Int J Endocrinol Metab 2007; 4: 147-152

ORIGINAL ARTICLE

Surgery for Acromegaly: The Outcome Based on Stringent Criteria of Remission

Taghavi M, Abutorabi R, Rajabian R, Khazaei MH

Endocrine Research Center, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, I.R. Iran

Acromegaly is a rare disease with increased mortality rate. Present literature documents the treatment of choice for acromegaly is surgery, curative in 91% of pituitary microadenomas and up to 73% of macroadenomas. The aim of this study was to present our experience in the diagnosis and treatment of a series of patients suffering from acromegaly, and to compare the results concerning control of disease with other series using modern criteria for therapy.

Materials and Methods: Of fifty patients (31 men, 19 women) referring to the Mashhad Endocrine Out-patient Clinic between 2001 and 2005, diagnosed with acrimegaly. 40 underwent surgery as initial therapy. We used a combination of modern, evidence-based remission criteria including basal GH below 2.5 μg/L (5 mU/L), a nadir GH below than 1.0 μg/L (2 mU/L) after an oral glucose tolerance test, and normal age-related IGF-I levels 6 months after surgery for the definition of cure in our patients.

Results: Fifteen of the 40 patients operated (37.5%) remained in remission after just transsphenoidal surgery; 80% of patients with microadenomas but only 31.4% of patients with macroadenomas achieved remission; 50% intrasellar macroadenomas showed remission, compared with only 21.7% extrasellar extended macroadenomas. The rate of biochemical 'cure' correlated with the magnitude of the initial GH levels, the tumor size and invasion.

Conclusion: In conclusion, using stringent criteria of remission, our results compared well with similar series of microadenomas and intrasellar macroadenomas, whereas outcomes for extrasellar macroadenomas were less than satisfactory .

Correspondence: Morteza Taghavi, Endocrine Research Center, Ghaem Hospital, Mashhad of University Medical Sciences, I.R. Iran
*E-mail:*Mortezataghavi2003@yahoo.com

Key Words: Acromegary, Surgery, Remission criteria

Received: 08.04.2007**Accepted**: 11.08.2007

Introduction

Acromegaly is a rare but serious chronic disorder caused by a growth hormone (GH)-producing pituitary adenoma in more than 99% of cases. Ectopic GH or GH-releasing hormone production or a pituitary carcinoma may also, very infrequently, cause acromegaly. Several retrospective cohort studies suggest that mortality in acromegaly cases is at least twice that in the general population. The cause of death is most commonly a vascular accident, but significant increases have been reported for both respiratory disorders and malignancies.[1-4]

Transsphenoidal surgery is the treatment of choice in most specialized centers,[5,6] and it offers the best chance of immediate normalization of GH levels in comparison to medical treatment and pituitary radiotherapy.[7]

Many biochemical criteria for remission have been suggested in the past, including a random GH measurement below 2.5 μg/L,[2,8,9,10] mean GH value from a day curve

less than 2.5 μg/L,[11,12] nadir GH value after an oral glucose tolerance test (OGTT) less than 1.0 μg/L and a normal age-related IGF-I level.[13,14,15] The importance of adequate treatment is highlighted by recent data indicating that lowering GH levels to less than 2.5 μg/L reverses the premature mortality of acromegaly,[9,11] and an international consensus conference in 1999 suggested rigorous criteria for remission (cure) of acromegaly including normal age-related IGF-I and nadir GH levels during an OGTT of less than 1.0 μg/L.[15] This was further ratified in May 2000 by the Acromegaly Treatment Workshop in their consensus statement.[16]

The aim of this study was to evaluate the results of surgery of acromegalic patients operated in our center using the current internationally accepted criteria for biochemical "cure" of the disease and to compare the results concerning control of disease with similar reports of other centers. It is very important to understand the results of surgery and the causes of surgery failure to improve earlier diagnoses and better management of acromegaly.

Materials and Methods

This is an analysis of the data of all acromegalic patients referred over five years to the Endocrine Outpatient Clinic at the Ghaem Hospital in the Mashhad in northern east of Iran. Data collected included symptoms and signs, preoperative imaging and laboratory results of basal serum GH level, nadir GH values following OGTT and IGF-I results before and 6 months after surgery.

Patients: From November 2001 to July 2006, 50 patients with acromegaly were diagnosed. Acromegaly was defined as a GH nadir over 2 ng/mL after 100 gram oral glucose suppression test and/or an elevated IGF-I level with the presence of a sellar mass on the imaging study.

