Preoperative growth hormone (GH) peak values during a GH releasing peptide-2 test reflect the severity of hypopituitarism and the postoperative recovery of GH secretion in patients with non-functioning pituitary adenomas

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Abstract. Non-functioning pituitary adenoma (NFPA) is one common cause of adult growth hormone deficiency (AGHD). In Japan, a GH-releasing peptide (GHRP)-2 test is used to evaluate GH secretion. Although the cut-off for peak GH during a GHRP-2 test for severe AGHD is ≤9 ng/mL, severe AGHD may further diminish responses (range, nearly no-response to ≤9 ng/mL). We studied whether the peak GH responses during a GHRP-2 test could be predicted based on clinical characteristics of patients with NFPA. We compared patients with almost no-response during a GHRP-2 test with other patients considered as severe AGHD. Among the 76 patients with NFPA who were admitted to our institution, 36 patients (mean age, 61 years; male/female, n = 23/m = 13) were diagnosed with severe AGHD based on a preoperative GHRP-2 test. Based on the preoperative median peak GH concentration (2.83 ng/mL), patients were divided into two groups (<median = low or group L, n = 18; ≥median = moderate or group M, n = 18). Clinical manifestations, body mass index, severity of hypopituitarism and tumor size, volume, and extension were analyzed retrospectively. Compared with group M, group L patients were significantly older and more gonadotropin and ACTH deficient. A lower peak GH release during a GHRP-2 test was associated with a higher number of anterior pituitary hormone deficiencies across all 76 patients. Postoperatively, seven in group M and no patient in group L were assessed as having no longer severe AGHD, respectively. Preoperative peak GH concentrations assessed during a GHRP-2 test reflected the severity of hypopituitarism and the recovery of postoperative GH secretion.

Key words: GH releasing peptide (GHRP)-2 test, Non-functioning pituitary adenomas (NFPA), Adult growth hormone deficiency, Hypopituitarism
patients with non-functioning pituitary adenomas (NFPA). The diagnosis of AGHD is comparatively well-established; it requires comprehensive evaluations for the presence of pituitary and/or hypothalamic disease and GH stimulation tests. Basal IGF-I concentrations are also of diagnostic utility. In Japan, besides insulin-induced hypoglycemia and arginine and glucagon tests, a growth hormone-releasing peptide (GHRP)-2 test is often performed to evaluate GH secretion. GHRP-2 is administered intravenously at a dose of 100 μg. The threshold for severe AGHD is a peak GH concentration of ≤9 ng/mL during a GHRP-2 stimulation test, and a peak GH release of ≤1.8 ng/mL in other stimulation tests [5]. In clinical practice, peak GH values during a GHRP-2 test in patients with severe AGHD may range from nearly no response to ≤9 ng/mL. However, it is not clear whether variations within this range are reflected in any of the clinical characteristics of patients with severe AGHD.

In this study, we examined whether a peak GH secretory response during a GHRP-2 test was affected by any of the clinical characteristics of patients with NFPA complicated by severe AGHD. We compared patients with extremely low GH response and other patients by divided into two groups based on the median of peak GH during a GHRP-2 test.

Patients and Methods

Patients
A retrospective chart analysis was performed on 76 treatment-naive patients (male/female, n = 42/n = 34; mean age ± standard deviation [SD], 60 ± 13 years; age range, 20–82 years) with NFPA that were confirmed by clinical and pathological findings. The patients underwent transsphenoidal surgery at Nippon Medical School Hospital between October, 2012 and November, 2017. Among them 36 patients whose preoperative peak GH values during a GHRP-2 test was ≤9 ng/mL (male/female, n = 23/n = 13; mean age ± SD, 61 ± 14 years; age range, 20–81 years) were regarded as having severe AGHD.

Study design
The relationship between peak GH concentrations during a GHRP-2 test and the severity of hypopituitarism was analyzed for 76 patients. Thereafter, the 36 patients identified with severe AGHD were divided into two groups (n = 18 each) based on the preoperative median peak of GH release during a GHRP-2 test (<median = low or group L; ≥median = moderate or group M; Fig. 1). In this study, the median peak GH concentration was 2.83 ng/mL.

