

Clinical Features and Outcome of Surgery in 30 Patients with Acromegaly

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Introduction

Acromegaly is an uncommon disease with an annual incidence of 3/million and an estimated prevalence of 40/million population.¹ In the majority of patients it is caused by a pituitary adenoma and is associated with significantly shortened life span that is not due to direct effect from the tumour but results from cardiovascular, respiratory and cerebrovascular complications.² In addition there is an increased risk of malignancy.³ Acral growth, coarsened facial features and soft tissue swelling are the most common symptoms of acromegaly⁴ which develop slowly over time so the diagnosis is delayed for years.⁵ Optimal therapy should be aimed at alleviating symptoms, reducing tumour bulk, preventing regrowth and reducing mortality without the development of hypopituitarism.⁶ Surgery remains the treatment of choice as this offers a rapid permanent reduction of Growth hormone (GH) level and relief from the mass effect of the tumour. In those patients in whom operative cure is not achieved, radiotherapy and/or medical therapy are useful treatment modalities. Biochemical cure is considered as GH level <2.5 ng/ml, normal IGF level and post Oral Glucose Tolerance Test (OGTT), GH level <1 ng/ml.^{7,8} Using strict criteria for cure, rate as high as 67% have been reported for surgery alone.⁹ Outcome of surgery is inversely correlated to preoperative GH level¹⁰, tumour size¹¹ and tumour stage.¹²

We retrospectively analyzed the medical records of patients with acromegaly who were operated upon, to assess the surgical outcome of hypophysectomy, the difference in outcome of microadenoma and macroadenoma and development of postoperative hormonal deficiencies.

Patients and Methods

A retrospective review of medical records was performed on 45 patients with the diagnosis of Acromegaly who presented at Aga Khan University

Hospital between 1989-2002. Ten patients who had had previous pituitary surgery or irradiation were excluded. Five patients who did not undergo surgery were also excluded. Information regarding presentation, investigations like hormonal and radiological assessment, details of surgery and postoperative outcome were recorded. All patients exhibited signs and symptoms of acromegaly with confirmation of diagnosis by elevated baseline GH levels and OGTT suppression test. An Oral Glucose Tolerance Test was performed by fasting the patient overnight and then taking a 0900 h basal blood sample. The patient was then given an oral dose of 75 g of glucose. Blood samples were collected every 30 min for 120 min and were analyzed for GH and glucose levels. Preoperative MRI/CT scan were done and tumours were classified into macro (>10 mm) or microadenomas (<10 mm). The postoperative cure was assessed by measuring random GH levels in most of the patients and postoperative OGTT suppression test was done in five patients. The hormonal assessment was done within two weeks of surgery. Biochemical cure was considered to be achieved when there was suppression of random GH level of <2.5 ng/ml or serum GH <1 ng/ml after OGTT, remission when GH level was between 2.5 and 5.0 ng/ml and failure to surgical treatment when persistently elevated random GH levels or failure to suppress/paradoxical rise of GH on OGTT.^{7,13}

Postoperative workup also included repeat MRI scan of pituitary and hormonal assessment for pituitary insufficiency. GH measurement was done using Immulite® 2000 analyzer (Diagnostic Product Corp. Ltd.) with chemiluminescence assay. The normal adult range for this kit was 0.06-5.0 ng/ml.

Statistical Method

Results were expressed as mean + standard deviation, median with range for all continuous variables (e.g, age, duration of symptoms etc.) and

number (percentage) for categorical data (e.g. gender, surgical outcome etc.). Univariate analysis was performed by using the Pearson Chi-square test, Fisher Exact test, and Mann Whitney U-test whenever appropriate. A p-value <0.05 was considered as statistically significant. All p-value were two sided. The Statistical package for social science SPSS (Release 10.0.5, standard version, copyright © SPSS; 1989-99) was used for data analysis.

