Anterior Pituitary Function in Patients with Nonfunctioning Pituitary Adenoma: Results of Longitudinal Follow-up

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Abstract. Studies of anterior pituitary function in patients treated for nonfunctioning pituitary adenomas have been limited by their short duration. The purpose of the present study was to examine pituitary function longitudinally among three types of patients: those with complete tumor removal (group A); those with subtotal or partial adenomectomy (group B); and those in group B who underwent additional radiation therapy (group C). The subjects were 33 patients whose anterior pituitary function was evaluated by provocative tests such as insulin induced hypoglycemia, thyrotropin releasing hormone administration test and luteinizing hormone releasing hormone administration test. They underwent preoperative evaluation and postoperative reevaluations at 2 weeks, 3 months, 6 months and annually thereafter, for over 10 years. Anterior pituitary function was restored within a year after surgery, if at all. No additional function was restored after one year from treatment. In group A, no one developed impairment of anterior pituitary function after one year from surgery. In group B, however, new impairment was noted at intervals, due to tumor regrowth. In Group C, deficiencies developed after one year, irrespective of tumor regrowth. In conclusion, lifelong endocrinological follow-up is recommended for patients receiving postoperative irradiation, and for patients with potential for tumor regrowth. On the other hand, patients with total adenomectomy may be exempted from periodic endocrinological follow-up if they do not need postoperative hormonal replacement therapy.

Key words: Nonfunctioning pituitary adenoma, Anterior pituitary function, Longitudinal follow-up, Surgery, Irradiation

Although the main symptom of nonfunctioning pituitary adenoma (NPA) may be visual disturbance [1, 2], almost all patients are also found to have some degree of endocrine imbalance [3–5]. Reports on the effect of NPA tumor resection on visual disturbance, or short-term reports of anterior pituitary function following surgery and/or radiation therapy can be found in the literature [3, 6–11], but there are few reports on the long-term effects on anterior pituitary function following treatment. Given the benign nature of the tumor, the subsequent longevity of patients and the relevance of endocrine function to patients’ well-being, it is important that we learn more about such patients’ postoperative anterior pituitary function over time. We here present findings on anterior pituitary function before treatment and up to more than 10 years postoperatively in the patients with NPA.
Materials and Methods

Patients

From 1974 to 1982, 50 patients with NPA were managed at Hiroshima University Hospital. Thirty-three patients could be followed up for more than 10 years. They comprised 17 males and 16 females. Age at diagnosis ranged from 33 to 69 years, with a median of 52 years. The follow-up period ranged from 10 to 18 years (mean=13 years). The patients were analyzed for the first 10 years of follow-up in this study.

The main symptom was visual disturbance in 26 patients and headache in 5; two patients were found incidentally. The transsphenoidal procedure was employed for tumor removal in 21 cases and the transcranial procedure in 12 cases. Fourteen patients underwent total adenomectomy, 12 subtotal adenomectomy and 7 partial adenomectomy. Postoperative radiotherapy was performed in 8 patients, including 6 patients with subtotal adenomectomy and two with partial adenomectomy. With a linear accelerator (Linac), a total dose of 50 Gy was given in a daily fraction of 2 Gy, 5 fractions per week. Radiotherapy was initiated one month after the surgery. Based on the treatment and results of the first operation, patients were assigned to one of three groups:

Group A – total adenomectomy (n=14)
Group B – subtotal or partial adenomectomy (n=11)
Group C – subtotal or partial adenomectomy in combination with postoperative irradiation (n=8).

The mean tumor size in group A (mean ± SD; 21 ± 7.7 mm diameter) was statistically smaller than in group B (32 ± 9.8 mm) and C (37 ± 11 mm) (P<0.05). No one in group A developed recurrence. In group B, however, 5 out of 11 patients (45%) developed symptomatic regrowth of the tumor (visual deterioration) and underwent further surgery. In group C, 5 out of 8 patients (63%) developed symptomatic regrowth of the tumor (visual deterioration) and underwent further surgery.

Study protocol

In all groups, anterior pituitary functions were evaluated before surgery and reevaluated postoperatively at 2 weeks, 3 months, 6 months, 1 year and then annually throughout the course of the follow-up period. In group C, postoperative anterior pituitary function was evaluated at 2 weeks after surgery, and irradiation was initiated at one month after surgery. Because it took one month to complete irradiation therapy, anterior pituitary function was evaluated at 2 months, 5 months, one year and then annually after irradiation. Serum GH, cortisol, TSH, PRL, LH and FSH were measured by means of the specific radioimmunoassay for each one. The coefficient of variation of each assay was below 10%. Provocative tests such as the following were used: insulin induced hypoglycemia (insulin 0.1–0.15 U/kg body weight iv) for GH and cortisol, TRH test (TRH 0.5 mg iv) for TSH and PRL, and LHRH test (LHRH 0.1 mg iv) for LH and FSH. The pituitary-adrenal axis was evaluated by measurement of cortisol instead of ACTH. Hyperprolactinemia was not included in impaired PRL secretion, since hyperprolactinemia was functionally caused by impairment of prolactin inhibiting factor (PIF). Impaired pituitary hormone secretion was defined as a low basal value and/or response to hormonal stimulation. The revised criteria for the normal basal value and normal response to stimuli used in this study are shown in Table I [12].

