CLINICAL STUDY

GH deficiency in patients after cure of acromegaly by surgery alone

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Abstract

Objective: The aim of this study was to determine the frequency and characteristics of severe GH deficiency (sGHD) in patients after treatment of acromegaly by surgery alone.

Design and methods: One hundred and eighty-six patients fulfilling the criteria for cure of acromegaly were examined by GH-releasing peptide-2 stimulation test or arginine stimulation test as well as oral glucose tolerance test (GTT). In addition, the Japanese adult hypopituitarism questionnaire was completed to determine the quality of life (QoL).

Results: sGHD was found in 17 patients (9.1%; the GH-deficient group), and not found in 169 patients (90.9%; the GH-sufficient group). There were no significant differences in preoperative serum GH levels, IGF1 levels, incidence of hyperprolactinemia, tumor volumes, or incidence of microadenoma between the two groups. Upon follow-up examination, IGF1 levels and Z-scores of IGF1 levels were significantly lower in the GH-deficient group than in the GH-sufficient group, whereas neither basal GH levels nor nadir GH levels during 75 g GTT were significantly different between the two groups. Moreover, sGHD patients had a substantially higher incidence of multiple pituitary failures (17.6 vs 2.4%) and dyslipidemia (60 vs 16.2%). sGHD patients had a substantially poorer condition-related QoL.

Conclusions: This is the first large-scale, single-center, clinical study to evaluate sGHD in patients after cure of acromegaly by surgery alone. This study found that sGHD occurred in ~9% of patients and assessment of GHD by stimulation tests is critical after successful treatment of acromegaly by surgery.

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Introduction

The goals of GH-secreting pituitary adenoma treatment include normalization of excessive GH and IGF1 secretion and alleviation of pituitary mass effects while preserving other pituitary functions. Transsphenoidal surgery (TSS) for removal of tumors remains the first-line therapy for most patients (1). As the criteria for cure of acromegaly become more stringent (2), pituitary surgeons have struggled to meet them. The result is that less attention is given to possible postoperative GH deficiency (GHD). Indeed, there have been few reports on GHD after radiotherapy for acromegaly (3–6) and there have only been few and contradictory studies conducted on small numbers of patients of GHD after TSS alone (7–10). Therefore, a large number of patients undergoing surgery who were later deemed cured by the recent stringent criteria for cure of acromegaly were studied to determine the characteristics of GH-deficient patients with prior acromegaly.

Materials and methods

Patients

A total of 631 acromegalic patients underwent surgery performed by the same surgeon (S Y) at Toranomon Hospital in Tokyo between 1988 and 2008. Of the 631 patients, long-term follow-up was possible for 532 patients of the 554 patients in whom primary surgery was performed as the first choice of treatment for acromegaly. Acromegalic patients were followed up after surgery once every year or 2 years by 75 g oral glucose tolerance test (GTT) and measurement of serum IGF1 levels. The outcome for 437 patients (82.1%) was judged complete remission by surgery alone at the time of final follow-up because the Cortina consensus criteria were fulfilled (11). Among these 437 patients, 211 patients visited between 2009 and 2010 to take follow-up examinations and constitute the patient pool of this study.

Pre- and postoperative evaluation of anterior pituitary hormones other than GH

The other basal anterior pituitary hormones (prolactin (PRL), TSH, LH, FSH, and ACTH) and their target hormones (free tri-iodothyronine, free thyroxine, testosterone, free testosterone, estradiol, and cortisol) were measured pre- and post-operatively to evaluate hypopituitarism. Moreover, pituitary stimulation tests were done pre- and post-operatively (usually 2 weeks after surgery) with a combination of corticotrophin-releasing hormone (100 µg), TSH-releasing hormone (500 µg), and LH-releasing hormone (100 µg). GH, PRL, TSH, LH, FSH, and ACTH levels were measured at 0, 15, 30, 60, 90, and 120 min after stimulation tests. In this study, there were no patients showing pituitary apoplexy after stimulation tests.