Factors related to differences in peak GH concentrations were examined using medical charts to retrospectively analyze the initial symptoms, blood biochemical findings, comorbidities (including hypertension, diabetes mellitus, and dyslipidemia), and endocrine data for each patient. Age, sex, body mass index (BMI), and tumor size, volume, and extension (suprasellar extension and lateral invasion) of pituitary adenomas were also evaluated.

Evaluation of hormone secretion
Anterior pituitary hormone secretions were mainly evaluated by measuring basal hormone values from the pituitary gland and target organs as follows. Hormone secretion was evaluated preoperatively and postoperatively (i.e., a median 10, range 7–22 days after surgery).
Gonadotropin deficiency was evaluated on the basis of basal gonadotropin and sex steroid hormone values. Secondary hypogonadism was diagnosed in men with low serum testosterone concentration without an elevated concentration of gonadotropin. Postmenopausal women were diagnosed as gonadotropin deficient when gonadotropin concentration was not elevated in accordance with the menopausal reference value despite low serum estradiol concentration. In this study, there were two premenopausal women. One 29-year-old patient was excluded because of a suspected decrease in gonadotropin due to hyperprolactinemia. The other female patient was 47 years old and had normal gonadotropin secretion based on serum estradiol and gonadotropin concentrations.

For evaluating hormone secreting capacities of ACTH-adrenal axis, results of a corticotropin-releasing hormone (CRH)-stimulation test (100 μg) were also adopted. Patients were classified as ACTH deficient if their peak ACTH concentration was less than twice their basal value and/or peak cortisol concentration was <18 μg/dL during the CRH stimulation test. Patients who received replacement therapy preoperatively were also regarded as ACTH deficient. Patients with basal cortisol levels <18 μg/dL who did not undergo the CRH stimulation test were excluded from the study.

TSH deficiency was evaluated using serum TSH and free T4 concentrations and diagnosed when free T4 levels below the reference range in conjunction with a low or normal TSH concentration.

Patients were diagnosed with hyperprolactinemia, when a serum prolactin concentration was higher than the upper limit of reference value.

**Pituitary adenomas: MRI findings**

Pituitary adenoma size was evaluated by measurements of maximal dimensions on MRIs (Fig. 2). In addition, pituitary adenoma volume was calculated using the following equation:

\[ \text{Volume} = \left[ \frac{4}{3}\pi \left(\frac{a}{2} \cdot \frac{b}{2} \cdot \frac{c}{2}\right) \right] \]

where \(a\) = coronal width, \(b\) = coronal height, and \(c\) = sagittal width.

Knosp classification was used for lateral (cavernous sinus) invasion [6]. The suprasellar extension of tumors was ranked from grades 0–3 as follows: 0 = no suprasellar extension, 1 = slight suprasellar extension without reaching the optic chiasm, 2 = suprasellar extension reaching the optic chiasm, and 3 = suprasellar extension reaching the third ventricle.

**Comorbidities**

Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg at admission to Nippon Medical School Hospital or using antihypertensive medicines. Patients with a random plasma glucose concentration ≥200 mg/dL and HbA1c ≥6.5%, or who used Glucose-lowering medicines met the criteria for diabetes mellitus. Patients were classified as having dyslipidemia when their non-high-density lipoprotein (HDL) cholesterol was ≥170 mg/dL and/or if treatment with cholesterol-lowering medications was necessary.

**Assays**

Serum IGF-I levels were determined using the commercially available IGF-I immunoradiometric sandwich assay kit “Daiichi” (FUJIREBIO INC. Tokyo, Japan), with recombinant human IGF-I standards. The standard deviation scores (SDSs) for serum IGF-I levels were adjusted for gender and age according to the constructed reference [7].

**Ethics**

This study was approved by the Nippon Medical
School and Faculty of Medicine Ethics Committee (No. 28-04-575) and conducted in accordance with the principles of the Declaration of Helsinki. The study was registered with the University Hospital Medical Information Network (UMIN No. 000035557).

