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ORIGINAL

Postoperative growth hormone dynamics in clinically nonfunctioning pituitary adenoma

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Abstract. Growth hormone deficiency (GHD) is an endocrine disorder characterized by insufficient production of growth hormone (GH). Non-functioning pituitary adenoma (NFPA) is one of common causes of GHD. Although most patients with NFPA have transsphenoidal surgery, the time-dependent changes in GH after operation have yet to be investigated. In this study, we analyzed patients with NFPAs that underwent transsphenoidal surgery. Postoperatively, GH secretion was evaluated in response to GH-releasing peptide-2 (GHRP2) infusion. We also investigated how several factors affected GH dynamics. Of 119 patients analyzed, 94 (79.0%) had peak GH levels less than 9.0 ng/mL and were diagnosed with severe GHD (sGHD) immediately after surgery. Of those patients, 27 (28.7%) recovered from sGHD within 1–2 years after surgery. Univariate analyses confirmed that sGHD recovery improved significantly in patients that were younger, had only undergone a single primary surgery, had not had anterior hormone deficiency except GH, and had cystic adenoma or normal insulin-like growth factor-1 (IGF1) standard deviation score (SD-S) levels immediately after surgery. Multivariate analyses confirmed that younger age and absence of hormone replacement therapy significantly predicted sGHD recovery within 1–2 years after surgery. Taken together, our results indicated that postoperative sGHD should be assessed by GHRP2 infusion, regardless of IGF1 SD-S levels. Furthermore, recovery from sGHD occurs more frequently at 1–2 years after surgery especially in younger patients and/or those with GH deficiency alone. These patients, therefore, should be reassessed for GHD by appropriate tests including GHRP2 test at 1–2 years after surgery.

Key words: Non-functioning pituitary adenoma, Transsphenoidal surgery, Growth hormone deficiency, GH-releasing peptide-2

GROWTH HORMONE DEFICIENCIES (GHDs) are characterized by insufficient production of growth hormone (GH) and are most frequently observed in patients with adult hypopituitarism [1, 2]. The most prominent cause of adult-onset GHD is pituitary adenoma, followed by craniopharyngioma. Taken together, they account for 65% of GHD cases, as indicated by data derived from KIMS (Pharmacia & Upjohn International Metabolic Database) [1]. Non-functioning pituitary adenomas (NFPAs) are the most common (31%) type of adenoma that cause GHD in adult patients [1]. Fortunately, diagnosing GHD in adults is usually straightforward, and consensus guidelines are generally accepted [2]. However, the appropriate GH treatment onset for NFPAs is still under debate, especially after surgery. This is in part because NFPA-induced GHDs are variable and may be transient after tumor debulking. In the current study, we evaluated patients with clinical NFPAs after transsphenoidal surgery (TSS) to better characterize time-dependent changes in GH responses. These changes were measured in response to GH-releasing peptide-2 (GHRP2) infusion to diagnose GHD and analyze long-term patient recovery.

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Subjects and Methods

Patients

All investigations were performed and approved by the ethics committee at Toranomon Hospital (Serial No. 1553). Between 2007 and 2011, 608 consecutive NFPAs were surgically removed at Toranomon Hospital (Tokyo, Japan). Of this population, 119 patients were selected for further analysis.

In these 119 patients, GH secretion was evaluated in response to GHRP2 infusion (Kaken Pharmaceutical Co. Ltd., Tokyo, Japan), which was performed at 2 weeks and 1–2 years after surgery. Briefly, GHRP2 (2 μg/kg) was injected (maximum dose of 100 μg) intravenously, and blood samples were obtained at 0, 15, 30, 45 and 60 min after administration. For outpatients, GH secretion was assessed with fasting after 30 min of bed rest. Patients with peak GH levels less than 9.0 ng/mL after GHRP2 infusion were diagnosed with severe GHD (sGHD). No provocation tests, including GHRP2, were performed to assess pituitary functions before surgery. We were concerned about the incidence of pituitary apoplexy since every tumor assessed in this study was a macroadenoma. We also assessed several factors for their effects on GH dynamics, including age, gender, tumor size, history of clinical or pathologically confirmed pituitary apoplexy, repeat surgery, deficiency in another anterior pituitary hormone, presence of a solid or cystic adenoma, and normal insulin-like growth factor-1 (IGF1) standard deviation score (SD-S) levels at 1–2 weeks after surgery.

