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Acromegaly: surgical results in 548 patients

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Abstract
Purpose The goal of this study was to quantified the results of microsurgery, in all the patients with acromegaly treated by the same endocrinologist and the same surgeon between 1975 and 2015.
Methods A series of 548 patients with acromegaly were operated and followed-up from 6 months to 40 years. Patients were selected according to five criteria: (1) Operated by the same surgeon. (2) No previous treatment. (3) Complete endocrinological preoperative studies including GH, OGTT, IGF-I, PRL test and TC/MRI. (4) Complete postoperative endocrinological evaluation for at least one determination of GH, OGTT, PRL test and IGF-I six months after surgery. (5) All the patients were supervised by the same endocrinologist.
Results Microadenomas were present in 119 patients and 109 (91,5%) achieved remission. Non invasive macroadenomas were present in 200 patients and 164 achieved remission (82%). Results were worse for invasive macroadenomas but even with great invasions some patients achieved clinical remission. Follow-up range from 6 months to 40 years (mean 3.3 ± 2.3) A long term follow-up of 15 years was achieved in 61 patients. Four of them had a recurrence 4, 7, 8, 12 years after surgery (6.5%). There was not mortality and the rate of complications was low.
Conclusions Surgery remains the first line of therapy for a majority of acromegalic patients. This series proves to be very valuable in circumscribed adenomas but also in invasive tumours. Levels of GH and IGF-I were decreased in almost all the patients without remission.

Keywords Acromegaly · Microsurgery · Pituitary adenomas · Transsphenoidal approach

The original version of this article was revised: The value of PRL in Preoperative hormonal values section is corrected and column headers in Table 3 are corrected.

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Introduction

Transsphenoidal microsurgery remains a valid and widely used method of treating acromegaly [1, 2].

This procedure that has been proved relatively safe, achieves selective adenomectomy in great number of cases and a successful outcome in about 75–85% of patients with non invasive adenomas [3–6].

The definition of surgical success in controlling acromegaly have changed with authors and time. Years ago postoperative reductions in serum basal GH to below 10, 5 or 2 ng/ml were considered as acceptable. However, experience showed that single measurements of GH were insufficient as a criterion of cure, and both, the value of

postoperative IGF-I and the results of GH responses to dynamic testing, must also be considered [7–9].

The rates of surgical "cure" have changed over the last twenty years as a result of the modifications in these criteria, but also because of improvements in diagnosis and surgical techniques [10, 11].

Our study involves 548 selected acromegalic patients who had been treated with transsphenoidal microsurgery in our hospital. None of these patients have had any other treatment before surgery.

Patients and methods

A series of 548 acromegalic patients were selected from more than 5000 pituitary tumours, operated by transsphenoidal surgery in our hospital between 1975 and 2015.

Patients were selected according to five criteria: (1) Operated by the same surgeon (J.G.U). (2) No previous treatment. (3) Complete endocrinological preoperative studies including GH, OGTT, IGF-I, and TC/ MRI. (4) Complete postoperative endocrinological evaluation for at least one determination of GH, OGTT, and IGF-I six months after surgery. (5) All the patients were supervised preoperatively and postoperatively by the same endocrinologist. (T.L.M).

A retrospective review and follow-up evaluation of the patients in these series were conducted through their clinical files.

Overall surgical results were quantified for the entire study of 548 patients. In addition, the patients were divided into four groups of patients according to the period in which the surgery was performed. The first group involved patients operated between 1975 and 1984, the second group included patients operated between 1985 and 1994, the third group included patients operated between 1995 and 2004 and the fourth group included patients operated between 2005 and 2015.

Tumour classification

The tumours were classified according to size and extension in CT or MRI as follows: Grade I: microadenomas. Grade II: non invasive macroadenomas and tumours with moderate suprasellar extension into the cystern. Grade III: macroadenomas with localized invasion (local perforation of the sellar floor, or local invasion of the cavernous sinus and/or suprasellar extension that obliterates the recesses of the third ventricle or displace the third ventricle) and Grade IV: gigantic adenomas with diffused destruction of the sellar floor and diffused invasion of the cavernous and/ or intracranial, intradural extension.