Study design, hormone assays and imaging studies: Laboratory testing consisted of blood sampling at 8 a.m. for GH and IGF-I levels, after an overnight fast, and additional testing of GH levels at 60 and 120 minutes after drinking of 100 g of oral glucose. The glucose-suppressed GH value was considered to be the nadir level of GH measured after administration of the oral glucose. These tests were repeating every 6 months in all patients during follow up. Duration of follow up was 6 to 54 months. Cure was defined due to the results of these tests 6 months after surgery.

GH and the IGF-I were measured using competitive binding RIA (IRMA); Cortisol, T_4, T_3, testosterone levels in men were ascertained using current radioimmunoassay (RIA) and prolactin, luteinizing hormone and follicle-stimulating hormone levels were measured using competitive binding RIA (IRMA).

Tumor size was determined using preoperative magnetic resonance imaging (MRI) with Godolinium contrast agent. A microadenoma was defined as a tumor measuring 10 mm or less, and a macro-adenoma as a tumor measuring more than 10 mm in MRI. Macroadenomas were further divided into intrasellar (IS) and extrasellar (ES), with ES macroadenomas showing evidence of extension into the suprasellar cistern or third ventricle or lateral invasion into the cavernous sinus.

Surgical procedures: Of the 40 patients who underwent surgery, 35 patients had transsphenoidal microsurgical adenomectomy via a transseptal approach while for 4 patients, a transcranial approach was selected. In one patient, both operations were performed (initially transsphenoidal and then transcranial adenomectomy) because of the large size of the tumor; 9 patients with microadenoma and one with macroadenoma refused surgery and were excluded from follow up studies; other operated patients were followed for at least 6 months.

Statistical analysis: Statistical analysis of data regarding influence of the tumor size, invasion, preoperative GH levels or remission rate, was performed using the Mann-Whitney

test. Level of significance was set at $P< 0.05$. Data analysis was performed using the SPSS 11.0 for Windows statistical package.

Results

There were 19 women and 31 men in the series (male: female ratio 1.63:1.0) with a mean age of 36 years (range 14-60 years). All patients presented with typical signs and symptoms of acromegaly and 3 of them presented also had gigantism.

In 40% of patients, prolactin levels were elevated to 30 ng/mL (range 33–500 ng/mL); 23% of the patients were diabetic.

Based on preoperative measurement of the morning cortisol level, thyroid functions tests, luteinizing hormone and follicle-stimulating hormone levels, testosterone level in men, and menstrual history in women, 23 (46%) of the patients had preoperative evidence of impaired anterior pituitary function; 8 had panhypopituitarism; 13 had only hypogonadism (secondary amenorrhea in women or low testosterone levels in men); 1 patient had hypogonadism with secondary adrenal insufficiency and the last one had only isolated secondary adrenal insufficiency.

Tumor size was determined from preoperative magnetic resonance imaging, revealing 36 (72%) macroadenomas and 14 (28%) microadenomas; of the macroadenomas, 12 (33.3%) were intrasellar, whereas 24 (66.7%) had extrasellar extensions.

Surgery was performed in 40 patients; the mean duration of follow-up was 26 months and maximum at least 6 months. The mean preoperative GH level of operated patients was 118.7 ng/mL, with a range of 6.3 to 280 ng/mL. Postoperative mean basal serum GH concentration decreased to 48.5 µg/L with a range of 0.1 to 120 ng/mL .There was no correlation between preoperative GH and IGF1 level.

There was statistical correlation between preoperative GH value and cure rate, but there was no correlation between preoperative IGF1 value and cure rate (Table 1).

Table 1. Cure rates in pituitary micro- and macroadenomas and the correlation between preoperative GH and remission rate

	Microadenomas	Macroadenomas	Total
Number of operated cases	5	35	40
Mean preoperative GH level (µg/L)	40	130	119
Mean postoperative GH level (µg/L)	2.9	55	48.5
Cure rate (%)	80	31.4	37.5

In 16 (40%) patients, IGF-I level normalized after surgery and basal GH decreased to less than 2.5 µg/L. Nadir GH value of below 1.0 µg/L after OGTT was achieved in 17 of 40 (42.5%) patients. According to the presence of three criteria of cure (random morning GH measurement less than 2.5 µg/L, nadir GH value after an oral glucose tolerance test less than 1.0 µg/L, and a normal age-related IGF-I level, 15 of 40 patients (37.5%) showed criteria of remission 6 months after surgery; i.e. 4 of 5 (80%) patients operated with microadenomas and 11 of 35 (31.4%) with macroadenomas, had all the criteria of remission after surgery.

