Turkish Journal of Endocrinology and Metabolism, (1999) 1 : 33-36 **ORIGINAL ARTICLE**

Investigation of the Pituitary Functions of Patients with Acromegaly Treated by Transsphenoidal Route: A Retrospective Analysis of 39 Case s

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In this study we analyzed the pituitary functions of 39 patients with acromegaly (22 male, 17 female; age (X±SD), 38±11 years; range, 16-64 years) treated by the transsphenoidal route between 1982-1996. Thirty-three patients had macroadenomas and 6 had microadenomas. The mean follow-up after surgery was 35±25 months (range:1-117 months). In 17 (43.6%) patients, there was complete remission after transsphenoidal surgery. Adjunctive radiation therapy was administered to 17 of 22 patients who did not experience a remission after surgery alone. An additional four of these were in remission by the end of the follow-up period. So the ratio of remission after surgery + radiation therapy was 21 in 39 (53.8%). The diagnosis of hypopituitarism was established according to clinical grounds and basal hormone levels in most of the patients. Eighteen of the 39 patients (46.2%) received no replacement therapy. Ten patients with panhypopituitarism received full replacement therapy. The most frequent replacement therapy was that of sex hormones (17 patients - 43.6%), the second one was glucocorticoid (14 patients - 36.8%) and the last one was thyroid hormone replacement therapy (13 patients - 34.2%). Permanent diabetes insipitus was seen in only two patients (5.1%). Relationships between the frequency of the replacement therapy and gender, tumor size, adjuvant radiotherapy, cure ratio, age, preoperative GH and prolactin levels and duration of the follow-up period are evaluated. There was a significant relationship between basal GH levels and frequency of glucocorticoid and thyroid hormone replacement therapy ($p<0.05$).

KEY WORDS Acromegaly, transsphenoidal surgery, hypopituitarism

Introduction

Acromegaly is a rare disorder which is caused by GH-secreting pituitary adenomas, which constitute the second common type of primary pituitary tumors and, in rare cases, by ectopic production of GRH with resultant hypersecretion of GH (1). Important systemic manifestations include acral enlargement, swelling, disfigurement, glucose intolerance and diabetes, hypertension, nerve entrapment, arthropathy, cardiac disease and increased incidence of tumor formation in different tissues. Tumor-related major manifestations are visual impairment, oculomotor paralysis, and hypopituitarism. Morbidity is substantial, and mortality is increased in inadequately treated cases (2). The major aims of the therapy are (I) to reduce the growth hormone levels in order to stop the acral enlargement and prevent further metabolic complications and (II) to avoid the impairment of pituitary functions due to local effects of the tumor tissue. Therapy is mandatory and consists of surgical removal of the pituitary adenoma (usually

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by the transsphenoidal route) or of the ectopic source of GRH (carcinoids or islet cell tumors). Adjunctive radiation and/or drug therapy is often necessary if complete surgical ablation of the adenoma is not possible. Radiation therapy can be administered as conventional supervoltage x-ray treatment or in the from of heavy particle beams. Drugs effective in partially lowering GH levels are bromocriptine and somatostatin analogues (3,4). Among these, transsphenoidal surgery by experienced surgeons is the treatment of choice in the last 20 years, having a more rapid effect and low morbidity and mortality without impairing normal pituitary function which is very important for the quality of life of the patient (5-7).

In this study we analyzed the pituitary functions of 39 acromegalic patients who underwent transsphenoidal surgery between 1982-1996 in our clinic.

Materials and Methods

Pituitary functions of 39 patients (22 male, 17 female; age (X±SD), 38±11 years; range, 16-64 years) with acromegaly who were operated on by the transsphenoidal route between 1982-1996 were evaluated. Thirty-three patients had macroadenomas and 6 had microadenomas. The mean follow-up after surgery was 35±25 months (range:1-117 months). Suppression of GH levels below 2 ng/mL during the standard oral glucose loading is taken as the criteria for remission. Adjunctive radiation therapy was administered to 17 of 21 patients who were not in remission after surgery alone in the early postoperative period (e.g. 1-6 months after the surgery). The diagnosis of partial or complete hypopituitarism was established according to clinical grounds and basal hormone levels in most of the patients. In a few patients further stimulation tests were carried out. Correlation between the remission rate and patient's age and gender, tumor dimension, preoperative GH, TSH, prolactin, LH and FSH levels was determined.