Follow-up examinations

To confirm cure of acromegaly, serum IGF1 levels were measured and a GTT was performed for each patient after overnight fasting. GH and glucose levels were measured at baseline and every 30 min for 2 h after introduction of glucose. After confirming cure of acromegaly based on those data, the GH-releasing peptide-2 (GHRP2) stimulation test was performed by i.v. administration of 100 µg dose of GHRP2 after overnight fasting to screen for GHD. GH levels were assayed 0, 15, 30, 45, and 60 min after administration of GHRP2 (12). Moreover, severe GHD (sGHD) was further confirmed by the arginine stimulation test (0.5 g/kg to a maximum of 30 g i.v. administration, and GH levels were measured at baseline and every 30 min for 2 h) when other anterior pituitary hormone levels were judged normal in patients diagnosed with sGHD by the GHRP2 test. The patients were assessed as sGHD when peak GH levels were ≤ 9 ng/ml for the GHRP2 test and ≤ 1.8 ng/ml for the arginine test (12, 13). Glucose metabolism was categorized as normal, impaired glucose tolerance (IGT), and diabetes mellitus (DM) based on GTT. Lipid profiles were evaluated by measuring serum total cholesterol, high-, low-density lipoproteins, and triglyceride levels.

Assays

Assay of GH was performed by the ST AIR-PACK hGH immunoassay (TOSOH Corporation, Tokyo, Japan) since May 1, 2005. The minimum detectable concentration was 0.07 ng/ml. The inter-assay coefficients of variation (CV) were 3.1% at 0.39 ng/ml, 3.4% at 4.68 ng/ml, and 4.8% at 17.68 ng/ml, while the intra-assay CV were 2.9% at 0.38 ng/ml, 2.3% at 4.83 ng/ml, and 1.4% at 17.98 ng/ml. WHO 2nd International Standard 98/574 was used as the GH standard in this assay. GH levels obtained by different methods before May 2005

were all converted by several conversion equations to the values similar to those after May 2005. Serum IGF1 levels were determined by the commercially available 'Daiichi' IGF1 IRMSA IRMA (FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan). The standards of the kit were derived from recombinant human IGF1, which was originally calibrated by International Reference Preparation 87/518. The inter-assay CV were 3.9% at 48 ng/ml, 3.0% at 148 ng/ml, and 4.1% at 634 ng/ml, while the intra-assay CV were 2.4% at 52.2 ng/ml, 3.5% at 161 ng/ml, and 2.2% at 612 ng/ml. The IGF1 range was chosen to encompass the published physiological range across genders and various age groups (14).

Tumor size

The volume of the tumor before surgery was calculated by the formula $0.5 \times \text{width} \times \text{length} \times \text{height}$ using 1.5 tesla preoperative magnetic resonance imaging (MRI) (15). Moreover, tumors were divided into microadenoma (maximum diameter ≤ 10 mm) and macroadenoma based on their preoperative MRI or operative findings.

Questionnaire for quality of life assessment

A quality of life (QoL) questionnaire was completed by 90 patients according to the protocol evaluated and approved by the ethics committee at Toranomon Hospital, Tokyo. The Japanese adult hypopituitarism questionnaire (JAHQ), which has been uniquely developed in Japan, is a disease-sensitive, self-administered questionnaire to evaluate QoL for Japanese adults with hypopituitarism. The questionnaire was constructed with two domains, psychosocial and condition-related, which consisted of five and seven subdomains respectively. Within the psychosocial domain, a 34-item questionnaire spanned five subdomains, which were: i) depression, ii) limitation of social activities, iii) vigor, iv) sleep, and v) anxiety about the treatment. Within the condition-related domain, a 40-item questionnaire spanned seven subdomains, which were: i) control of body temperature, ii) physical strength, iii) hypothalamic impairment, iv) urination, v) condition of skin and hair, vi) body weight, and vii) sexual interest. JAHQ has been validated and widely used in clinical studies in Japan (16). Responses to each question are multiple choice, with seven scaled options per question. Higher scores indicate a poorer QoL.