Assays

GH levels were assessed using the ST AIA-PACK hGH immunoenzymatic assay (Tosho Corp., Tokyo, Japan), with a minimum detectable GH concentration of 0.07 ng/mL. Serum IGF1 levels were determined using the commercially available "Daiichi" IGF1 IRMA kit (FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan), with recombinant human IGF1 used as standards.

Statistical analysis

All data are expressed as mean ± S.D. IGF1 SD-S levels were calculated using age- and gender-adjusted normalized IGF1 ranges [3]. Differences between categorical variables were assessed using the Student's *t* test, chi-square test, and logistic regression analyses. A two-tailed *p* value less than 0.05 was considered statistically significant.

Results

Patient demographic and clinical data

Demographic and medical information for the 119 patients included were as follows: age = 53.6 ± 11.7 years old, range 23 to 78 years; gender ratio = 60 males/59 females; tumor size = 28.1 ± 6.7 mm, range 13 to 51 mm; and body mass index (BMI) = 23.5 ± 3.6, range 13.6 to 40.8. Preoperatively, one patient received hydrocortisone replacement, and two received both hydrocortisone and levothyroxine. Eighty-one patients underwent complete tumor resection, 18 underwent prior surgery, and 13 received postoperative radiation therapy.

Replacement of other anterior pituitary hormones after surgery

Postoperatively, eight patients received hydrocortisone replacement, 17 received levothyroxine, and 17 received both. We administered these hormone replacements based on both basal values and the results of triple stimulation (corticotropin-releasing hormone, thyrotropin-releasing hormone, and luteinizing hormone-releasing hormone) tests performed approximately 10 days after surgery.

Postoperative GH response to GHRP2 infusion

We evaluated GH levels after GHRP2 infusion in 119 patients at 1–2 weeks and 1–2 years after TSS. At 1–2 weeks after surgery, 94 patients (79.0%) were diagnosed with sGHD, while the remaining 25 patients had peak GH levels higher than 9.0 ng/mL (Fig. 1). One to two years after TSS, 67 patients of these patients (71.3%) still showed evidence of sGHD (GHD continued group), whereas 27 patients of them (28.7%) had recovered from sGHD, as indicated by peak values greater than 9.0 ng/mL after GHRP2 infusion (GHD recovery group; Fig. 1). Thus, most of the patients initially diagnosed with sGHD maintained this diagnosis at 1–2 years after TSS.

Relationship between IGF1 SD-S and GHD severity

Of the 94 patients initially diagnosed with sGHD, IGF1 SD-S levels were subnormal, normal, supranormal in 28, 65, and one patient, respectively. Specifically, the majority of patients (70.2%) diagnosed as sGHD had normal or supranormal IGF1 SD-S. Similarly, of the 67 patients assessed as sGHD at 1–2 years after surgery, IGF1 SD-S levels were subnormal, normal, supranormal in 32, 35, and 0 patients, respectively. Thus, by 1–2 years after TSS, 35 patients (52.2%) diagnosed with sGHD had