Statistical analyses
Continuous variables were expressed as the mean ± SD. Sex, initial symptoms (i.e., visual field defect, headache, nausea, and diplopia), and the prevalence of comorbidities (hypertension, diabetes mellitus, and dyslipidemia) were compared between each group using a Chi-square test. Age, BMI, adenoma size, volume and invasion, peak GH concentrations, and IGF-I SDSs were analyzed using the Student’s t test. The Jonckheele test was employed to analyze peak GH concentrations during a GHRP-2 test and the number of anterior pituitary hormone deficiencies besides GH.

The cut-off, sensitivity, and specificity of preoperative peak GH values during the GHRP-2 test that can be expected to recover were derived from the receiver operating characteristic (ROC) analysis. P < 0.05 was considered significant. JMP Pro 13.1 software (SAS Institute, Cary, NC) and SPSS 21.0 (IBM Co. Ltd., Armonk, New York, USA) were used for our analyses.

Results
Relationship between peak GH values during the GHRP-2 test and the severity of hypopituitarism
The relationship between peak GH values during the GHRP-2 test and the number of anterior pituitary hormone deficiencies among all 76 patients is depicted in Fig. 3. Lower peak GH values during the GHRP-2 test were associated with a higher number of anterior pituitary hormone deficiencies.

Clinical characteristics of patients with severe AGHD
Among the 76 patients, 36 patients had severe AGHD and their clinical characteristics are shown in Table 1. The mean age of these patients was 61 ± 14 years, 23 out of 36 patients (64%) were male, and mean BMI of these 36 patients was 25 ± 4 kg/m². The most frequent initial symptoms reported were visual field defect (42%) and headaches (19%). The most common comorbidities were dyslipidemia (69%) and hypertension (44%). The peak GH values during the preoperative GHRP-2 test among the 36 patients with severe AGHD was 3.5 ± 2.4 ng/mL and the IGF-I SDS was −1.47 ± 2.00. Other endocrine data for these patients are shown in Table 2. Of the deficiencies evaluated, gonadotropin deficiency was the most common (22/36, 63%) followed by ACTH deficiency (14/36, 45%). Fifteen patients (42%) had hyperprolactinemia.

Differences in clinical characteristics according to GH response
The clinical characteristics of patients in group L and group M are shown in Table 1. Patients in group L were significantly older than patients in group M (p = 0.01). Mean BMI was significantly lower in group L versus...
group M ($p = 0.03$). Headache was a more frequent initial symptom in group M versus group L, although there were no reports of nausea within group M. The incidence of comorbidities was not different between groups. Pituitary adenoma volume, suprasellar extension grades, and Knosp classification of adenomas were not significantly different between groups; however, the mean longitudinal diameter of adenomas (in terms of coronal height) was longer in group L than in group M ($p = 0.02$).

