CLINICAL STUDY

The characteristics of acromegalic patients with hyperprolactinemia and the differences in patients with merely GH-secreting adenomas: clinical analysis of 279 cases

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Abstract

Objective: The aim of this study is to evaluate clinical data from a large cohort of acromegalic patients with and without hyperprolactinemia.

Design and methods: Between January 2002 and June 2010, a set of data on 279 acromegalic patients undergoing transsphenoidal surgery was available. Based on preoperative GH and prolactin (PRL) levels, patients were divided into GH and GH+PRL groups. A stabilization or a further improvement of postoperative changes in clinical, hormonal, immunohistochemical, and magnetic resonance imaging parameters was observed in all patients throughout the follow-up period.

Results: The GH group had significantly more coarse facial features, large hands and feet, hypertension, and diabetes mellitus compared with the GH+PRL group but significantly less menstrual disorders (13.8 vs 54.3%, $P<0.001$) and galactorrhea (3.1 vs 22.4%, $P<0.001$). The GH group had a higher age at diagnosis compared with the GH+PRL group (45.6 ± 13.9 vs 40.4 ± 11.4 years, $P=0.001$). The GH group had a smaller mean maximal diameter of the adenomas (2.2 ± 0.9 vs 2.6 ± 1.1 cm, $P=0.004$). There were no significant correlations between hormone levels and the immunohistochemical results. According to the criteria for hormonal cure of acromegaly, the surgical control rates in the GH and GH+PRL groups were 68.4 and 59.7% respectively ($P=0.187$). Tumor size was an important factor that affected the results of the operations. The rates of surgical control in GH and GH+PRL groups were 80.7 and 69.1% respectively ($P=0.037$), and the recurrence rates in the two groups were 7.1 and 11.3% respectively ($P=0.185$).

Conclusions: Compared with patients with merely GH-secreting adenomas, acromegalic patients with hyperprolactinemia are characterized by an earlier onset of disease, lesser acromegalic features, lower GH levels, but larger tumor sizes, whereas in female patients, GH–PRL secreting adenomas are associated with higher incidences of menstrual disorders and galactorrhea.

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Introduction

Acromegaly is a rare disease characterized by excess secretion of GH and increased circulating concentrations of insulin-like growth factor 1 (IGF1) (1). It is characterized by slowly and progressively acquired somatic disfigurement (mainly involving face and extremities) and systemic manifestations. The disease is associated with increased morbidity and premature mortality, due to cardiovascular, cerebrovascular, or respiratory causes (1, 2, 3, 4, 5). In general, the underlying abnormality in most cases is hypersecretion of GH by the pituitary GH-producing tumors. Nonetheless, about 16–27% of these patients have increased GH and prolactin (PRL) levels (6, 7, 8). Most of the previous studies focused on some particular aspects of

the clinical course of acromegaly and its treatment. However, there are only limited comprehensive detailed data available on acromegalic patients with hyperprolactinemia. Therefore, we aim to evaluate the clinical features and hormonal changes in acromegalic patients with hyperprolactinemia treated with transsphenoidal surgery in a retrospective study in a single center.

Patients and methods

Patients

A retrospective chart review was performed on all patients with GH-producing adenomas treated between January 2002 and June 2010 at the

Department of Neurosurgery, Provincial Hospital Affiliated to Shandong University, Jinan, People's Republic of China. A total of 342 acromegalic patients underwent primary transsphenoidal surgery. Of these, 279 patients had a complete set of data before and 1 year after surgery. Magnetic resonance imaging (MRI) examinations were done in all patients. Based on the preoperative GH and PRL levels, patients were classified as follows: GH group (acromegalic patients with elevated GH levels) and GH+PRL group (acromegalic patients with both elevated GH and PRL levels). The research was approved by the Research Ethics Committee of Shandong University, China. Informed consents were acquired from all patients.