Results

Patient population Out of 30 patients, eighteen were males (60%) and 12 were females (40%). The mean age of patients at the time of diagnosis was 35.6 ± 10.4 years (range, 16-52) (Figure 1). The mean duration of symptoms reported by the patient at the time of diagnosis was 3.2 ± 2.4 years. The majority of tumours were macroadenoma, i.e. 25 patients (83%) but 5 had microadenoma (17%). Out of 25 macroadenomas, 19 had suprasellar extension and 12 were with optic chiasmal compression. Cavernous sinus involvement was present in 3 patients and sellar floor destruction with sphenoid sinus involvement in 3 patients

Table 1. Summary of characteristics of adenomas.

Characteristics	MRI size of adenoma		P-value
	Macro (n=25)	Micro (n=5)	
Pre-op GH level	30.4 (5.8-534)	12.5 (5.3-19)	0.015
Post-op GH level	5.7 (0.5-213)	0.9 (0.4-19)	0.021
Age (years)	31 (16-52)	45 (37-51)	0.016
Duration of symptoms (years)	2 (0.5-10)	5 (0.3-9)	0.552

Preoperative mean GH level was 42.4ng/ml with range of 2.5 to 534 ng/ml. In patients with microadenoma GH level was between 4.5 - 17.5ng/ml whereas higher levels were seen with macroadenoma. Preoperative OGTT suppression was done in 10 patients and was found to be Table 2. Surgical outcome.

	Pre-op MRI size of adenoma	Macro micro	Outcome of Surgery			
			Cure	Remission	Failure	Total
	Macro		8 (32%)	4 (16%)	13 (52%)	25 (100%)
	micro		5 (100%)			5 (100%)
	Total			4 (13.3%)	13 (43.3%)	30 (100%)

abnormal in all. Out of 30 patients who underwent surgery, thirteen patients had serum GH level of <2.5 ng/ml, four had levels between 2.5-5 whereas 13 had elevated levels. Postoperative OGT was done in 5 patients and no suppression of GH was there in four cases. Thus 13 had biochemical cure, 4 patients were in remission and 13 failed to respond to surgical treatment(Table 2). The outcome in microadenoma was better than in

macroadenoma i.e., 100% vs. 32%. Preoperatively four patients had panhypopituitarism, who did not recover from suppression after surgery. Postoperatively, additional six patients (20%) had panhypopituitarism.

Discussion

Acromegaly is a slowly progressive disease characterized by disfigurement and disability.¹⁴ Mortality in untreated acromegalics is probably two to three times that of healthy people.^{1,15} The observation that this increased mortality is decreased to normal in a population of cured acromegalics¹⁶ highlights the importance of achieving a biochemical cure. Treatment by surgery not only offers the

[(2)] advantage of an immediate decline of GH levels¹⁷ but also relieves the local pressure effects, reducing the systemic morbidity and normalizing the mortality. Surgery thus remains the first line treatment modality with adjuvant therapy consisting of radiotherapy and/or medical treatment. We retrospectively analyzed the clinical features and outcome of transsphenoidal hypophysectomy, in patients with acromegaly. There was male preponderance i.e. 60% whereas other studies suggested nearly equal sex distribution.^{18,19} We found that the mean age was lower than that reported in other studies i.e., 35.6 years as compared to 46.3²⁰ and 50¹⁸ years. The changes in appearance occur insidiously, so that very often the disorder is diagnosed only when a new physician replaces the usual doctor and sees the patient for the first time or when photographs of the patient taken over a number of years are collected together.⁵ Hence there can be a delay of 5-8 years^{18,19} in the diagnosis. From the charts reviewed it was noted that the mean duration of symptoms reported by the patients, was 3.3 ± 2.4 years (Table 1). This comparatively short duration can either be because of more aggressive disease but more likely this can be due to delay on part of the patient in observing the subtle changes in the features until they become very obvious. Majority of patients had macroadenoma which is in accordance with literature.^{16,18} It has been suggested that young patients with acromegaly generally have larger and more rapidly growing tumours at the time of diagnosis than older patients.²¹ Our data also showed that macroadenoma was seen in younger age group i.e. between 16-52 years with median of 31 years, whereas in case of microadenoma median age was 45 (Table 1). The definition of cure of acromegaly has been a matter of controversy. Till 1980s, a post therapeutic GH level <5 ng/ml was