### Table 1  Characteristics of patients with severe AGHD

|                          | Total          | Low response, group L | Moderate response, group M | $p$ value |
|--------------------------|----------------|-----------------------|----------------------------|-----------|
| Mean age (years)         | $n = 36$       | $n = 18$              | $n = 18$                   |           |
|                          | $61 \pm 14$    | $67 \pm 11$           | $56 \pm 14$               | 0.01*     |
| Sex, male/female         |                |                       |                            |           |
|                          | $23/13$        | $11/7$                | $12/6$                     |           |
| Mean BMI (kg/m$^2$)      |                |                       |                            |           |
|                          | $25 \pm 4$     | $24 \pm 3$            | $27 \pm 5$                | 0.03*     |
| Number of complications and symptoms (%) |            |                        |                            |           |
| Visual field defect (%)  |                |                       |                            | 0.31      |
|                          | $15 (42\%)$    | $9 (50\%)$            | $6 (33\%)$                |           |
| Headache                 | $7 (19\%)$     | $1 (6\%)$             | $6 (33\%)$                | 0.04*     |
| Nausea                   | $5 (14\%)$     | $5 (28\%)$            | $0 (0\%)$                 | 0.02*     |
| Diplopia                 | $2 (6\%)$      | $0 (0\%)$             | $2 (11\%)$                | 0.15      |
| Dyslipidemia             | $25 (69\%)$    | $15 (83\%)$           | $10 (56\%)$               | 0.07      |
| Hypertension             | $16 (44\%)$    | $8 (44\%)$            | $8 (44\%)$                | 1.00      |
| Diabetes mellitus        | $3 (8\%)$      | $3 (17\%)$            | $0 (0\%)$                 | 0.07      |
| Tumor size/invasion      |                |                       |                            |           |
| Coronal width (mm)       |                |                       |                            | 0.43      |
|                          | $26 \pm 7$     | $26 \pm 5$            | $25 \pm 8$                |           |
| Coronal height (mm)      |                |                       |                            | 0.02*     |
|                          | $25 \pm 9$     | $28 \pm 9$            | $21 \pm 7$                |           |
| Sagittal width (mm)      |                |                       |                            |           |
|                          | $20 \pm 7$     | $21 \pm 8$            | $20 \pm 5$                |           |
| Volume (mm$^3$)          |                |                       |                            | 0.52      |
|                          | $8,089 \pm 7,347$ | $9,917 \pm 8,992$    | $6,260 \pm 4,815$         | 0.14      |
| Median Knosp classification |              |                       |                            | 1.00      |
|                          | $2$            | $2$                   | $2$                        |           |
| Median suprasellar extension (grade) |        |                       |                            | 0.32      |
|                          | $2$            | $2$                   | $2$                        |           |
| Endocrine data           |                |                       |                            |           |
| Peak GH (ng/mL)          |                |                       |                            |           |
|                          | $3.5 \pm 2.4$  | $1.6 \pm 0.8$         | $5.5 \pm 1.9$             | <0.001*    |
| IGF-I (ng/mL)            |                |                       |                            |           |
|                          | $97 \pm 52$    | $72 \pm 10$           | $124 \pm 47$              | 0.0016*    |
| IGF-I (SD score)         |                |                       |                            |           |
|                          | $-1.47 \pm 2.00$ | $-2.23 \pm 2.36$     | $-0.67 \pm 1.11$          | 0.02*     |

Data are the mean ± standard deviations (SD) unless otherwise indicated.

* $p < 0.05$ was considered a significant difference between group L and group M.

AGHD, adult growth hormone deficiency; BMI, body mass index; IGF-I, insulin-like growth factor-I.

### Table 2  Endocrinological abnormalities of patients

|                          | Total          | Low response, group L | Moderate response, group M | $p$ value |
|--------------------------|----------------|-----------------------|----------------------------|-----------|
| Number of abnormalities (%) |              |                       |                            |           |
| Gonadotropin deficiency  | $22 (63\%)$   | $15 (83\%)$           | $7 (41\%)$                 | 0.01*     |
| ACTH deficiency           | $14 (45\%)$   | $11 (61\%)$           | $3 (23\%)$                 | 0.04*     |
| TSH deficiency            | $9 (26\%)$    | $6 (35\%)$            | $3 (17\%)$                 | 0.21      |
| Hyperprolactinemia        | $15 (42\%)$   | $11 (61\%)$           | $4 (22\%)$                 | 0.02*     |

* $p < 0.05$ was considered a significant difference between group L and group M.
Differences in the severity of hypopituitarism according to GH response

A comparison of the number of anterior pituitary hormone deficiencies, besides a GH deficiency, is shown in Fig. 4. Two patients in group L, but no patient in group M, had deficiencies of three pituitary hormones. Similar to the observations among all patients, there were more anterior pituitary hormone deficiencies in group L than in group M as is indicated in Table 2. Gonadotropin deficiency and ACTH deficiency were significantly more frequent in group L than in group M (p = 0.01 and p = 0.04, respectively). Hyperprolactinemia was also significantly more frequent in group L versus group M (p = 0.02).

Preoperative compared with postoperative GH secretion

The change in peak GH concentration during the preoperative and postoperative GHRP-2 tests are depicted in Fig. 5. Postoperatively, seven patients in group M but no patients in group L, had a peak GH concentration >9 ng/mL, indicating improvement of severe AGHD. Moreover, peak GH was ≥4.62 ng/mL during the preoperative GHRP-2 test in those patients. When preoperative peak GH concentrations during the GHRP-2 test were ≥4.59 ng/mL, the recovery of postoperative GH release was revealed by the area under the ROC curve which was 0.88177 (Fig. 6). This cut-points determined by ROC analyses afforded 83% sensitivity with 100% specificity.

