Predictive factors for recovery from adult growth hormone deficiency after transsphenoidal surgery for nonfunctioning pituitary adenoma

Yasuyuki Kinoshita, MD, PhD; Akira Taguchi, MD; Atsushi Tominaga, MD, PhD; Kazunori Arita, MD, PhD; and Fumiyuki Yamasaki, MD, PhD

1Department of Neurosurgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima; 2Department of Neurosurgery and Neuro-Endovascular Therapy, Hiroshima Prefectural Hospital, Hiroshima; and 3Department of Neurosurgery, Izumi Regional Medical Center, Izumi, Japan

OBJECTIVE Recovery from adult growth hormone deficiency (AGHD) after transsphenoidal surgery (TSS) has not been well discussed because of the lack of examinations including pituitary provocation tests (PPTs) before and after the procedure. This study aimed to evaluate the growth hormone (GH) axis function of patients with nonfunctioning pituitary adenoma (NFPA) via pre- and postoperative PPTs. Moreover, the predictive factors for recovery from AGHD after TSS were evaluated to facilitate surgery for AGHD in patients with NFPA.

METHODS In total, 276 patients (median age 60.0 years) who underwent TSS for NFPA were included in this study. PPTs were performed before and 3 months after TSS. Then, the relationships between recovery from AGHD after TSS and clinical, surgical, and hormonal factors, including peak GH level based on PPTs, were evaluated statistically.

RESULTS In this study, 114 patients were diagnosed with preoperative AGHD. Approximately 25.4% recovered from AGHD after TSS. In contrast, among the 162 patients without preoperative AGHD, 13 (8.0%) had newly developed postoperative AGHD. The predictive factors for recovery from AGHD were younger age, female sex, initial TSS, and high peak GH level based on preoperative PPT. According to the receiver operating characteristic curve analysis, patients who were aged ≤ 62.2 years and had a peak GH level of ≥ 0.74 μg/L based on preoperative PPT were likely to recover from AGHD (sensitivity: 82.8%, specificity: 72.9%, and area under the curve: 0.8229).

CONCLUSIONS AGHD caused by NFPA can improve after initial TSS among young patients with certain peak GH levels assessed by preoperative PPT. Whether TSS for NFPA can promote recovery from AGHD is worth considering in some patients.

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KEYWORDS adult growth hormone deficiency; hypopituitarism; nonfunctioning pituitary adenoma; transsphenoidal surgery; pituitary surgery

TRANSSPHENOIDAL surgery (TSS) for nonfunctioning pituitary adenoma (NFPA) primarily aims to improve or prevent visual disturbances caused by a tumor compressing the chiasma. However, whether TSS should be performed to improve preoperative hypopituitarism has not been elucidated. Recently, several studies showed improvement in preoperative hypopituitarism after TSS for pituitary adenoma. The improvement rates ranged from 7.4% to 55.0%.

The remarkable variation in rates might be caused by a small number of patients, varying types of tumors, different evaluation periods, and various criteria for hypopituitarism improvement. Furthermore, pituitary functions were evaluated using the basal anterior pituitary hormone levels. However, the growth hormone (GH) axis function can be evaluated only via the pituitary provocation test (PPT).

The GH axis is likely impaired by hypothalamic pituitary tumor. GH axis dysfunction in adults causes various abnormalities in body composition and substrate metabolism, which further cause cardiovascular diseases and impaired quality of life.

Recently, GH replacement therapy was found to be important for patients with adult hypopituitarism.
GH deficiency (AGHD). However, this therapy imposes a burden among patients receiving long-term treatment because of the necessity of self-injections and the high cost of the GH preparation. Patients can significantly benefit from surgery, which facilitates recovery from preoperative AGHD. This study aimed to retrospectively examine patients with NFPA who underwent pre- and postoperative PPTs and to identify the predictive factors for recovery from AGHD after TSS. Furthermore, we discussed the appropriate indications for TSS in NFPA, which aim to improve AGHD.