The best results of surgery of macroadenomas were achieved in the intrasellar macroadenomas, a group with a cure rate of 50% (6 of 12). Remission rate showed a tendency to drop in the more extensive macroadenomas; 21.7% (5 of 23) of suprasellar tumors considered had all three criteria for biochemical cure. There was statistical correlation of tumor size and invasion to suprasellar region with cure rate (Table 2).

Table 2. Cure rates in pituitary micro-and macroadenomas (with and without invasion) and the correlation between tumor size, invasion and remission rate

	Micro-adenomas	Macroadenomas with invasion	Macroadenomas without invasion
Number of operated cases	5	23	12
Diameter of tumor (mm)	2-8	13-35	11-29
Cure rate: no (%)	4 (80)	5 (21.7)	6 (50)

The remaining 25 patients, not completely cured, received medical therapy (dopamine agonists and/or somatostatin analog), and 22 of these underwent external radiotherapy in addition.

Discussion

The goals of surgical therapy in acromegaly include initial endocrinological remission with normalisation of the dynamic GH secretion pattern as well as normalisation of basal IGF-I to give regression of the signs and symptoms of the disease and prevention of recurrence and elimination of mass effects resulting in restoration of normal neurological function.[5,6]

As a result of the difficulties in defining postoperative endocrinological cure and the variations in criteria used by different investigators,[15] the success rates in terms of achievement of these goals vary significantly in data available, published from different centers.

Evaluating the endocrinological outcome in this study, facilitated not only the identifyication of a number of postoperative patients with normal IGF-I levels abnormal nadir GH levels, after oral glucose, but for a number of patients the elevated levels of IGF-I even if during OGTT, GH levels, could eventually be suppressed to below 1 μg/L. We chose to define remission as achievement of a basal postoperative GH less than 2.5 μg/L, a nadir GH value after OGTT of less than 1.0 μg/L, and a normal age-related IGF-I level 6 months after surgery. Using all of these stringent criteria, our overall remission rate was 37.5% which compares unfavorably with most other series of 33,[8] 34,[17] 42,[11] 49,[10] 55,[18] 56,[19] 67,[20] 68,[12] and 70%.[21]

The evaluation of our patient outcome led to detection of some predictors of the surgical result, such as tumor size, extrasellar growth and secretory activity. Regarding the growth characteristics of the lesions, microadenomas have a more favorable outcome than macroadenomas; in microadenomas, a remission rate of as high as 80% could be achieved. With increasing tumor diameter and extrasellar extension, remission drops stepwise to 50% for intrasellar macroadenomas and 21.7% for extrasellar extended macroadenomas. Therefore, our results, in keeping with many others, indicate that remission after surgery is dependent not only on tumor size but also on intrasellar confinement.[22,23]

The secretory activity of the adenoma also influences the response to surgical therapy, as observed in several published series.[11,22,23]

We did not measure mean GH value from a day curve, but we used other internationally accepted criteria for biochemical ‘cure’ of the disease, and this may overestimate cure rate in our patients.

Presence of typical coarse features of acromegaly in all of our patients, of overt diabetes mellitus and hypopituitarism in many of them (23% and 46% respectively) and extension of tumor to extrasellar region in most of patients (48% of all patients and 57.5% of operated patients) may be related to late diagnosis or treatment of the disease.

Ten of our patients refused operation and 7 of the operated patients had been diagnosed at least 2 years previously. Delay in diagnosis or treatment may cause more enlargement of tumor and its extension to suprasellar region and this may have been the cause of the limited success of sugery in macroadenomas in our patients.

In conclusion, using stringent criteria of remission, our results compare well for microadenomas and intrasellar macroadenomas but not so well for suprasellar extended macroadenomas with similar series.

Outcomes for macroadenomas when extended to suprasellar region are less than satisfactory, although with the new enhanced success for acromegaly surgery and the increased experience of surgeons, results may continue to improve with further reductions in morbidity and mortality.