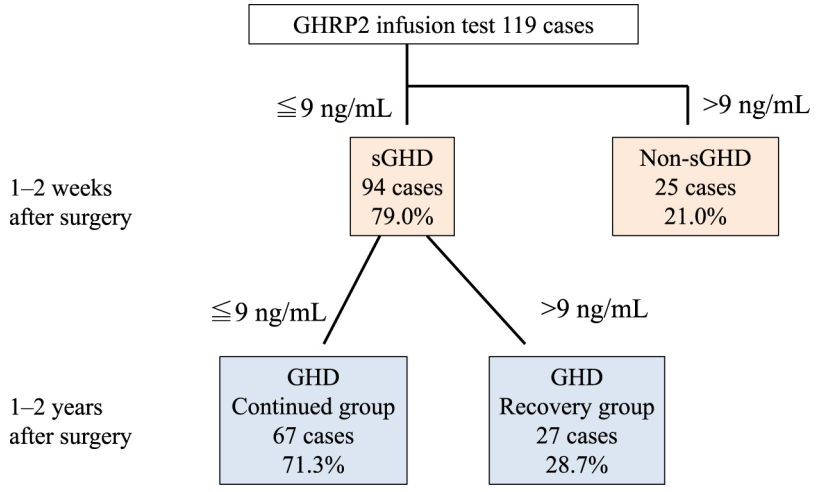

Fig. 1 Flowchart indicating time-dependent changes in growth hormone (GH) secretion for our patient population. GHRP2, growth hormone-releasing peptide-2; sGHD, severe growth hormone deficiency.

normal IGF1 SD-S levels. These data indicate that IGF1 SD-S levels do not fully reflect the severity of GHD.

Factors affecting GHD recovery

We then investigated which clinical factors affected GHD recovery, as indicated by GH levels following GHRP2 infusion. Univariate analyses revealed that younger age ($p < 0.05$), a single, primary surgery ($p < 0.05$), absence of hormone replacement therapy ($p < 0.001$), and presence of a cystic adenoma ($p < 0.05$) or normal IGF1 SD-S levels 1–2 weeks after surgery ($p < 0.001$; Table 1) were all significantly associated with GHD recovery.

Multivariate analyses confirmed that an absence of hormone replacement therapy (odds ratio [*OR*] 4.21) and younger age (*OR* 3.55) were the most important independent factors that predicted recovery from sGHD at 1–2 years after TSS (Table 2).

Discussion

Clinically NFPAs are a common cause of GHDs. However, little is known regarding the long-term dynamics of GH after TSS in clinically NFPAs. Although the insulin tolerance test (ITT) is the gold standard for the diagnosis of adult GHD, this test often has side effects. In this study, we used GHRP2 infusion to evaluate GHD. Importantly, GHRP2 is a validated test for GHD that is widely used in Japan [4]. This test is simple to implement, has few side effects, shows favorable reproducibility, and is not influenced by gender. Decreased responses with age or adiposity also do not affect this test's ability to discriminate between healthy control subjects and GHD patients, and its diagnostic capacity for sGHD is very high, irrespective of the underlying hypothalamic or pituitary cause.

Importantly, IGF1 SD-S levels did not predict GHD in our study. This is consistent with the results from previous reports [5, 6]. Indeed, there were a considerable number of patients with disparate IGF1 SD-S and GHRP2 infusion results (70.2% at 1–2 weeks after TSS, 52.2% at 1–2 years after TSS). However, IGF1 SD-S levels lower than –2 SD were frequently found in patients with sGHD. Together, these data indicate that IGF1 SD-S alone does not accurately indicate sGHD.

Using this GHRP2 infusion test, we evaluated patients with clinically NFPAs that underwent TSS for time-dependent changes in GHD severity. Univariate analyses demonstrated that the following factors significantly predicted favorable improvements in GHD (recovery from sGHD within 1–2 years after surgery): younger age, a single primary surgery, absence of hormone replacement therapy, and presence of cystic adenoma or normal IGF1 SD-S levels. Moreover, multivariate analysis confirmed that younger age and absence of hormone replacement were the two most important independent predictors of long-term improvements in GHD.

Younger age may predict recovery from sGHD, as younger patients have greater pituitary gland plasticity. Jahangiri *et al.* [7] reported that younger age was associated with potential endocrine normalization after surgery in their 305 NFPAs undergoing TSS.