Methods
This retrospective cohort study was approved by the Ethical Committee for Epidemiology of Hiroshima University. There were 378 patients who underwent surgery for NFPA at Hiroshima University Hospital between January 2006 and January 2021. In total, 304 patients had PPTs before and after TSS and preoperative 3-Tesla MRI. Moreover, 28 patients did not present with sufficiently induced hypoglycemia (blood glucose nadir of < 50 mg/dL or < 50% of the pretest blood glucose levels) based on the insulin tolerance test (ITT). Finally, 276 patients were included in this study (143 men and 133 women; median age at surgery 60.0 [range 17–89] years). These patients were diagnosed with clinical NFPA according to preoperative endocrinological examination and postoperative histological findings. The characteristics of 102 patients excluded from this study are shown in Supplemental Table 1.

The following data were collected from the medical records of the study patients: age, sex, presence of acute pituitary apoplexy, initial or repeated TSS findings, maximum tumor diameter and Knosp grade on preoperative MRI, insulin-like growth factor–1 (IGF-1) SD score based on a reference range of concentrations established for the Japanese population according to both age and sex, peak GH levels according to the pre- and postoperative PPTs, achievement of complete tumor removal with or without intraoperative cerebrospinal fluid leakage, and use of fat tissues for reconstruction.

Endocrinological Studies
PPTs were conducted in a total of 276 patients before and 3 months after TSS. Of these, 138 patients underwent the ITT for the evaluation of GH axis function. The remaining 138 patients, who were aged ≥ 65 years or had a history of heart disease or epilepsy, underwent an arginine-loading test rather than the ITT to avoid complications caused by induced hypoglycemia. PPTs were conducted according to the guidelines established by the Japan Endocrine Society. Based on the PPT results, the medical costs of AGHD (which is considered a rare and intractable disease by the Japan Ministry of Health, Labor and Welfare) were subsidized in 2009.

In the current study, AGHD was diagnosed based on a peak GH level of ≤ 1.8 µg/L according to PPT. The IGF-1 level was evaluated as the SD score based on a reference range established for the Japanese population according to both age and sex. The serum GH levels were evaluated via immunoenzymometric assay (TOSOH II HGH E-test, TOSOH Co.) using a recombinant 22-kD GH calibrator (International Reference Preparation: 98/574). The serum IGF-1 levels were assessed via immunoradiometric assay (Somatomedin C II, Siemens Healthcare Diagnostics KK).

Surgical Procedures
TSS was generally recommended to patients with NFPA touching or compressing the chiasma and those with NFPA that increased in size during the follow-up period and that could cause visual disturbance. TSS was performed by two surgeons (A. Tominaga and Y. Kinoshita) via one nostril under both microscopic and endoscopic observations before 2009. A complete endoscopic procedure was adopted in 2010. After removal of an adenoma intracapsularly, tumor pseudocapsule resection was attempted. The details of our surgical procedures have been described in a previous report. In this study, complete tumor removal was defined as resection of the whole intracapsular adenoma without consideration of pseudocapsule resection.

Statistical Analyses
All statistical analyses were performed using the JMP Pro 15.0 software (SAS Institute Inc.). The values were expressed as the median. The median values were compared using the Mann-Whitney U-test, Fisher’s exact test, and chi-square test with 95% confidence intervals (CIs). The logistic regression model was used to calculate the adjusted odds ratios (ORs) with 95% CIs for recovery from preoperative AGHD. The multivariate logistic regression model was performed after adjusting for all potential confounding factors; p values < 0.05 were considered statistically significant. Receiver operating characteristic (ROC) curves were calculated to identify the cutoff values for age and peak GH level based on the preoperative PPT among those expected to recover from preoperative AGHD.