Endocrine evaluation

The diagnosis of acromegaly was made on the basis of an elevated IGF1 level as matched for age and gender and failure to suppress GH in response to the 75 g oral glucose tolerance test (OGTT) to a level of <1 ng/ml (9, 10). GH was measured using a chemiluminescence immunoassay (Snibe Co. Ltd., Shenzhen, China) with a sensitivity of 0.25 ng/ml. The intra-assay coefficient of variation (CV) was $<10\%$ and the interassay CV was $<15\%$. Serum IGF1 was measured using a chemiluminescence immunoassay (Snibe Co. Ltd.) with a sensitivity of 2.5 ng/ml. The intra- and interassay CV were <10 and $<15\%$ respectively.

Serum PRL was measured with commercially available kits (Beckman Coulter, Inc., CA, USA). The normal range was 2.58–18.12 ng/ml in males and 1.20–29.93 ng/ml in females.

GH and PRL levels were assessed before surgery and 3 days, 3 months, and 12 months after surgery respectively.

Tumor classification

Pituitary adenomas were classified by size on MRI findings: tumor diameters <1 cm were defined as microadenoma, ≥ 1 and <2 cm as mesoadenoma, and ≥ 2 cm as macroadenoma, consistent with earlier reports (11, 12).

Treatment protocol

All the patients were treated by transsphenoidal surgery at the authors' hospital. All operations were performed or supervised by experienced neurosurgeons. All or most of the tumors were resected, which was confirmed by postoperative MRI. Adjuvant treatments for those patients with insufficient disease control were individualized on the basis of size and localization of the residual tumor, biochemical parameters, available medical therapy, and patient's medical condition and preference (13). In order to evaluate the effect

of operation, patients treated by surgery alone were included in this clinical study, whereas those treated with medical therapy or stereotactic radiotherapy were excluded.

Immunohistochemistry

The pathological evaluation was performed at the Department of Pathology in the authors' hospital. All specimens were fixed in 10% formalin, embedded in paraffin, and stained by the hematoxylin–eosin method. All the resected tissues were examined by immunohistochemistry with antibodies against GH and PRL.

Statistical analysis

All the measured data were normal distribution and presented as mean $\pm$ s.d. The PASW Statistics 18.0 (SPSS, Inc., Chicago, IL, USA) was used to set up a database of the patients. Differences in percent discordance of clinical manifestations and complications of the two groups were compared using Fisher's exact test. Correlations between parameters were evaluated by Spearman rank correlation. A two-sided P value <0.05 was considered statistically significant.

Results

Clinical features before treatment

In GH group, 182 patients were assessed, and 50.5% were male; the mean age at diagnosis was 45.6 ± 13.9 (range, 11.4–75.2) years (Table 1). The mean time interval from the onset of acromegaly-specific symptoms and signs to the date of diagnosis was 66.0 ± 65.3 (range, 0.5–324) months. The mean maximal diameter of adenomas was 2.2 ± 0.9 (range, 0.6–4.2) cm.

In GH+PRL group, there were 97 patients, and 42.3% were male; the mean age at diagnosis, the mean time interval, and the mean maximal diameter of adenomas were 40.4 ± 11.4 (range, 20.1–72.6) years, 52.8 ± 49.4 (range, 1.0–240) months, and 2.6 ± 1.1 (range, 0.5–5.8) cm respectively.

The mean age at diagnosis and mean maximal diameter of adenomas were significantly different between the two groups ($P=0.001$ and $P=0.004$ respectively), but gender and the mean time interval had no significant differences ($P=0.209$ and $P=0.067$ respectively).

Clinical manifestations and complications

The most common presenting clinical manifestations and complications encountered in the two groups (GH group vs GH+PRL group) were coarse facial features (75.4 vs 54.3%, $P=0.013$), large hands and feet (73.8 vs 58.6%, $P<0.001$), headache (38.5 vs 41.9%, $P=0.613$), dizziness (10.0 vs 10.1%, $P=1.0$), nausea

Table 1 Characteristics of patients in GH and GH+PRL groups before surgery.