Hormonal studies

Pre and postoperative endocrinological studies were carried out according to a protocol designed in our hospital with a complete study of pituitary function.

Hormonal quantification included, pre and postoperative mean baseline values of GH, IGF-I and oral glucose tolerance test (OGTT). Thyrotropin releasing hormone stimulation and L-Dopa stimulation replace OGTT in patients with diabetes mellitus.

Surgery

The surgical approach was essentially the same in all the patients, a microsurgical technique following the sublabial, rhinoseptal, transsphenoidal approach. Through the years, the sellar exposure has become increasingly wide and the selective removal of the tumour was associated with a more aggressive coagulation of the pituitary surface in the neighborhood with the tumour.

Intraoperative assessment of tumour extension and dural invasion were correlated with preoperative CT and MRI in all the patients with special attention in cases classified as radiological non invasive adenomas (grades I and II).

Postoperative evaluation was routinely carried out 2–21 days after surgery, and repeated after 3–6 months in all of these patients and when possible, on a yearly basis thereafter.

Surgical results have been quantified according to different parameters: (1) Basal GH <5 ng/ml. (2) Basal GH <2.5 ng/ml. (3) Basal GH <2 ng/ml. (4) GH after OGTT <1 ng/ml. (5) IGF-I normal. (6) Basal GH <2 ng/ml, GH <1 ng/ml after an OGTT and normal IGF-I, the criteria of choice for remission in our hospital.

Statistical analysis

Numerical data are expressed as mean and standard deviation. Descriptive analysis have been performed by means of mean, standard deviation, minimum and maximum values in case of numerical variables and absolute and relative frequencies for categorical variables.

Results

Patients

The series of 548 acromegalic patients were recruited between patients operated in our hospital from 1975 to 2015. Sixteen patients presented gigantism (3%).

In our study the mean age was 41.3 ± 13.3 years. (Range: 9–77 years). Patients were female in 330 cases (60.2%) and

Table 1 Age and sex

Period	Patients	Age (years) Mean/Range	Female	Male
1975–84	78 (14.2%)	38.5/9–68	45 (57.7%)	33 (42.3%)
1985–94	155 (28.3%)	45.9/17–75	87(56.1%)	68 (43.9%)
1995–04	205 (37.4%)	46.3/14–74	132 (64.4%)	73 (35.6%)
2005–15	110 (20.1%)	45.8/14–77	66 (60%)	44 (40%)
Total	548 (100%)	41.3/9–77	330 (60.2%)	218 (39.8%)

218 were men (39.8%). Age and sex distribution by periods is shown in Table 1.

The first group included 78 patients (14.2%) operated between 1975 and 1984. The second group included 155 patients (28.3%) operated between 1985 and 1994. The third group included 205 patients (37.4%) operated between 1995 and 2004. The fourth group included 110 patients (20.1%) operated between 2005 and 2015.

Tumour size

According to preoperative CT or MRI, Grade I was present in 119 of the patients (21.7%). Grade II was present in 200 patients (36.4%). Grade III was present in 177 patients (32.2%). Grade IV was present in 52 patients (9.5%). (Table 2).

When compared the different groups of patients, the percentage of microadenomas increased progressively from 1 patient (1.3%) in the first group to 20 patients (12.9%), 60 patients (29.2%) and 38 patients (34.5%) in groups two, three and four.

Furthermore the percentage of macroadenomas decreased from 77 patients (98.7%) in the first group, to 134 patients (86.4%), 140 patients (68.2%), and 78 patients (70.9%). (Fig. 1).

Preoperative hormonal values

Mean preoperative GH in this series was 31.9 ng/ml ± 45 (range 2-415 ng/ml).