Results
Recovery From Preoperative AGHD and Onset of Postoperative AGHD
Of the 276 patients who underwent TSS for NFPA, 114 patients were diagnosed with preoperative AGHD. Among them, 29 (25.4%) recovered from AGHD after TSS. However, of the remaining 162 patients without preoperative AGHD, 13 (8.0%) had newly developed AGHD after TSS. Among 98 patients with AGHD at 3 months postoperatively, 16 received GH replacement.

Characteristics of Patients With Preoperative AGHD
Table 1 shows the background characteristics of patients who recovered from AGHD and those who did not after TSS. Younger age and high peak GH level assessed by preoperative PPT were significant predictive factors for recovery from preoperative AGHD (age, p = 0.0009 [Fig. 1 left]; peak GH level, p < 0.0001 [Fig. 1 right]). Furthermore, female sex, IGF-1 SD score, and initial TSS were significant predictive factors for recovery from AGHD via univariate analysis.
Characteristics of Patients Without Preoperative AGHD

Table 2 depicts the background characteristics of patients with or without AGHD after TSS. Elderly patients were likely to develop new postoperative AGHD ($p = 0.0094$) (Fig. 2 left). Furthermore, low peak GH level based on preoperative PPT was a significant predictive factor for new postoperative AGHD ($p = 0.0007$) (Fig. 2 right) in univariate analysis. In contrast, the variety of surgical procedures did not affect the postoperative GH axis function.

Predictive Factors for Recovery From Preoperative AGHD

Table 3 shows the adjusted ORs of recovery from AGHD in multivariate analysis. Younger age, female sex, initial surgery, and high peak GH level based on preoperative PPT were significantly associated with recovery from AGHD, with adjusted ORs of 0.9208 for younger age (95% CI 0.8771–0.9666, $p = 0.0001$), 4.0361 for female sex (95% CI 1.3071–12.4626, $p = 0.0137$), and 8.0568 for peak GH level (95% CI 2.3125–28.0695, $p = 0.0004$).

Cutoff Values of Age and Peak GH Level for Recovery From Preoperative AGHD

To identify the cutoff values for recovery from preoperative AGHD, the sensitivity and specificity were examined using ROC curves for age and peak GH level based on preoperative PPT. The appropriate cutoff values for age and GH level were 62.2 years and 0.74 µg/L among patients expected to recover from AGHD (sensitivity 82.8%, specificity 72.9%, and area under the curve [AUC] 0.8229) (Fig. 3).

Prospective Rates of Recovery From Preoperative AGHD

Table 4 shows the rates of recovery from preoperative AGHD in the categorized groups based on the cutoff values for age and peak GH level calculated using ROC curves. Of 96 patients who underwent initial TSS, 12 (70.6%) who were aged ≤ 62 years and who had a peak GH level ≥ 0.74 µg/L recovered from AGHD. In contrast, all patients who were aged > 62 years and had a peak GH level of < 0.74 µg/L did not recover from AGHD.

Discussion

The current study showed that patients who were aged ≤ 62 years and had a peak GH level of ≥ 0.74 µg/L based on preoperative PPT were likely to recover from AGHD after the initial TSS for NFPA. Previous studies have shown that younger age is a predictive factor for improvement in preoperative hypopituitarism. Jahangiri et al. revealed that younger age could be a predictor of improvement in preoperative pituitary dysfunction after TSS for NFPA. However, younger patients did not experience significant improvement of the GH axis function. Moreover, Hwang et al. showed that younger age was associated with...
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a likelihood of postoperative endocrine recovery. However, the GH axis function was not evaluated. In two previous studies, pituitary functions including that of the GH axis were evaluated based on basal hormone levels, not via PPTs. Younger age was known to be one of the predictive factors for improvement in preoperative hypopituitarism. However, in the current study we first verified the likelihood of recovery from GH deficiency among young patients based on accurate PPT findings.