References

1. Beauregard C, Truong U, Hardy J, Serri O. Long-term outcome and mortality after transsphenoidal adenomectomy for acromegaly. Clin Endocrinol (Oxf) 2003; 58: 86-91.
2. Orme SM, McNally RJ, Cartwright RA, Belchetz PE. Mortality and cancer incidence in acromegaly: a retrospective cohort study. United Kingdom Acromegaly Study Group. J Clin Endocrinol Metab 1998; 83: 2730-4.
3. Rajasoorya C, Holdaway IM, Wrightson P, Scott DJ, Ibbertson HK. Determinants of clinical outcome and survival in acromegaly. Clin Endocrinol (Oxf) 1994; 41: 95-102.
4. Swearingen B, Barker FG 2nd, Katznelson L, Biller BM, Grinspoon S, Klibanski A, et al. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab 1998; 83: 3419-26.
5. Fahlbusch R, Honegger J, Schott W, Buchfelder M. Results of surgery in acromegaly. Journal of Endocrinology Ltd.1994: 49–54
6. Kendall-Taylor P, Osman IA, James RA, Chatterjee S et al. Outcome of surgery for acromegaly. Journal of Endocrinology Ltd.1994: 65–68
7. LinksBarkan AL. Acromegaly. Diagnosis and therapy. Endocrinol Metab Clin North Am 1989; 18: 277-310.
8. Jenkins D, O'Brien I, Johnson A, Shakespear R, Sheppard MC, Stewart PM. The Birmingham pituitary database: auditing the outcome of the treatment of acromegaly. Clin Endocrinol (Oxf) 1995; 43: 517-22.
9. Bates AS, Van't Hoff W, Jones JM, Clayton RN. An audit of outcome of treatment in acromegaly. Q J Med 1993; 86: 293-9.
10. Osman IA, James RA, Chatterjee S, Mathias D, Kendall-Taylor P. Factors determining the long-term outcome of surgery for acromegaly. QJM 1994; 87: 617-23.
11. Sheaves R, Jenkins P, Blackburn P, Huneidi AH, Afshar F, Medbak S, et al. Outcome of transsphenoidal surgery for acromegaly using strict criteria for surgical cure. Clin Endocrinol (Oxf) 1996; 45: 407-13.
12. Ahmed S, Elsheikh M, Stratton IM, Page RC, Adams CB, Wass JA. Outcome of transphenoidal surgery for acromegaly and its relationship to surgical experience. Clin Endocrinol (Oxf) 1999; 50: 561-7.
13. Buchfelder M, Brockmeier S, Fahlbusch R, Honegger J, Pichl J, Manzl M. Recurrence following transsphenoidal surgery for acromegaly. Horm Res 1991; 35: 113-8.
14. Stoffel-Wagner B, Springer W, Bidlingmaier F, Klingmuller D. A comparison of different methods for diagnosing acromegaly. Clin Endocrinol (Oxf) 1997; 46: 531-7.
15. Giustina A, Barkan A, Casanueva FF, Cavagnini F, Frohman L, Ho K, et al. Criteria for cure of acromegaly: a consensus statement. J Clin Endocrinol Metab 2000; 85: 526-9.
16. Melmed S, Casanueva FF, Cavagnini F, Chanson P, Frohman L, Grossman A, et al; Acromegaly Treatment Consensus Workshop Participants.Guidelines for acromegaly management. J Clin Endocrinol Metab 2002; 87: 4054-8.
17. Kaltsas GA, Isidori AM, Florakis D, Trainer PJ, Camacho-Hubner C, Afshar F, et al. Predictors of the outcome of surgical treatment in acromegaly and the value of the mean growth hormone day curve in assessing postoperative

disease activity. J Clin Endocrinol Metab 2001; 86: 1645-52.
18. LinksLosa M, Oeckler R, Schopohl J, Muller OA, Alba-Lopez J, von Werder K. Evaluation of selective transsphenoidal adenomectomy by endocrinological testing and somatomedin-C measurement in acromegaly. J Neurosurg 1989; 70: 561-7.
19. Fahlbusch R, Honegger J, Buchfelder M. Surgical management of acromegaly. Endocrinol Metab Clin North Am 1992; 21: 669-92.
20. Laws ER, Vance ML, Thapar K. Pituitary surgery for the management of acromegaly. Horm Res 2000; 53 Suppl 3: 71-5.
21. Kreutzer J, Vance ML, Lopes MB, Laws ER Jr. Surgical management of GH-secreting pituitary adenomas: an outcome study using modern remission criteria. J Clin Endocrinol Metab 2001; 86: 4072-7.
22. Related Articles, LinksRoss DA, Wilson CB. Results of transsphenoidal microsurgery for growth hormone-secreting pituitary adenoma in a series of 214 patients. J Neurosurg 1988; 68(6): 854-67.
23. Tindall GT, Oyesiku NM, Watts NB, Clark RV, Christy JH, Adams DA. Transsphenoidal adenomectomy for growth hormone-secreting pituitary adenomas in acromegaly: outcome analysis and determinants of failure. J Neurosurg 1993; 78: 205-15.