 ± 10.3 vs 0.2 ± 0.6 ng/ml, respectively).These values exceeded the normal serum GH concentrations described for healthy women (7 ng/ml or less). Following surgical removal of the adenoma, serum GH concentrations showed a marked decline of GH levels in all patients.*

Conclusion: *A purely endoscopic endonasal trans-sphenoidal adenoma resection leads to a high rate of gross – total tumor resection and endocrinological remission in acromegalic patients, even those harboring macroadenomas with wide suprasellar extension. Extended approaches and angled endoscopes are useful tools for increasing the extent of resection.*

Key Words: *Growth hormone – secreting pituitary adenoma,Cavernous sinus, Remission induction.*

INTRODUCTION

Acromegaly results from supraphysiological growth hormone (GH) release from pituitary somatotroph adenomas (99% of cases), resulting in persistently high circulating levels of GH.[1] The name acromegaly comes from the Greek words for "extremities" and "enlargement," reflecting one of its most common symptoms — the abnormal growth of the hands and

feet. Swelling of the hands and feet is often an early feature, with patients noticing a change in ring or shoe size, particularly shoe width. Gradually, bone changes alter the patient's facial features: The brow and lower jaw protrude, the nasal bone enlarges, and the teeth space out.[1,2]

Acromegaly is most often diagnosed in middle – aged adults, although symptoms can appear at any age. If not treated, acromegaly can result in serious illness and premature death.[2] Acromegaly is treatable in most patients, but because of its slow and often "sneaky" onset, it often is not diagnosed early or correctly. The most serious health consequences of acromegaly are type 2 diabetes, high blood pressure, increased risk of cardiovascular disease, and arthritis. Patients with acromegaly are also at increased risk for colon polyps, which may develop into colon cancer if not removed.[3]

It has an annual incidence of three to four cases per 1 million people and a prevalence of approximately 60 per million.[3] Overall, there appears to be no difference in race, gender or ethnicity among individuals affected with this condition. Several retrospective cohort studies suggest that mortality in acromegaly is at least twice that in the general population.[2,5-8] The cardiovascular effects such as hypertension, cardiomyopathy and valvular heart disease are associated with increased morbidity and premature mortality, and significant increases have been reported for both respiratory disorders and malignancies.[8-10] The most recent consensus guidelines for the management of acromegaly suggest surgery as the first – line therapy, either alone or in combination with medical treatment, conventional radiotherapy and/or radiosurgery.[10-12] But, the cavernous sinus invasion renders the tumor surgically unresectable even in skilled hands, and remains one of the greatest challenges in neurosurgery. The residual tumor within the cavernous sinus can continue to cause endocrinological symptoms, which necessitates further treatment such as pharmacological therapy or radiotherapy. We analyzed the surgical results of 07 patients with GH – secreting pituitary adenomas in a sample of local population.

MATERIALS AND METHODS

Study Population

The present study initially included 7 patients 4 men and 3 women, of 23 – 50 years of age with FPAs. All patients underwent pituitary tumour surgery. The adenoma was removed in all patients through transsphenoidal route. All cases were operated at the Department of Neurosurgery, Lahore General Hospital, Lahore between January 2005 and February 2007.

The study also included 7 sex and age matched healthy subjects that served as the control group with 23 – 50 years of age. Subjects included in the control group had no medical history of any chronic disease 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 study was approved by the Ethical Committee and the Advanced Studies and Research Board of the University of Health Sciences, Lahore.

Sample Collection

Blood samples from patients with pituitary adenomas were obtained prior to surgery and 2 months after removal of the pituitary adenoma. Following surgery, patients received 10 mg prednisolone daily for 6 weeks. Postsurgical serum samples were obtained 2 weeks after the prednisolone treatment was discontinued. Blood samples were also obtained from an equal number of age and sex matched control subjects for purpose 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 -30ºC 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^{o}C.

Tissue Biology

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 GH was determined by ELISA in duplicate using standard procedures with commercially available assay GH: BioCheck, Inc, Foster City, CA, USA; PRL: Monobind Inc, Costa Mesa, CA, USA) with an

automated EIA analyzer (Coda, Bio-Rad Laboratories, Hercules, CA, USA).