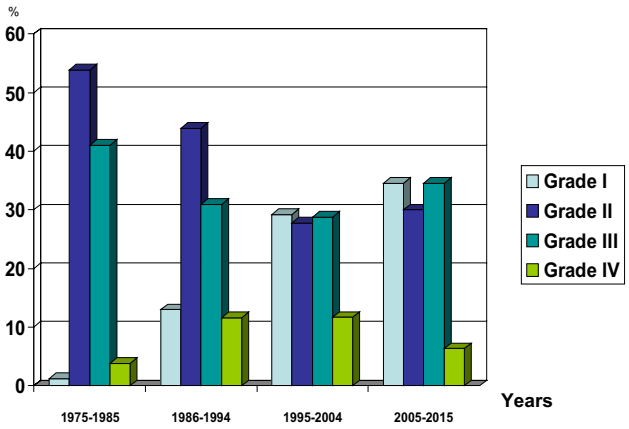

Fig. 1 Grade's tumor distribution by years

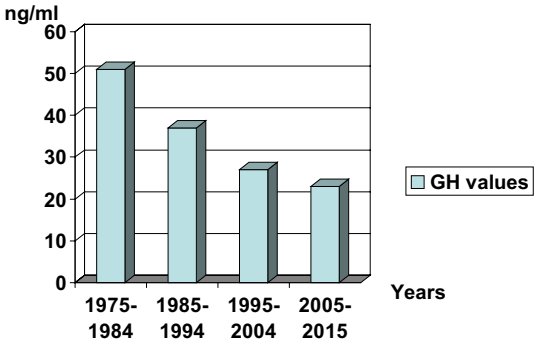

Fig. 2 Basal GH preoperative values

In the first group the mean of GH was 50.8 ng/ml (range 2.2–400 ng/ml). In the second group the mean GH was 36.5 ng/ml (range 2–415 ng/ml). In the third group the mean GH was 26.4 ng/ml (range 3–320 ng/ml). In the fourth group the mean of GH was and 22.7 ng/ml (range 2–252 ng/ml). (Fig. 2).

In this series mean preoperative IGF-I was 940.7 ± 520.1 ng/ml (range 173–3564 ng/ml).

In many patients of the first group, IGF-I was not quantified, because it was not available for that period. In the

Table 2 CT-MRI Grade preop

Period	Patients	Grade I	Grade II	Grade III	Grade IV
1975–84	78 (14.2%)	1 (1.3%)	42 (53.8%)	32 (41.0%)	3 (3.8%)
1985–94	155 (28.3%)	20 (12.9%)	68 (43.9%)	48 (31.0%)	18 (11.6%)
1995–04	205 (37.4%)	60 (29.2%)	57 (27.8%)	59 (28.8%)	24 (11.7%)
2005–15	110 (20.1%)	38 (34.5%)	33 (30%)	38 (34.5%)	7 (6.4%)
Total	548 (100%)	119 (21.7%)	200 (36.4%)	177 (32.2%)	52 (9.5%)

*Grade I (microadenoma); Grade II (macroadenoma intrasellar); Grade III (macroadenoma with limited invassion) Grade IV (macroadenoma with diffuse invassion)

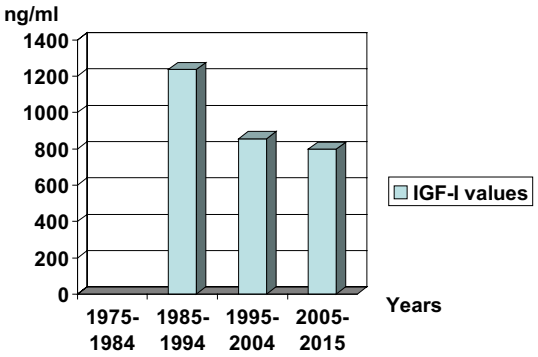

Fig. 3 IGF-I preoperative values

second group the mean IGF-I was 1236 ng/ml (range 173–3564 ng/ml). In the third group the mean of IGF-I was 856 ng/ml (range 371–2109 ng/ml). In the fourth group the mean of IGF-I was 798.99 ng/ml (range 340–1805 ng/ml) (Fig. 3).