Soga et al. conducted pre- and postoperative GH-releasing peptide–2 (GHRP-2) tests to evaluate the functional change in GH axis after TSS for NFPA. Results showed that preoperative peak GH levels (≥ 4.59 µg/L) based on the GHRP-2 test could predict recovery from AGHD. The AGHD criterion in the GHRP-2 test is a peak GH level of ≤ 9.0 µg/L, which is equal to a peak GH level of ≤ 1.8 µg/L based on the ITT or arginine test. The criterion of a peak GH level (≥ 0.74 µg/L), which can predict recovery from AGHD in the current study, was similar to the criterion of a peak GH level (≥ 4.59 µg/L) in the GHRP-2 test. These results indicate that recovery from AGHD is based on the remaining GH axis function before surgery. Moreover, Soga et al. examined the other predictive factors for recovery from AGHD. However, other factors could not be identified because only a small number of patients were included. In contrast, the preoperative IGF-1 SD score was not a predictive factor for recovery from AGHD. IGF-1 levels in patients with AGHD were reported to overlap with those in healthy participants. Furthermore, patients with adult-onset AGHD or elderly AGHD patients (61–85 years) were likely to have normal IGF-1 values, findings that were consistent with those for patients included in the present study. It may be difficult to predict postoperative recovery from AGHD based on preoperative IGF-1 values.

In the current study, the initial TSS was considered a predictive factor for recovery from AGHD. Repeated TSS was found to be associated with a high incidence of postoperative diabetes insipidus in a large series. However, it was not a predictive factor for the deterioration of anterior pituitary functions. Whether initial TSS is advantageous in terms of improving hypopituitarism has not been statistically validated. Nevertheless, a previous study showed that none of the patients recovered from hypopituitarism after repeated TSS. This result is similar to that of our study. Patients undergoing initial TSS for NFPA are

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**TABLE 2. Characteristics of patients without preoperative AGHD**

<table>
<thead>
<tr>
<th></th>
<th>New AGHD</th>
<th>w/o Deterioration</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of pts (n = 162)</td>
<td>13</td>
<td>149</td>
<td></td>
</tr>
<tr>
<td>Median age, yrs</td>
<td>65.0 (60.5 to 70.5)</td>
<td>54.0 (45.0 to 67.5)</td>
<td>0.0094</td>
</tr>
<tr>
<td>Female sex</td>
<td>7 (53.8%)</td>
<td>88 (59.1%)</td>
<td>0.7736</td>
</tr>
<tr>
<td>Median preop peak GH level, µg/L</td>
<td>2.99 (2.20 to 4.15)</td>
<td>6.37 (3.38 to 11.83)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Median preop IGF-1 SD score</td>
<td>−1.00 (−1.65 to −0.10)</td>
<td>−0.55 (−1.23 to 0.13)</td>
<td>0.4134</td>
</tr>
<tr>
<td>Median tumor diameter, mm</td>
<td>22.0 (20.0 to 25.0)</td>
<td>22.0 (18.0 to 26.5)</td>
<td>0.7060</td>
</tr>
<tr>
<td>Knosp grade 0–2</td>
<td>12 (92.3%)</td>
<td>105 (70.5%)</td>
<td>0.1142</td>
</tr>
<tr>
<td>Initial TSS</td>
<td>11 (84.6%)</td>
<td>135 (90.6%)</td>
<td>0.6202</td>
</tr>
<tr>
<td>Total intracapsular tumor removal</td>
<td>12 (92.3%)</td>
<td>120 (80.5%)</td>
<td>0.4652</td>
</tr>
<tr>
<td>Intraop CSF leakage</td>
<td>4 (30.8%)</td>
<td>51 (34.2%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Use of fat tissues</td>
<td>3 (23.1%)</td>
<td>41 (27.5%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Median postop peak GH level, µg/L</td>
<td>0.95 (0.40 to 1.48)</td>
<td>8.02 (4.56 to 13.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median postop IGF-1 SD score</td>
<td>−0.40 (−1.20 to −0.10)</td>
<td>−0.50 (−1.20 to 0.20)</td>
<td>0.9621</td>
</tr>
</tbody>
</table>

Data are expressed as number (%) of patients or median (IQR) unless otherwise indicated.