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 (GH)

Males

Significant differences were observed between pre- and postsurgical serum GH levels in male patients with Acromegalic tumors (Tables 1, 2 and Fig. 1) although mean serum GH concentrations were slightly but discernibly higher in patients as compared to controls (30.2 ± 3.1 vs 0.4 ± 0.1**)**.

Females

In all the three premenopausal female patients included in the study, the individual pre-surgical serum GH levels were greater than those following surgery (Table 3). The mean value was significantly higher than of the controls (38.9 ± 10.3 vs 0.2 ± 0.6 ng/ml, respectively). As shown in Table 3, 4 and Fig 2. These values exceeded the normal serum GH concentrations described for healthy women (7 ng/ml or less). Following surgical removal of the adenoma, serum GH concentrations showed a marked decline of GH levels in all patients.

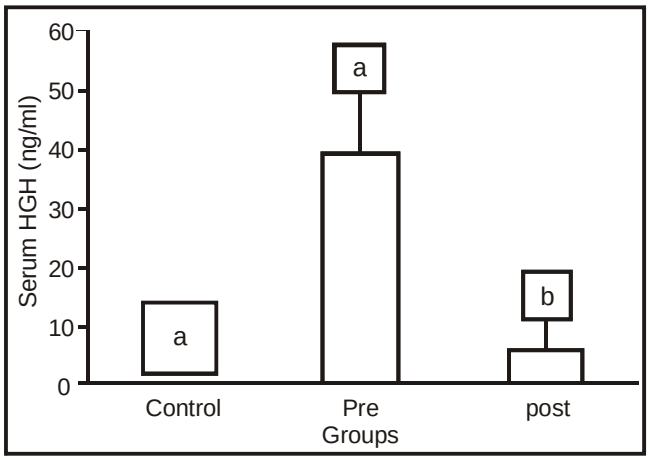

Figure 1: Mean ± SEM serum concentration of GH (ng/ml) in 04male patients with FPA and age – matched control subjects. The values with different superscripts (a,b) are different from each other ($P < 0.05$; ANOVA followed by Duncan's t-test).

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. Preoperative data such as age and sex distribution, 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 85% 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

Table 1: *Serum GH levels in male patients with Functioning Pituitary Adenomas and in age – matched control subjects.*

	HUMAN GROWTH HORMONE SERUM SAMPLES					
			Pre-surgical		Post-surgical	
ID	**Sex**	**Age Years**	**wt. of Pituitary adenoma (mg)**	**Pre GH (ng/ml)**	**Post GH (ng/ml)**	**Control GH (ng/ml)**
P.A 23	Male	40	124.1	31.3	1.4	0.5
P.A 25	Male	42	114.2	22.2	3.5	0.2
P.A 27	Male	35	8.4	7.5	8.6	0.4
P.A 11	Male	32	19.2	19.8	4.3	0.9

Table 2: *Mean ± SEM serum GH levels of male patients with Functioning Pituitary Adenomas and in normal subjects.*

Group	Serum GH (ng/ml)
Males Control Subjects (n = 04) Patients with pituitary adenoma (n = 07)	0.4 ± 0.1
Pre-surgical	30.2 ± 3.1
Post-surgical	4.4 ± 1.5*****

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

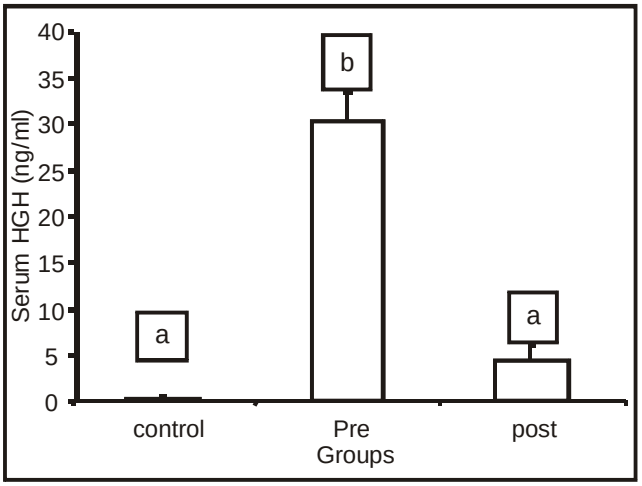

Figure 2: Mean ± SEM serum concentration of GH (ng/ml) in 03 female patients with NFPA and age – matched control subjects. The values with different superscripts (a, b) are different from each other (P < 0.05; ANOVA followed by Duncan's t-test).