Statistics

Means and standard deviations were calculated. Student's t-test for independent samples (two-tailed), the Chi-square test, the non-parametric Mann-Whitney U-test, and the non-parametric Wilcoxon signed ranks test were used.

Results

Growth hormone levels decreased in nearly all of the patients. Mean basal GH levels were decreased from 36,7±23,3 ng/mL to 17,3±29,3 ng/mL post-operatively ($p<0.001$). OGTT-suppressed GH levels (the nadir GH during the OGTT) also decreased from 41,7±30.5 ng/mL to 9,2±5,9 ng/mL ($p<0,5$). In 17 (43.6%) patients there was complete remission after transsphenoidal surgery. There was no statistically significant relationship between the outcome of the surgery and patient's age (p:0.352), gender (p:0.445), size of the tumor (p:0.976), preoperative basal GH (p:0.162), nadir GH level during OGTT (p:0.085), mean GH level during OGTT (p:0.407), TSH(p:0.199), prolactin (p:0.383), LH (p:0.867) and FSH (p:0.905) levels. Adjunctive radiation therapy was administered to 17 of 22 patients who were not in remission after surgery alone in the early postoperative period (e.g. 1-6 months after the surgery). An additional four of these were in remission by the end of the follow-up period. So the ratio of remission after surgery + radiation therapy was 21 in 39 (53.8%). By the end of the follow-up period mean basal GH level was 10.4±4.3 ng/mL, and was statistically significantly lower than the preoperative value (36.7 ±23.3 ng/mL, $p<0.001$).

Eighteen of the 39 patients (46.2%) received no replacement therapy at the end of the follow-up period. The rest needed at least one of the anterior pituitary hormones. Ten patients with panhypopituitarism received full replacement (i.e. glucocorticoid plus thyroid plus sex hormone) therapy. As a whole, the most frequent replacement therapy was that of sex hormones (17 patients-43.6%), the second one was glucocorticoid (14 patients-36.8%) and the last one was thyroid hormone replacement therapy (13 patients-34.2%). The results are shown in Table 1. While 7 patients developed polyuria in the early postoperative period, permanent diabetes insipitus was seen in only two patients (5.1%) during the follow-up. There was no statistically important relationship between the frequency of the replacement therapy and gender, adjuvant

radiotherapy, or cure ratio. The relationships between preoperative tumor size, age, preoperative GH and prolactin levels and duration of the follow-up period are shown in Tables 2 to 5. The ohly statistically significant relationship was between basal GH levels and frequency of glucocorticoid and thyroid hormone replacement ($p<0.05$).

Table 1. Frequency of replacement therapy after transsphenoidal surgery.

	number of patients
glucocorticoid replacement	14 (36.8%)
sex hormone replacement	17 (43.6%)
thyroid hormone replacement	13 (34.2%)
no replacement therapy	18 (46.2%)
1 hormone replacement	8 (20.5%)
2 hormones replacement	3 (7.7%)
3 hormones replacement	10 (25.6%)
diabetes insipitus	2 (5.1%)

Table 2. Relationship between tumor size and replacement therapy.

	microadenoma	macroadenoma	p:
glucocorticoid repl.	16,6%	39,4%	NS
sex hor. repl.	33,3%	45,5%	NS
thyroid h. repl	16,6%	36,4%	NS

Table 3. Effects of various factors on glucocorticoid replacement therapy (mean ±SD).