	GH	GH+PRL	P value
n	182	97	—
Males (n, %)	92 (50.5)	41 (42.3)	0.209
Mean age at diagnosis (years)	45.6±13.9	40.4±11.4	0.001
Mean time interval (months) ^a	66.0±65.3	52.8±49.4	0.067
Mean max. diameter of adenoma (cm)	2.2±0.9	2.6±1.1	0.004

^aFrom the onset of symptoms and signs to the date of diagnosis.

and vomiting (4.6 vs 3.9%, $P=1.0$), fatigue (3.8 vs 3.9%, $P=1.0$), distension and numbness (3.8 vs 1.6%, $P=0.447$), hypertension (10.0 vs 3.9%, $P=0.085$), diabetes mellitus (17.7 vs 6.9%, $P=0.013$), and those of pituitary endocrinological disturbances: polyuria and polydipsia (16.2 vs 5.4%, $P=0.008$), hyposexuality (4.6 vs 10.9%, $P=0.066$), and in female patients, menstrual disorders (13.8 vs 54.3%, $P<0.001$) and galactorrhea (3.1 vs 22.4%, $P<0.001$; Table 2). So, the data indicated that there were higher incidences of coarse facial features, polyuria and polydipsia, large hands and feet, and diabetes mellitus in GH group patients, but the incidences of menstrual disorder and galactorrhea in female patients were extremely lower than those of GH+PRL group.

Hormonal results before and after surgery

In GH group, the GH levels decreased from 42.4 ± 30.5 ng/ml before surgery to 20.4 ± 18.3 ng/ml at 3 days, 19.3 ± 18.2 ng/ml at 3 months, and 23.9 ± 20.0 ng/ml at 12 months after surgery, whereas the pre- and postoperative PRL levels remained within the normal range (Table 3).

In GH+PRL group, the GH levels decreased from 23.4 ± 15.8 ng/ml before surgery to 13.6 ± 10.9 ng/ml at 3 days, 13.2 ± 11.5 ng/ml at 3 months, and 14.8 ± 11.6 ng/ml at 12 months after surgery, and PRL from 131.3 ± 76.6 to 33.0 ± 15.9 , 31.8 ± 17.6 , and 33.4 ± 15.4 ng/ml respectively.

The current consensus criteria for cure of acromegaly were basal GH concentration <2.5 ng/ml, nadir GH (OGTT) <1 ng/ml, and normalization of IGF1 for age and sex (13). Based on the postoperative hormone levels at 12 months, we found that GH was controlled in 78.5%, IGF1 levels in 80.8%, and PRL levels in 100% in GH group. In GH+PRL group, those were 82.3, 84.3, and 76.4% respectively. The PRL normalization rate in GH+PRL group was significantly lower than that of GH group ($P<0.05$), whereas GH and IGF1, as expected, did not ($P>0.05$ and $P>0.05$ respectively). According to the criteria for hormonal cure of acromegaly, we found that the surgical control rates in GH and

GH+PRL groups were 68.4 and 59.7% respectively. So, no significant difference was observed between the two groups ($P=0.187$).

Immunohistochemistry evaluation

The rates of positive staining for GH and PRL in GH group were 91.2 and 30.7% and in GH+PRL group were 84.5 and 86.6% respectively. So, a significant difference was observed between the PRL-positive rates of the two groups ($P<0.05$), whereas GH, as expected, did not ($P=0.11$). Moreover, no significant correlations between the preoperative mean GH or PRL concentrations and the immunostaining-positive rates were observed ($r=+0.348$, $P>0.05$, and $r=+0.457$, $P>0.05$ respectively).

MRI findings

The proportion of preoperative meso- and macroadenoma of GH+PRL group was significantly higher than that of GH group (60.4 vs 45.1%, $P=0.041$). According to the MRI findings at 3 months after surgery, the rate of surgical control in GH+PRL group was distinctly lower than that of GH group (69.1 vs 80.7%, $P=0.037$).

Recurrence rate

Hormone and MRI examinations were performed on all patients 12 months after surgery. According to the results, we found that the recurrence rates of GH and GH+PRL groups were 7.1 and 11.3%, and no significant difference was observed between the two groups ($P=0.185$).