hypersecretion after surgery.[4]

However, for patients with cavernous sinus invasion of Knosp grade III and IV,[15] invasive GH – secreting pituitary adenoma may be unresectable due to the involvement with structures of the cavernous sinus; the GH level can't be normalized, the surgical cure rate is low while the incidence of complications is high and the GH level must still be observed after the operation.

In general, adjuvant treatment is necessary in patients with remnant tumors without remission. But, there is debate surrounding the starting point of adjuvant treatment. Although the patient has not achieved a hormonal remission state, careful observation could be an alternative option if there are no hormonal symptoms.[6, 26] Since their introduction into clinical use more than a decade ago, the octreotide long – acting release (LAR) have been considered primary or secondary medical therapy for acromegaly.

In a recent study, it was found that there may be a role for pre-operative medical management if tumor shrinkage can be achieved prior to surgery. Surgical outcomes may also be improved by lowering preoperative GH and IGF-I levels.[4,5] For residual tumor within the cavernous sinus area after medical or surgical treatment, gamma knife radiosurgery is a viable option. It is known from the present literature that although

Table 3: *Serum GH levels in female patients with Functioning Pituitary Adenomas and in age – matched control subjects.*

	HUMAN GROWTH HORMONE SERUM SAMPLES					
			Pre-surgical		Post-surgical	
ID	**Sex**	**Age Years**	**wt. of Pituitary adenoma (mg)**	**Pre GH (ng/ml)**	**Post GH (ng/ml)**	**Control GH (ng/ml)**
P.A5	Female	23	49.8	33.6	15.3	0.1
P.A13	Female	35	32.7	58.7	0.8	0.2
P.A20	Female	50	18	24.2	0.9	0.2

Table 4: *Mean ± SEM serum GH levels of female patients with Functioning Pituitary Adenomas and in normal subjects.*

Group	Serum GH (ng/ml)
Females Control Subjects (n = 03) Patients with pituitary adenoma (n = 03)	0.2 ± 0.6
Pre-surgical	38.9 ± 10.3
Post-surgical	5.7 ± 4.8*****

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

gamma knife radiosurgery can be effective in controlling the tumor volume of patients who are refractory to drug or surgical treatment, the biological cure rate is very low.[9,20,23,28]

Studies have claimed that GH values were normalized in 62 – 83% of all acromegalic patients treated by fractionated radiotherapy over a 5 – 15 year period.[8,11]

Reported complications included optic neuropathy and pituitary insufficiency.[17] Gamma knife radiosurgery is not only able to deliver a higher biological effective dose than fractionated radiotherapy, but it can do so without any of the usual associated complications.[9,17,23] It can thus be strongly argued that gamma knife radiosurgery should be considered before fractionated radiotherapy as an adjuvant therapy.

The exact effect of cavernous sinus invasion on pituitary adenoma is unknown. However, the presence of a sensitive molecular marker for tumor invasiveness will allow a more focused and cost – effective follow-up and long term management for these patients.[13] However, these markers can only provide limited predicting information. Recently, Isono et al.[12] immunohistochemically examined the expression of leptin in pituitary adenomas and found that leptin expression correlated to the invasive potential of functioning adenomas. The polysialylated neural cell adhesion molecule was found strongly related to pituitary tumor invasion.[27] However, these factors have not been tested clinically, so further study is needed. 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 a prospective study 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 not 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.

ACKNOWLEDGEMENTS

I would like to thank Dr. Khalid Mahmood, Prof. Tariq Sallahudin, Prof. Anjum Habib for providing us samples. I would also like to thank Prof. Naseer A. Chaudhry for the histopathology reports. I am thankful to our learned Prof. Dr. Malik Hussain Mubbashar (HI, SI), Vise Chancellar, University of Health Sciences, Lahore, for his support and for providing me all the facilities for my research work.

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