PRL evaluation was realized in 453 patients (82.6%). Hyperprolactinemia > 5 ng/ml was associated with acromegaly in 95 patients (20.9%), (64 women and 31 men.). PRL > 100 ng/ml was found in twelve patients (2.64%), (7 women and 5 men).

Hypo pituitary function of one or more hormones was present before surgery in 82 patients (14.9%). None of the patients has preoperative diabetes insipidus.

Postoperative hormonal values

After surgery (2–21 days), 34 patients achieved GH basal levels between 5 and 2.5 ng/ml. 25 patients achieved GH basal levels between 2.4 and 2 ng/ml and 356 patients achieved GH basal levels <2 ng/ml (Table 3).

When the surgical results were quantified according to postsurgical OGTT and IGF-I, (3–6 months after surgery) we found incomplete or elusive data in 26 patients.

In the remaining 522 patients, 322 (61.7%) achieved the criteria of remission (Basal GH <2 ng/ml, GH <1 ng/ml after an OGTT and normal IGF-I). 200 patients remained with active disease (38.3%) (Table 4).

Table 4 Surgical Results (522 cases)

Period	"Remission"	"Active"	Total
1975–84	26 (33.3%)	52 (66.7%)	78
1985–94	93 (60.7%)	60 (39.3%)	153
1995–04	134 (69.4%)	59 (30.6%)	193
2005–2015	69 (70.4%)	29 (29.6%)	98
Total	322 (61.7%)	200 (38.3%)	522 (100%)

*Remision when: GH basal < 2 ng/ml, OGTT < 1 ng/ml and normal IGF-I levels

Table 5 Postop. MRI grade (515 patients)

Period	Normal MRI	Abnormal MRI
1975–84	20 (25.6%)	58 (74.4%)
1985–94	83 (54.6%)	69 (45.4%)
1995–04	124 (65.9%)	64 (34.1%)
2005–15	65 (67%)	32 (33%)
Total	292 (56.7%)	223 (43.3%)

[a]Abnormal MRI: tumour rest or postsurgical changes

In the patients with persistent disease, the mean GH decreased from 43.8 ng/ml preoperatively to 16.3 ng/ml postoperatively (63.8%) and mean IGF-I decreased from 1044.8 ng/ml preoperatively to 781.3 ng/ml postoperatively (25.3%).

Postoperative MRI control

MRI was realized 3–5 months after surgery in 515 patients.

In 292 (56.7%) patients the image was considered normal. In 223 (43.3%) the image was considered abnormal. (Table 5). In 130 of these patients, the existence of an incomplete resection of the adenoma was unequivocal. In the other 93 patients, MRI showed abnormalities which could be related to the surgery and required further post operation control. In 55 of these patients MRI remained without changes. In 22 out of the remaining 38, MRI showed an increase of size in the image which was considered as a regrowth of the tumour. In 16 patients there were minor MRI changes.

Table 3 Postoperative GH-levels (548 patients)

Period	GH >5 ng/ml	GH 5–2.5 ng/ml	GH 2.4–2 ng/ml	GH <2 ng/ml
1975–84	40 (51%)	7 (9%)	2 (3%)	29 (37%)
1985–94	39 (25%)	9 (6%)	6 (4%)	101 (65%)
1995–04	35 (17%)	11 (5.4%)	11 (5.4%)	148 (72.2%)
2005–15	19 (17%)	7 (6%)	6 (5%)	78 (70%)
Total patients	133 (24.2%)	34 (6.2%)	25 (4.5%)	356 (65%)