Statistical analysis

All continuous data were expressed as mean $\pm$ s.d. All variables not normally distributed were compared by the Wilcoxon test. Z-scores were calculated using reference data from age- and sex-matched healthy Japanese individuals. The Fisher's exact test or χ^2 test was used to assess differences between categorical

Table 1 Clinical characteristics in GH-sufficient and GH-deficient patients after successful surgery for acromegaly.

	GH-sufficient group	GH-deficient group	P value
Number of cases	169	17	
Preoperative characteristics			
BMI	24.0 ± 3.5	25.1 ± 4.1	0.3023 (NS)
Preoperative GH levels	17.1 ± 20.6	41.6 ± 62.7	0.1291 (NS)
Preoperative IGF1 levels	702.8 ± 293.8	753.7 ± 367.9	0.6829 (NS)
Z-scores of IGF1 level	7.58 ± 2.68	7.93 ± 3.43	0.5296 (NS)
Hyperprolactinemia (no/yes)	139/30	13/4	0.5201 (NS)
Tumor volumes	777.1 ± 967.4 (126)	1622.7 ± 1687.1 (10)	0.2973 (NS)
Microadenoma/macroadenoma	34/135	2/15	0.5333 (NS)
Follows-up results			
Times since surgery (months)	56.3 ± 40.9	42.2 ± 38.3	0.1528 (NS)
Age (years)	52.5 ± 12.4	54.0 ± 10.7	0.6296 (NS)
Sex (female/male)	92/77	13/4	0.1221 (NS)
BMI	23.8 ± 3.6	25.8 ± 4.5	0.0817 (NS)
GH levels	0.99 ± 1.70	0.491 ± 0.426	0.3336 (NS)
IGF1 levels	156.4 ± 51.0	103.8 ± 37.8	<0.0001
Z-scores of IGF1 level	0.278 ± 1.047	-1.180 ± 1.883	0.0003
Nadir GH levels on 75 g GTT	0.154 ± 0.096	0.134 ± 0.084	0.3327 (NS)
Pituitary deficiency (no/yes)	164/4 (168)	14/3	0.0184
Glucose metabolism (N/IGT/DM)	95/68/6	5/12/0	0.0504 (NS)
Dyslipidemia (no/yes)	88/17 (105)	6/9 (15)	0.0006

BMI, body mass index; N, normal glucose tolerance; IGT, impaired glucose tolerance; DM, diabetes mellitus; figures in parantheses indicate, number of patients examined; NS, not significant.

variables. A two-tailed *P* value <0.05 was considered statistically significant. In this study, the score obtained in each domain of the JAHQ was converted such that higher scores indicated a better QoL to facilitate statistical analysis.

Results

GHD in acromegalic patients cured by surgery alone

Between 2009 and 2010, 211 patients whose conditions had been judged complete remission by surgery alone visited to take follow-up examinations. However, new criteria for cure of acromegaly had been published during this period (2), so these 211 patients were reassessed based on these new criteria. One hundred and eighty-six patients (88.2%) met the new criteria for cure of acromegaly and the remaining 25 patients were excluded, although they fulfilled the Cortina consensus criteria. Of the 186 patients, sGHD was found in 17 patients (9.1%; GH-deficient group), whereas peak GH levels from the GHRP2 test were >9 ng/ml in the remaining 169 patients (90.9%; GH-sufficient group). Of the 17 GH-deficient patients, 15 patients underwent the arginine test to further confirm sGHD. There were no patients who did not meet the criterion of sGHD on the arginine test (GH ≤1.8 ng/ml) among those 15 patients. The arginine test was not performed in the remaining two patients because deficiency of pituitary hormones other than GH already coexisted in these two patients.

Clinical characteristics of the GH-sufficient and GH-deficient groups

Serum GH levels, IGF1 levels, Z-scores of IGF1 levels, incidence of hyperprolactinemia or microadenoma, and tumor volumes were preoperatively evaluated and there were no significant differences in these parameters between the two groups, although mean values of preoperative GH levels and tumor volumes in GH-deficient patients were approximately two times those in GH-sufficient patients (Table 1). At the time of

Figure 1 Correlation between Z-scores of IGF1 level and peak GH levels during GHRP2 stimulation test. White symbols, GH-sufficient patients; black symbols, GH-deficient patients. Black circles indicate patients examined by not only GHRP2 stimulation test but also arginine stimulation test.