Table 1 Patients profiles and factors influencing recovery from sGHD: Results of univariate analyses

1–2 weeks after surgery	Non-sGHD	sGHD		
1–2years after surgery		GHD recovery group	GHD continued group	GHD recovery group *vs.* GHD continued group
Factor	(n = 25)	(n = 27)	(n = 67)	p value
BMI				0.7657
mean	23.4	22.5	24.0	
SD	3.1	3.1	4.0	
Age				< 0.05
≥ 60 yrs	6	6	30	
< 60 yrs	19	21	37	
Gender				0.1606
female	14	16	29	
male	11	11	38	
Tumor size				0.3448
≥ 30 mm	2	13	24	
< 30 mm	21	14	40	
History of pituitary apoplexy (including clinically and pathologically)				0.8077
present	1	2	6	
absent	24	25	61	
Numbers of surgery				< 0.05
primary surgery	23	26	53	
repeat surgery	2	1	14	
Other anterior hormone deficiency				< 0.001
present	3	4	38	
absent	22	23	29	
Solid/Cyst				< 0.05
solid	22	20	61	
cyst	3	7	6	
IGF1 SD-S levels immediately after surgery				< 0.001
mean	–0.07	–0.3	–1.66	
SD	0.96	1.06	1.98	

Table 2 Factors influencing recovery from sGHD: Results of multivariate analyses

Factor	Category	*OR* (95% CI)	p Value
Hormone replacement therapy	present/absent	4.21 (1.06–16.7)	0.0415
Age	≥ 60 yrs/< 60 yrs	3.55 (1.08–11.7)	0.0365

Regarding the effects of the number of prior surgeries, the complication rate of repeat TSS is higher than that after primary surgery, even when performed by an experienced neurosurgeon [8-10]. Precise exposure of a sellar floor, tumor, and selective tumor resection are all more difficult to perform during a repeat surgery than during a primary one due to tissue scarring and distortion of the intrasellar anatomy from the previous surgery [10]. Additionally, selective adenomectomy that does not affect the residual normal pituitary gland is more difficult during a repeat surgery than during a primary one. Thus, repeat surgeries result in more frequent postoperative anterior pituitary hormone deficiencies [9, 10]. Alternatively, removal of a cystic adenoma is easier to perform than that of a solid tumor, as cystic adenomas have fluid components and do not adversely affect the surrounding normal pituitary gland.

Previous reports show that the incidence of sGHD in patients with various levels of other anterior pituitary hormones is higher than that in patients who have not undergone hormone replacement therapy [11, 12]. Postoperatively, Sauer *et al.* [13] suggested that early GH replacement significantly improves patient quality-of-life and body composition after pituitary surgery. Pituitary function, especially production of luteinizing hormone and follicle stimulating hormone, is also more likely to recover with early GH replacement.

It will be, therefore, reasonable to start GH replacement therapy at an early stage in patients who are diagnosed as severe GHD at 1–2 weeks after TSS in nonfunctioning macroadenomas but it is recommended that GH should be reassessed again at 1–2 years after surgery in patients who are younger than 60 years old and/or do not receive other anterior hormone replacement therapy, because there is higher possibility that GH secretion will be recovered in such patients at 1–2 years after surgery.

Conclusion

We conclude that postoperative sGHD should be assessed using appropriate provocation tests such as GHRP2 infusion, regardless of IGF1 SD-S levels. For patients diagnosed with sGHD, GH replacement therapy should be initiated early (within 3–6 months of surgery), particularly in those with other anterior hormone disturbances. However, our data also revealed that approximately 30% of patients diagnosed with sGHD immediately after surgery recovered within 1–2 years. This improvement occurs more frequently in younger patients and those who did not have anterior hormone deficiency except GH. Thus, these patients should be reassessed for GHD by GHRP2 infusion test at 1–2 years after surgery.

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Disclosure

None of the authors have any potential conflicts of interest to disclose.

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