Other factors that affected on postoperative GH recov-
ery were also investigated. The patients \((n = 36)\) were devided into groups by preoperative severity of hypopituitarism, i.e. severe hypopituitarism group defined by patients with more than two anterior pituitary hormone deficiencies besides GH \((n = 16)\) and mild hypopituitarism group consisted with remaining 20 patients (Table 3). Seven patients who had a post-surgical peak GH concentration >9 ng/mL were all classified in mild hypopituitarism group. Postoperatively, six out of 36 patients (17%) had residual tumors, five of them were classified in mild hypopituitarism group preoperatively. Among six patients with residual tumors, peak GH during GHRP-2 test improved (>9 ng/mL) in two, but deteriorated (changed group L from group M) in one (Fig. 5).

**Discussion**

A retrospective chart analysis was performed to evaluate whether the peak GH response during a GHRP-2 test was related to clinical characteristics and the severity of hypopituitarism in patients with NFPAs complicated by severe AGHD.

The mean age of group L was significantly higher than that of group M. Chihara et al. have reported that the peak GH response during a GHRP-2 test was significantly reduced in patients >40 years when compared with younger adults in a control group \([5]\). Attenuation of the somatotroph axis with aging may explain such results \([8]\). Monson et al. have reported that peak GH release in response to provocative testing was significantly lower in >65-year-old female patients with AGHD compared with younger patients, although age dependent responses were not observed among male patients \([9]\).

Together, these results suggest that our data might also support alterations in the GH axis that are age-dependent.

In this study, mean BMI was lower in group L compared with group M. In general, peak GH responses during a stimulation test tend to be blunted in obese individuals, or those with relative abdominal obesity \([8]\).
Chihara et al. have shown that the GH Cmax during the GHRP-2 test in control subjects was significantly lower in overweight or obese subjects than in lean subjects in the >20 years age group [5]. Moreover, BMI affected serum GH Cmax, even in healthy lean subjects. However, differences in the GH Cmax between lean and obese patients who were severe GH deficient were not directly compared in Chihara’s study. Other possible cause of the result might be weight loss due to adrenal insufficiency, as ACTH deficiency was significantly more frequent in group L than in group M.

Five patients in group L reported initial symptoms of nausea in contrast to no reports of nausea in group M. All five patients reporting nausea were ACTH-deficient and treated with hydrocortisone replacement therapy preoperatively. Furthermore, hyponatremia was confirmed in three of the same five patients. Collectively, these findings may indicate that relatively more initial nausea in group L is a result of hyponatremia due to ACTH deficiency.

Headache was a more frequent initial symptom in group M than in group L. Sellar expansion by pituitary tumors is recognized as one cause of headaches in patients with pituitary adenomas, although no relationship between headaches and pituitary volume has been established [10]. However, pituitary apoplexy is characterized by the sudden onset of a headache. In our study, one patient in group L, who reported a headache, was diagnosed with pituitary apoplexy. It is sometimes difficult to distinguish a pituitary adenoma-associated headache from primary headache disorders, and the reasons for more patients reporting a headache in group M than in group L is unknown.

The mean longitudinal diameter of pituitary adenomas in terms of coronal height was longer in group L than in group M. There have been no studies on relationships between the three dimensions of pituitary adenoma and hormone deficiency. Several studies have examined the maximum diameter of pituitary tumors and peak hormone secretion. Mukai et al. examined the relationship between NFPA size and the prevalence of each pituitary hormone deficiency with reference to responses of anterior pituitary hormones during an insulin tolerance test, an LHRH test, and a TRH test [11]. GH deficiencies were observed to be more severe in the group of patients with tumors of a larger diameter. Based on the results of our study, which were similar to the aforementioned investigations, increased tumor size was predictive of diminished GH secretion. Nevertheless, further study is required to confirm these findings.