Figure 2 Mean QoL scores were significantly higher in the condition-related domain but not the psychosocial domain for GH-sufficient patients than GH-deficient patients with prior acromegaly. White bar, GH-sufficient; gray bar, GH-deficient. Higher scores indicate better QoL.

follow-up, IGF1 levels and Z-scores of IGF1 levels were significantly lower in the GH-deficient group than in the GH-sufficient group, although Z-scores of IGF1 did not significantly correlate with peak GH values from the GHRP2 test (Fig. 1). In contrast, neither basal serum GH levels nor nadir GH levels from the GTT were significantly different between the two groups. As expected, a significantly higher percentage of GH-deficient patients had multiple pituitary failures (17.6 vs 2.4%; $P < 0.02$) and dyslipidemia (60.0 vs 16.2%; $P < 0.01$). There were three patients with isolated hypogonadism and one patient with hypogonadism plus hypothyroidism in 168 GH-sufficient patients examined, whereas there were three patients with hypogonadism in 17 GH-deficient patients. These hypopituitarisms have been treated properly by hormone replacement in all patients except one woman with GHD who has refused replacement therapy for hypogonadism. Abnormality of glucose metabolism tended to be more common in the GH-deficient group (70.6 vs 43.8%; $P = 0.05$). However, all 12 patients in the GH-deficient group in whom glucose metabolism

was abnormal were diagnosed with IGT on GTT, whereas of the 169 GH-sufficient patients, 68 were diagnosed with IGT and six were diagnosed with type II DM (Table 1).

QoL in GH-sufficient and GH-deficient patients

JAHQ was completed by 73 patients in the GH-sufficient group and all 17 patients in the GH-deficient group. As measured by all subdomains, the GH-deficient patients had a significantly poorer condition-related QoL ($P < 0.01$), whereas there was no significance but a trend toward poorer psychosocial-related QoL in GH-deficient patients compared with GH-sufficient patients ($P = 0.08$; Fig. 2). As for each subdomain score of the condition-related domain, significantly poorer QoL was seen for the GH-deficient group in the subdomains of physical strength ($P = 0.0049$), condition of skin and hair ($P = 0.0064$), and body weight ($P = 0.0013$), although the trend toward poorer QoL was not significant for control of body temperature ($P = 0.0685$) and urination ($P = 0.0826$; Fig. 3). In addition, there were no significant differences in the subdomains of hypothalamic impairment ($P = 0.1544$) and sexual interest ($P = 0.6407$). In contrast, regarding the subdomains of the psychosocial domain, there were significantly poorer QoL for GH-deficient patients in the subdomains of vigor ($P = 0.0278$) and sleep ($P = 0.0335$) and there was a trend (not significant) toward poorer QoL in the subdomain of anxiety about the treatment ($P = 0.0933$; Fig. 3). There were no significant differences between the two groups in the subdomains of depression ($P = 0.3892$) and limitation of social activities ($P = 0.1811$).

Discussion

To our knowledge, there have been no reports showing the frequency of sGHD after surgery in a study of large numbers of patients. Ronchi *et al.* (9) first revealed the rate of sGHD after surgery as 54.5% in a relatively large number of patients (33 patients) by GHRH plus arginine tests. Those 33 patients were judged as cured based on the Cortina consensus criteria. In contrast, our study is the first report demonstrating the frequency of sGHD evaluated by GHRP2 or GHRP2 plus arginine tests in a large number of cured patients fulfilling more stringent new criteria for cure of acromegaly. Compared with the report by Ronchi *et al.* (9), sGHD was less common in our patients and was found only in 17 (9.1%) of the 186 patients. This lower percentage of sGHD in our patients may be due to different methods to evaluate sGHD. However, the GHRP2 test has already been validated and has been widely used in Japan as a simple diagnostic test to evaluate severe adult GHD (12, 13). In this study, GHD was further confirmed by an arginine test when the patients were diagnosed with sGHD by the

Figure 3 Mean JAHQ questionnaire scores in the five psychosocial subdomains and the seven condition-related subdomains. White bar, GH-sufficient; gray bar, GH-deficient. Higher scores indicate better QoL.