*Surgical results (1975-2015) Postoperative GH 2-21 days after surgery

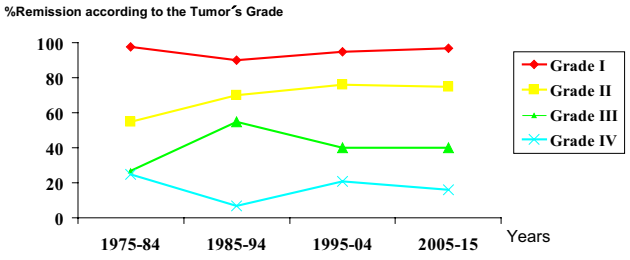

Fig. 4 Long term surgical results in 522 patients

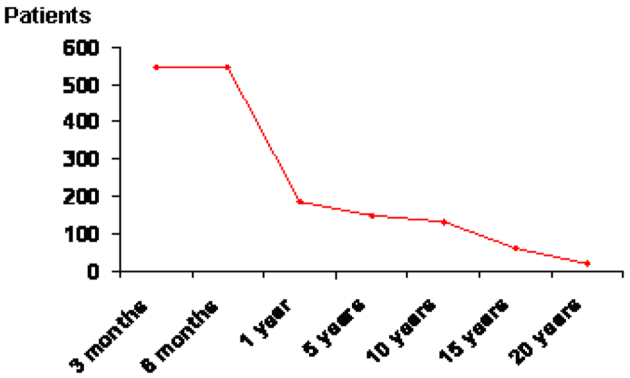

Fig. 5 Follow-up

Grade of tumour

Surgical results where related with the grade of the tumour and the existence and extension of the dural invasion.

A total of 119 patients had microadenomas and 109 achieved remission (91.5%). In 30 patients, an invasion of the dura by the microadenoma was observed during the surgical procedure, and the criteria of cure were achieved in only 26 of them (86%) a lower remission rate than expected for microadenomas.

When considering the different groups of patients with microadenomas, the surgical results achieved consistently more of 90% of remission.

In grade II, from a total population of 200 patients, 164 of them achieved criteria of remission (82%). In this group, 58 patients (29%) had invasion of the dura identified during the surgical procedure. Only 38 of them achieved criteria of cure (65.5%), again a lower rate than expected.

Results were worse in grades III and IV but even with great invasion a possibility of clinical remission with a surgical treatment still remains (Fig. 4).

Follow-up

Follow-up range from 6 months to 40 years. Mean follow-up was 3.3 ± 2.3 years.

A follow-up of 6 months was achieved in all the patients and in fact was a criterion for inclusion in this series.

In 186 patients the follow-up control was achieved for at least one year. In 150 patients such follow-up control was achieved for more than 5 years, with at least one yearly control. In 132 patients, follow up included at least a yearly control for over 10 years. In 61 patients, controls were at least once a year for over 15 years. In 19 patients, follow up, was controlled at least once a year for more than 20 years (Fig. 5).

Recurrence

Complete 5 years follow-up was achieved in 150 patients with only one recurrence (0.7%). A follow-up of 10 years was achieved in 132 patients and three (2.3%) had a recurrence of the disease.

Long term follow-up was quantified 15 years after surgery in 61 patients. Four of them had a recurrence of GH hypersecretion which have appeared 4, 7, 8 and 12 years after surgery. (6.5%).

Complications

There was not mortality in this series. There was a low rate of complications which included postoperative CSF leaks in 12 patients (2%). Meningitis in 3 patients (0.5%). Cranial nerves dysfunction in 5 patients (0.9%). Carotid Injury in 2 patients (0.3%). SIADH in 2 patients (0.3%). Diabetes insipidus was transitory in 63 patients (11.4%) and persisted more than a year in 3 patients (0.5%) (Table 6).

Surgery induced a pituitary deficit in approximately 2% of the patients.

Discussion

Since its first description in the early 1900s, the transsphenoidal approach has been a possible choice for the removal of pituitary tumours. The introduction of microsurgery by Hardy in 1969 [12] allowed a selective

Table 6 Complications. 548 patients

Mortality	CSF leak	Meningitis	III/VI pulsy	Carotid injury	Diabetes insipidus (1y,after surgery)	SIADH
0	12 (2%)	3 (0.5%)	5 (0.9%)	2 (0.3%)	3 (0.5%)	2 (0.3%)

adenomectomy with a preservation of the pituitary function. Since then, many series of acromegalic patients treated with transsphenoidal microsurgery have been published [1–6, 11].