Table 2 Clinical manifestations, main complications, and the incidences before surgery.

Main manifestations and complications	Patients (%)		P value
	GH	GH+PRL	
Dizziness	10.0	10.1	1.0
Nausea and vomiting	4.6	3.9	1.0
Fatigue	3.8	3.9	1.0
Headache	38.5	41.9	0.613
Distension and numbness	3.8	1.6	0.447
Hyposexuality	4.6	10.9	0.066
Coarse facial features	75.4	54.3	0.013
Polyuria and polydipsia	16.2	5.4	0.008
Large hands and feet	73.8	58.6	<0.001
Menstrual disorder	13.8	54.3	<0.001
Galactorrhea	3.1	22.4	<0.001
Hypertension	10.0	3.9	0.085
Diabetes mellitus	17.7	6.9	0.013

Table 3 The pre- and postoperative hormone levels of GH and PRL in the two groups.

	GH		GH + PRL		P value ^a	
	GH (ng/ml)	PRL (ng/ml)	GH (ng/ml)	PRL (ng/ml)	GH	PRL
Before operation	42.4 ± 30.5	15.2 ± 12.3	23.4 ± 15.8	131.3 ± 76.6	<0.001	<0.001
3 Days after operation	20.4 ± 18.3	16.1 ± 12.7	13.6 ± 10.9	33.0 ± 15.9	0.001	<0.001
3 Months after operation	19.3 ± 18.2	16.5 ± 13.1	13.2 ± 11.5	31.8 ± 17.6	0.003	<0.001
12 Months after operation	23.9 ± 20.0	15.9 ± 12.4	14.8 ± 11.6	33.4 ± 15.4	0.001	<0.001
P value ^b	<0.01	0.81	<0.01	<0.01	–	–
P value ^c	0.526	0.921	0.584	0.778	–	–

^aComparative analysis between the two groups at the same time point.^bComparative analysis between before and after operation.^cComparative analysis between different time points after operation.

Discussion

Acromegaly is a slow progressive disease characterized by 30% increase in mortality rate due to cardiovascular disease, respiratory complications, and malignancies (14). The estimated prevalence of the disease is 40–130 cases per million inhabitants with three to four new cases per million inhabitants per year, and ~30% of those patients develop acromegaly with hyperprolactinemia. Therefore, the relatively lower incidence becomes an important factor limiting the availability of extensive clinical trial data (2, 10, 14, 15). The cause of GH hypersecretion is a pituitary adenoma in almost 98% of patients. Other rare causes include ectopic production of GH-releasing hormone (GHRH) by lung or pancreatic tumors (10, 16). Treatment for acromegaly aims at decreasing hormone levels, ameliorating patients' manifestations, and decreasing the local compressive effects of the pituitary adenoma. Surgical treatment remains the first management option for virtually all acromegalic patients, unless the patients refuse to undergo or are too ill to undergo a surgical procedure or prefer the medical option to an operation (6, 8, 17, 18, 19, 20, 21).

In agreement with Andersen *et al.* (22), we found that a large proportion were females (57.7%) in GH + PRL group, but no significant difference in sex was observed between the two groups. Additionally, we found that the mean maximal diameter of adenomas was obviously different between the two groups, but in inverse proportion to the mean time interval, which was similar to that reported in the literature (3, 23, 24).

Hypersecretion of GH and/or PRL has a variety of manifestations as it affects many organs. Coarse facial features, large hands and feet, headache, hyposexuality and, in the case of females, menstrual disorder and galactorrhea (4), are the main clinical findings of acromegalic patients with hyperprolactinemia. In addition, our findings show that the incidences of acromegalic features, i.e. coarse facial features and large hands and feet, are obviously lower in patients with combined secretion of GH and PRL than in patients with merely GH-secreting adenomas, but the incidences of menstrual disorder and galactorrhea, probably due

to the similar pathogenesis caused by prolactinoma (25, 26, 27, 28, 29), are extremely higher. Considering the young age, the short interval from the onset of symptoms to the date of diagnosis, and the few physical features of acromegaly, we may conclude that the clinical manifestations due to hyperprolactinemia, i.e. galactorrhea and amenorrhea, lead to early diagnosis so that the high GH levels do not have much time to cause the physical changes in acromegalic patients.