GHRP2 test and did not show any other anterior pituitary hormone deficiency. All patients judged as sGHD by GHRP2 test also met the criterion of sGHD by arginine test. Our lower occurrence of hypopituitarism other than GHD (7/185, 3.8%) after successful surgery may also reflect this lower GHD occurrence rate, suggesting that less invasive selective adenomectomies were performed in those patients.

Regarding possible prognostic factors, Ronchi *et al.* (9) suggested that the presence of a macroadenoma and higher GH levels at the time of diagnosis together with the concomitant existence of other pituitary failures seemed to be the best candidates to predict GHD in patients successfully treated for acromegaly. Ronchi *et al.* (9) also speculated that a more aggressive surgical approach, which is often necessary to cure larger GH-secreting adenomas, might increase the risk of further pituitary failures. In contrast, neither preoperative serum GH levels, frequencies of microadenoma, nor tumor volumes were significantly different between GH-sufficient and GH-deficient patients in our study, although both mean values of GH levels and tumor volumes in GH-deficient patients were about twice as high as those of GH-sufficient patients.

IGF1 has not been widely used as a reliable marker for the diagnosis of GHD (17). Indeed, Z-scores of IGF1 at the time of follow-up did not significantly correlate with peak GH values from the GHRP2 test, but IGF1 levels and Z-scores themselves were significantly lower in GH-deficient patients than in GH-sufficient patients,

similar to a report by Wexler *et al.* (10) which suggests that IGF1 may be of some diagnostic value for sGHD if levels are below the age- and sex-adjusted normal range. In contrast, neither basal serum GH levels nor nadir GH levels from the GTT were significantly different between the two groups, indicating no clinical usefulness of either factor to predict sGHD after surgery. Consistent with previous studies (13, 18, 19), significantly higher incidences of multiple pituitary failures (17.6 vs 3.0%; $P < 0.03$) and dyslipidemia (60 vs 16.2%; $P < 0.01$) were also found in GH-deficient patients in this study. Moreover, dyslipidemia in the GH-deficient group may be mainly due to a metabolic disorder associated with GHD, because BMI was not significantly different between the groups.

These are the first data to demonstrate a reduced QoL in patients who develop sGHD compared with GH-sufficient patients after successful surgery in large numbers of the patients. Our results have strengthened the findings of other reports (10, 20) and further confirmed that patients with GHD after cure of acromegaly experience poorer QoL. Furthermore, we found that this diminished QoL is not due primarily to the residual effects of the acromegaly itself, as suggested by Wexler *et al.* (10). The JAHQ, which has been uniquely developed in Japan, is a disease-sensitive, self-administered questionnaire for the evaluation of QoL in Japanese adults with hypopituitarism whose culture and lifestyle differ from those of Europeans and North Americans. However, contrary to previous reports

(10, 21), there were no significant correlations between QoL levels and magnitude of GH levels or nadir GH values from the GTT in this study.

Little is known about the effects of GH replacement therapy in those who develop GHD after cure of acromegaly and reported data have been contradictory (5, 20, 22, 23). van der Klaauw *et al.* (23) recently concluded that the beneficial effects of GH replacement in patients with GHD during treatment of acromegaly are limited. In contrast, Miller *et al.* (24) demonstrated that GH replacement decreased visceral adipose tissue, increased fat-free mass, decreased high-sensitivity C-reactive protein (CRP), and improved QoL in patients with GHD after cure of acromegaly. Therefore, further studies of large numbers of sGHD patients with prior acromegaly are needed to draw definitive conclusions about clinical usefulness of GH therapy in those patients.

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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