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**TABLE 3. Results of multivariate logistic regression analysis of the predictive factors for postoperative recovery from AGHD**

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>0.9208</td>
<td>0.8771–0.9666</td>
<td>0.0001</td>
</tr>
<tr>
<td>Female/male sex</td>
<td>4.0361</td>
<td>1.3071–12.4625</td>
<td>0.0137</td>
</tr>
<tr>
<td>Peak GH level, µg/L</td>
<td>8.0568</td>
<td>2.3125–28.0695</td>
<td>0.0004</td>
</tr>
<tr>
<td>Initial TSS, yes vs no</td>
<td>NC</td>
<td>NC</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

NC = not calculated.

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**FIG. 2.** Graphs showing age (left) and peak GH levels based on the preoperative provocation tests (right) in the groups with new AGHD and without deterioration, comprising patients without preoperative AGHD (n = 162). The patients in the new AGHD group were significantly older (*p = 0.0094) and had lower peak GH levels based on the preoperative provocation tests (**p = 0.0007) than those in the group without deterioration.
likely to recover from preoperative AGHD because they have a shorter disease duration and less surgical damage in the pituitary gland than those receiving repeated TSS.

The relationship between sex and recovery from hypopituitarism has not been fully elucidated. We showed that female sex was associated with recovery from AGHD. However, Harary et al. revealed that male patients were likely to recover from hypopituitarism. By contrast, Galloyaw et al. demonstrated that male patients were likely to develop new endocrine deficits. Previous studies did not reveal significant differences between male and female participants in terms of recovery from hypopituitarism postoperatively. The different results may be caused by varying patient age and sex in each study. The age and sex of patients in the current study were similar to those of the general Japanese population. However, these were different from those of a previous report. Further studies should be conducted to validate the relationship between patient sex and recovery from hypopituitarism after TSS.

Limitations

The current study had some limitations. First, 74 patients were excluded from the analysis because either pre- or postoperative PPTs were not performed. There were a few reasons why some patients avoided PPTs, and these reasons included the diagnosis of acute pituitary apoplexy and giant tumor. The selection of patients receiving PPTs was not free from bias. Second, it might be premature to evaluate the GH axis function 3 months postoperatively. AGHD may have improved after PPTs were performed at 3 months postoperatively. Kobayashi et al. reported that 30% of patients with AGHD diagnosed at 1–2 weeks postoperatively recovered at 1–2 years. Recovery from AGHD after TSS might be examined for long periods postoperatively. However, Nomikos et al. examined postoperative pituitary function at 3 months and 1 year postoperatively based on provocation tests and reported that the pituitary function achieved at 3 months postoperatively did not improve after 1 year. We considered that the evaluation of postoperative pituitary function at 3 months postoperatively was rather appropriate. Third, the sensitivity and specificity were not sufficiently high based on the cutoff values for age and peak GH level calculated using ROC curves for predicting recovery from preoperative AGHD. Thus, the cutoff values for age and GH levels should be further explored in larger series. Despite these disadvantages, our study showed the importance of age and preoperative PPT for assessing the likelihood of recovery from AGHD after TSS.

Conclusions

AGHD caused by NFPA is likely to improve after initial TSS among young patients with certain peak GH levels assessed by preoperative PPT. Whether TSS for NFPA can promote recovery from AGHD is worth considering in some patients.

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References


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Kinoshita. Acquisition of data: Kinoshita, Taguchi, Tominaga. Analysis and interpretation of data: Kinoshita, Yamasaki. Drafting the article: Kinoshita, Yamasaki. Critical revision of the article: Arita, Yamasaki. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kinoshita. Statistical analysis: Kinoshita. Administrative/technical/material support: Tominaga, Yamasaki. Study supervision: Yamasaki.

Supplemental Information
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Correspondence
Yasuuyuki Kinoshita: Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. y-kinoshita@hiroshima-u.ac.jp.