Hypersecretion of GH or GHRH could lead to acromegaly. These tumors are usually comprised of cells with sparsely or densely granulated cytoplasm secreting GH alone or a colony of cells secreting either GH or PRL. Less commonly, the tumors are composed of mammosomatotroph cells or the more aggressive acidophilic stem cell adenoma secreting GH and PRL. Plurihormonal adenomas secreting GH and other hormones are rare (10, 16, 30, 31, 32, 33).

Elevated preoperative GH and PRL levels are detected in acromegalic patients with hyperprolactinemia. In this study, we find that acromegalic patients with high PRL levels often have relatively low serum GH levels, which is similar to that reported in the literature (24). In addition, our study confirms that acromegalic patients with hyperprolactinemia have elevated PRL levels but the degree of hyperprolactinemia, even in patients with large tumors, is generally moderate (24). As a result, the rate of normalization of PRL levels in acromegalic patients with hyperprolactinemia is generally higher than that of patients with meso- and macroprolactinomas (34, 35).

Strict criteria for hormonal cure are now widely accepted. Based on the hormonal levels 1 year after surgery, data show that the surgical control rate in acromegalic patients with hyperprolactinemia is not significantly different from that in patients with merely GH-secreting adenomas. However, considering the differences of PRL normalization rates between the two groups, we find that the preoperative PRL levels cannot be used as a factor for predicting the prognosis of these patients. Furthermore, we find that the normalization rates of GH and IGF1 are not different between the two groups, but the PRL normalization rates are

extremely lower in acromegalic patients with hyperprolactinemia, which indicates that PRL might have no influence on the decline of GH and IGF1 in acromegalic patients with hyperprolactinemia.

A number of factors have been suggested as useful predictors of the success of surgery, including tumor size (6, 36), preoperative hormone levels (37), and monohormonal status in immunocytochemistry (6). According to the pre- and postoperative MRI results, our findings confirm that the preoperative tumor size is an important factor that affects the result of the operation. However, considering the preoperative hormone levels, discrepancies in our study can be anticipated, with some patients showing either GH dysregulation but normalized IGF1 levels or adequate GH suppression but elevated IGF1 levels (38, 39, 40, 41). As a result, although IGF1 levels correlate well with clinical activity of acromegaly (42), it has been reported that they might be insufficient in predicting the long-term benefit of surgery (13, 43). These results provide evidence that the use of a single test, such as IGF1, may be of limited value in the outcome assessment of surgically treated acromegaly (36, 44). Additionally, the monohormonal status as a prognostic factor is not confirmed in this study.

The lack of recurrence cases limits the ability to evaluate the correlation between hormonal recurrence and the MRI recurrence. However, at the early stage of some recurrent patients, we find increasing hormone levels but no evidence on MRI findings, which indicate that the increasing hormone level is a more useful factor for predicting the recurrence. Furthermore, there is a remarkable discrepancy between surgical control rates and recurrence rates. One possible explanation might be that the follow-up time is not long enough so as not to reflect their real recurrence rates.

In conclusion, the current study is the first to report the characteristics of acromegalic patients with hyperprolactinemia and the differences between acromegalic patients with and without hyperprolactinemia. In this study we find that, compared with patients with merely GH-secreting adenomas, acromegalic patients with hyperprolactinemia are characterized by an earlier onset of disease, lesser acromegalic features, lower GH levels, but larger tumor sizes, whereas in female patients, GH-PRL secreting adenomas are associated with higher incidences of menstrual disorders and galactorrhea. This research might be helpful to get a deeper understanding of the characteristics and to improve the diagnosis and treatment of acromegalic patients with hyperprolactinemia. To better assess the effect of operation and treatment outcomes on acromegalic patients with hyperprolactinemia, further studies on the long-term follow-up are needed.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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