In terms of anterior pituitary abnormalities and the severity of hypopituitarism, gonadotropin and ACTH deficiencies, but not a TSH deficiency, were significantly more frequent in group L than in group M. Of the hormone deficiencies in NFPA, GH, gonadotropin (LH/FSH), ACTH, and TSH deficiencies were most prevalent, in that order [12]. Our results indicate that among patients with a severe GH deficiency, particularly in those with extremely low GH secretory capacity (<2.83 ng/mL, defined by peak GH below the median) there were more numerous pituitary hormone deficiencies. Hyperprolactinemia was significantly more frequent in group L compared with group M. We speculate that these results might be caused by the pituitary stalk effect, but there was no significant difference between hyperprolactinemia and the mean longitudinal diameter of the tumor in terms of coronal height.

In this study, as depicted in Fig. 3, a lower peak GH concentration during the GHRP-2 test was associated with a higher number of anterior pituitary hormone deficiencies, regardless of the presence of a severe GH deficiency. No studies to date appear to have addressed the relationship between peak GH values during a GHRP-2 test and the number of hormone deficiencies. Previous studies have evaluated the relationship between peak GH values and other types of GH stimulation tests. Toogood et al. investigated relationships between peak GH values in response to an insulin tolerance test (ITT) and the number of anterior pituitary hormone deficiencies in 190 patients with hypothalamic or pituitary disease [13]. For that study, patients were allocated to one of four groups in accordance with the number of anterior pituitary hormone deficiencies. A significant downward trend in median peak GH values was observed across groups as the number of anterior pituitary hormone deficiencies increased, as was evident in our study when GHRP-2 tests were assessed. Hartman et al. reported that median peak GH values in response to GH stimulation tests decreased in accordance with the number of additional pituitary hormone deficiencies [14]. In their study, arginine, L-Dopa (with or without propranolol or clonidine), and insulin (with or without GHRH) were used in 817 patients who were being considered for GH replacement therapy. In our study, peak GH values during a GHRP-2 test incontrovertibly reflected the severity of hypopituitarism, a result similar to what has occurred when other globally available GH-stimulating agents are used. Thus, the peak GH value during a GHRP-2 test is considered to be useful to assess the severity of anterior pituitary hormone deficiencies. However, plural dynamic tests are regarded as precipitating factors of pituitary apoplexy in patients with macroadenomas. It should be necessary to discuss whether preoperative GHRP-2 test is examined for any patient, because the risk of pituitary apoplexy of a GHRP-2 test is still unclear.

The postoperative changes in peak GH secretion were
Peak GH during GHRP-2 test in NFPA

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>9 ng/mL in seven patients in group M, whose peak GH was ≥4.62 ng/mL during a GHRP-2 test preoperatively. Kobayashi et al. has reported on postoperative time-dependent changes in GH release in 119 patients with NFPA, and investigated factors that affected GH secretory dynamics using the GHRP-2 test [15]. Severe GHDs recovered within 1-2 years post-surgery significantly in patients who were young (<60 years old), had only undergone a single primary surgery versus multiple surgeries, and who did not have an anterior hormone deficiency besides a GHD. Based on our results, when a preoperative peak GH value was ≥4.62 ng/mL during a GHRP-2 test in patients with NFPA, there was an improvement of 39% that the peak GH value could exceed 9 ng/mL during the GHRP-2 test immediately following transsphenoidal surgery, indicating an improvement of severe GHDs. We propose that postoperative recovery of GH secretion can be expected if patients have a peak GH concentration ≥4.59 ng/mL during a GHRP-2 test preoperatively. However, our results are only predictive of GH secretion recovery not long-term but immediately after surgery.

In this series, six patients had residual tumors. Postoperative recovery of GH secretion of these patients varied and the influence of surgical manipulation was unclear. To our knowledge, this is the first study to evaluate the preoperative to postoperative change in GH secretion by a peak GH during the GHRP-2 test.

One of the limitations of this study is that subjective symptoms among all the patients were not evaluated in the same way, because information was retrieved from medical charts. In addition, the timing of the evaluations of GH secretion was limited to immediately after surgery, and longer-term evaluations ranging from 1 to 2 years after surgery were not included in this study.

In conclusion, we found that a lower peak GH value during the GHRP-2 test in patients with NFPA was associated with a higher number of anterior pituitary hormone deficiencies and that peak preoperative GH values during a GHRP-2 test might reflect the recovery of postoperative GH status.

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Disclosure Statement

The authors declare no conflicts of interest.

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