After one hundred years, surgery remains the first line of therapy for a majority of the acromegalic patients, presenting several advantages over pharmacological treatment or radiotherapy. The removal of hypersecreting tumours, offers the best chance for immediate and definitive control of GH hypersecretion.

Medical treatment needs to be maintained indefinitely and is actually very expensive. Radiation therapy requires a long time to suppress GH and IGF-I levels, and the benefit of treatment may be partially or wholly obviated since disease duration and age predict higher mortality.

Despite of these reasons, most endocrinologist, would consider surgery only in cases of well circumscribed adenomas. During the last years, in our clinical practice, it is becoming increasingly unusual to operate cases without a previous, sometimes long period, of medical treatment. We believe that medical treatment is elected as a first choice treatment by many physicians in our country, even in cases of circumscribed adenomas.

In this series more than 90% of the patients with microadenomas achieved surgical remission. Microsurgery can also achieve a high level of objective success in a high number of circumscribed macroadenomas. We like to stand out, the existence of dural invasion in more than 20% of the called circumscribed adenomas (grade I and II), which are by definition non-invasive. We have also found a frequent invasion of the pituitary gland surface in contact with the tumour. This fact requires an exhaustive exploration, during surgery, of the neighborhood of the tumour with special attention to the dura. To achieve this, the magnification of the microscope is, in our opinion, a far better tool than the view offered by the endoscopy.

Our series have showed that the surgical treatment of somatotroph adenomas decreases the levels of GH, IGF-I in almost all the patients. This fact renders the medical treatment more effective, and justifies surgery even in case of failure [13].

The use of a single reliable criterion for cure remains elusive. The best method to quantify the surgical results, could be the suppression of integrated 24-h serum GH levels to <2 ng/ml. However, this parameter is not completely reliable and needs the determination of oral glucose load and serum IGF-I.

Endocrinological test are costly and this can prevent the follow up of the acromegalic patients. In Spain, the National Health System affords patients a comprehensive array of health services free of charge. This has allowed a long term follow up of an important number of our patients, most of them living in different cities in Spain. However even in this apparently favourable contour, long term follow-up remains elusive.

Our series showed a constant increase in the percentage of microadenomas and a progressive decrease in GH and IGF-I mean preoperative values, to be related to a shorter evolution of the disease before diagnosis.

There was also a constant increase in the rate of remission after surgery, which is thought to be related to an increase of the surgeon´s experience and the improvement of the surgical tools. This fact is less clear than should be, when comparing the different groups in these series, because the criteria for selection include patients operated from 1975. The microsurgical transsphenoidal treatment for pituitary adenomas started in our hospital in 1970 [4]. During the period ranging from 1970 to 1975 more than 500 patients were operated, with a higher rate of complications and less satisfactory results than those achieved in this series, showing a period of learning which is unavoidable. We like to point out that in a total of more than one thousand operations for acromegaly performed in our hospital, two acromegalic patients died after surgery. These two patients, as many others, were excluded in this series, because the criteria of selection. The goal of this study was to quantified the results, in a series, which would include all the patients treated in a similar way by the same endocrinologist and the same surgeon between 1975 and 2015, with a minimum follow-up of six months and not a review of the experience of a hospital.

The number of recurrences when the patients achieved the criteria of remission remains low, but recurrence appeared as late as 12 years after surgery.

During the last decade, microsurgery has been challenged by endoscopy in an effort to achieve more complete resections and lower morbidity rates. So far, none of these techniques have proved more effective than microsurgery for the treatment of acromegaly [14–19].

Conclusions

Improvement in the diagnosis and accurate MRI localization have combined over time to achieve an increasing number of cases operated in a stage of circumscribed adenomas, with improved results. The accumulation of surgeon´s experience, as in other fields, has also proven important. This series confirm the facts proved by others: Surgery achieves a high level of success in the treatment of acromegaly. Residual pituitary function is usually intact after resection of the adenoma and the level of complications remains low.

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Compliance with Ethical Standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers´bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval For this retrospective study, formal consent is not required.

Informed consent All of our patients have signed an informed consent before surgery that included scientific purpose.

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