considered to be consistent with disease cure²²⁻²⁴ but in the beginning of mid 1990s, a more stringent definition of cure has been used because analyses of long term outcomes have shown that mortality rates among treated acromegalics do not reach those of the normal population until GH levels drop below 2.5 ng/ml.²⁵ It was seen that with levels less than 5 ng/ml, there was recurrence of the disease in most of patients but with levels less than 2.5ng/ml, the long term cure rate went upto 97%.²⁶ Accordingly using the older criteria, many patients will experience remission of their disease rather than a cure. ¹³ According to the consensus statement issued in 19997, the cure is said to be achieved when circulating IGF-I is reduced to an age-adjusted normal range and nadir GH after an oral glucose load is less than 1 µg/L. In our study, 13 patients had GH level of <2.5 ng/ml and only 5 of them underwent dynamic study with OGTT with one patient having suppression of GH level. So there was a biochemical cure rate of 43.3% (Table 2) which is the same as reported by Sheaves et al²⁶ using the strict criteria. IGF 1 level measurement is not available in our country. Thus random GH levels and OGTT suppression test are only available tests to asses treatment outcome. The study had a number of limitations. It was a retrospective analysis of the charts, most of the patients followed up with neurosurgeons rather than endocrinologists, unavailability of IGF 1 level measurement and only few of them had dynamic testing done to asses the cure. The surgical outcome in microadenoma was better than with macroadenoma i.e., 100% vs. 32% but there were limited number of cases with microadenoma (n=5). Generally, the microadenomas do well postoperatively than macroadenomas. ²⁶ During selective adenomectomy, pituitary function is generally well preserved²⁷ and preoperative suppression also improves as a result of surgical removal of the tumour. Ross and Wilson showed that only nine (5.2%) of 172 patients had postoperative deterioration of pituitary function.²² We observed that preoperatively four patients had hypopituitarism which persisted postoperatively. In the present study postoperative hypopituitarism was seen in significant number of cases (20%). In conclusion, the data reviewed showed that acromegaly was seen at a much earlier age, more aggressive disease was seen in younger age group, the outcome of surgery was comparable to other studies and postoperative panhypopituitarism was seen in significant number of patients. The outcome in microadenoma was better than in macroadenoma but the number of patients seen

with microadenoma was small. Acknowledgement We wish to thank Mr Muhammad Islam, PGD (statistics), Research Coordinator, Department of Medicine, Aga Khan University Hospital for his help in statistical analysis.

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Abstract

Objective:

To assess the surgical outcome of hypophysectomy in acromegalic patients, differences in response to surgery in micro and macroadenoma and the development of associated hormonal deficiency after surgery.

Methods:

Retrospective analysis of charts of acromegalic patients who were operated upon at Aga Khan University Hospital, Karachi, was done. Information regarding presentation, laboratory data, radiological assessment, details of surgery and postoperative outcome was recorded. Surgical outcome was classified depending on the degree of disease control after surgery as biochemical cure, remission and treatment failure.

Results:

Out of 30 patients, eighteen (60%) were males and 12 (40%) females with mean age at the time of diagnosis 35.6 ± 10.4 years. The mean duration of symptoms was 3.2 ± 2.4 years. Twenty-five patients had macroadenoma and five had microadenoma. Preoperative mean GH level was 42.4ng/ml with range of 2.5 to 534 ng/ml. Following surgery, 13 had biochemical cure, 4 were in remission and 13 failed to respond. The outcome in microadenoma was better than in macroadenoma i.e. 100% vs. 32%. Preoperatively four patients had panhypopituitarism with additional six patients (20%) developing hypopituitarism postoperatively.

Conclusion:

Our study showed that acromegaly was seen at a much earlier age, outcome of surgery was comparable to other international studies and postoperative panhypopituitarism was seen in significant number of patients. The outcome in microadenoma was better than in macroadenoma but the number of patients seen with microadenoma was small (JPMA 54:315;2004).