	glucocorticoid replacement (+)	glucocorticoid replacement (-)	p:
follow-up period	40 ± 31 months	31 ± 20 months	NS
age	34.9 ± 12.5	39.7 ± 11.1	NS
preoperative basal GH	48.9 ± 28.2 ng/ml	29.5 ± 16.6 ng/ml	<0.05
preoperative OGTT-suppressed GH	40.4 ± 30.8 ng/ml	24.7 ± 15.2 ng/ml	NS
preoperative prolactin	46.1 ± 57.7 ng/ml	26.5 ± 24.2 ng/ml	NS

Table 4. Effects of various factors on sex hormone replacement therapy (mean ±SD).

	sex hormone replacement (+)	sex hormone replacement (-)	p:
follow-up period	42.1 ± 29 months	27.1 ± 17.1 months	NS
age	36.3 ± 11.7	39.3 ± 11.9	NS
preoperative basal GH	46.1 ± 29.2 ng/ml	28.9 ± 13.5 ng/ml	NS
preoperative OGTT-suppressed GH	37.9 ± 28.2 ng/ml	23.8 ± 14.9 ng/ml	NS
preoperative prolactin	45.4 ± 55 ng/ml	28.9 ± 25.2 ng/ml	NS

Table 5. Effects of various factors on thyroid hormone replacement therapy (mean ±SD).

	thyroid hormone replacement (+)	thyroid hormone replacement (-)	p:
follow-up period	46.3 ± 34.5 months	29.0 ± 16.5 months	NS
age	32.6 ± 9.6	40.8 ± 11.9	NS
preoperative basal GH	49.5 ± 28.7 ng/ml	29.5 ± 16.9 ng/ml	<0.05
preoperative OGTT-suppressed GH	41.4 ± 29.7 ng/ml	24.2 ± 15.6 ng/ml	NS
preoperative prolactin	51.6 ± 32.6 ng/ml	34.9 ± 29.2 ng/ml	NS

Discussion

In this study we analyzed the clinical records of 39 acromegaly patients treated with transsphenoidal microsurgery retrospectively. Seventeen (43.6%) patients were in complete remission after transs-phenoidal surgery. An additional four patients who received radiotherapy were in remission by the end of the follow-up period. So the ratio of remission after surgery + radiation therapy was 21 in 39 (53.8%). These results are consistent with some earlier series from our country, which report remission rates of 45% and 39% respectively (8,9) but somewhat lower than some series from western countries, which report remission rates between 56% and 88% (10,11).

Ten (25.6%) patients developed panhypopitui-tarism, while a total of 21 patients (53.8%) received at least one replacement hormone. These are somewhat higher values than those in the literatüre where hypopituitarism was reported to be frequent after transcranial surgery and radiotherapy (more than 50%) but very rare after transsphenoidal adenomectomy (between 12.5% and 17%) (12-14). This discrepancy might be due to the differences in preoperative tumor activity, because there is a significant relationship between preoperative basal GH levels and the frequency of postoperative replacement therapy in our study. As most of the patients in the study were referred to our clinic after the operation, we have limited information about the preoperative pituitary function of the patients. Perhaps the incidence of preoperative hypopituitarism was higher than that of other studies and this might be another explanation of this discrepancy.

In our study, the most common hormone deficiency is found to be that of sex hormones , the second one is glucocorticoid and the last one is thyroid hormone deficiency. This finding is not consistent with the literature (15), where the deficiency of gonadotrophins is followed by the deficiency of TSH and ACTH deficiency is the least common type. This difference may be explained by the urgency of the clinician in starting the glucocorticoid replacement therapy, which is much more vital than either thyroid or sex hormones. Perhaps corticotroph deficiency is much lower than the number of patients receiving glucocorticoid replacement therapy, but because of the risk of the insulin tolerance test in panhypopituitary patients, a subset of patients might incorrectly be accepted as deficient and given glucocorticoid therapy.

As a result, we conclude that transsphenoidal microsurgery remains a rapid and valuable treatment for acromegaly. Although it has a negligible mortality; it still has substantial morbidity, causing a high prevalence of partial or complete hypopituitarism.

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