The study protocol was approved by the Hospital Institutional Review Board.

Statistical method

Statistical analysis of differences between groups was tested by nonparametric test (Mann-Whitney U test).

Results

Preoperative anterior pituitary function

In two patients in group C, the endocrinological evaluation was not started until one year after surgery.

Preoperative endocrinological evaluation showed impaired secretion of GH in 30 out of 31 patients (97%), LH in 16 patients (52%), ACTH in 15 patients (48%), FSH in 13 patients (42%), TSH in 6 patients (19%) and PRL in two patients (6.5%). Hyperprolactinemia was found in 13 patients (42%).
**Postoperative anterior pituitary function**

Figures 1 to 3 show the number of patients with impaired function at the time of measurement in each group. Some patients transiently and some permanently developed impairment of anterior pituitary function after surgery. More than 85% of the patients whose function was restored after surgery reached this stage within the first 3 months after surgery, but it took 3 months to one year for other patients. No additional restoration in function was noted after one year from treatment.

Postoperative return of anterior pituitary function in patients who had preoperative impairment went as follows: 11 out of 15 patients (73%) had ACTH secretion restored, 4 out of 6 (67%) had TSH secretion restored, 2 out of 13 (15%) had FSH secretion restored and 2 out of 16 (13%) had LH secretion restored, but none with prior deficiency exhibited any return of GH secretion. Eleven out of 13 patients (85%) with hyperprolactinemia became normoprolactinemic.

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**Table 1. Criteria for normal basal value and normal response in endocrine studies**

<table>
<thead>
<tr>
<th>Test</th>
<th>Hormone</th>
<th>Basal value</th>
<th>Peak value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin induced hypoglycemia (0.1–0.15U/Kg body)</td>
<td>GH (ng/ml)</td>
<td>&lt;5.0</td>
<td>≥17.0</td>
</tr>
<tr>
<td></td>
<td>Cortisol (μg/dl)</td>
<td>6.4 – 18.8</td>
<td>≥15.9</td>
</tr>
<tr>
<td>TRH test (0.5mg/body)</td>
<td>TSH (μU/ml)</td>
<td>0.4 – 5.0</td>
<td>≥8.0</td>
</tr>
<tr>
<td></td>
<td>PRL (ng/ml)</td>
<td>1.5 – 9.7a</td>
<td>≥15.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.4 – 14.6b</td>
<td></td>
</tr>
<tr>
<td>LHRH test (0.1mg/body)</td>
<td>LH (mU/ml)</td>
<td>1.8 – 5.2a</td>
<td>≥30.0b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.0 – 34.9a</td>
<td>≥30.0b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.7 – 38.0b</td>
<td>≥140b</td>
</tr>
<tr>
<td></td>
<td>FSH (mU/ml)</td>
<td>2.9 – 8.2a</td>
<td>≥5.0b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.0 – 14.8b</td>
<td>≥5.0b</td>
</tr>
<tr>
<td></td>
<td></td>
<td>26.2 – 113.3b</td>
<td>≥48.0b</td>
</tr>
</tbody>
</table>

a), male; b), female; c), menstrual female; d), postmenopausal female.

The values measured by the RIA two sited method were converted into the values measured by the IRMA method. * A twofold increase in the value is a prerequisite.

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**Fig. 1.** Number of patients with impaired anterior pituitary function in Group A (n=14). None developed impairment of anterior pituitary function after one year postoperation.
To summarize, in Group A, none developed impairment of anterior pituitary function after one year postoperation. In Group B, however, some patients developed new impairment of anterior pituitary function at intervals, due to tumor regrowth. In Group C, patients developed impairment after more than one year, irrespective of tumor regrowth. Gonadal function in particular was impaired in all group C patients by the fourth or sixth year (see Fig. 3).

**Fig. 2.** Number of patients with impaired anterior pituitary function in Group B (n=11). Some patients developed new impairment of anterior pituitary function at intervals, due to tumor regrowth.

**Fig. 3.** Number of patient with impaired anterior pituitary function in Group C (n=8). No endocrine values were obtained for 2 patients until 1 year after surgery. Patients developed impairment after more than one year, irrespective of tumor regrowth. Gonadal function in particular was impaired by four or six years.

**Long-term results in anterior pituitary functions**

To summarize, in Group A, none developed impairment of anterior pituitary function after one year postoperation. In Group B, however, some patients developed new impairment at intervals, due to tumor regrowth. In Group C, patients developed impairment after more than one year, irrespective of tumor regrowth. Gonadal function in particular was impaired in all group C patients by the fourth or sixth year (see Fig. 3).

**Discussion**

The percentage of pre- and postoperative impairment was higher in GH and gonadotropin than in ACTH, TSH and PRL. These results support the results of our previous studies [12, 13], except that ACTH impairment was found to be greater in the current study. The percentages of preoperative impairment and postoperative restoration of each hormone reflect the fragility of tissues secreting them. It is also important to note that in our study the preoperative value for ACTH axis impairment was higher than that reported in some
previous studies [12, 14], yet was analogous to or lower than that reported in other studies [3, 10, 15]. This discrepancy may be due to differences in the method used in provocative testing or the criteria. For example, the metyrapone test [12, 14] may yield lower results than the insulin test used in our study, because the former stimulates the pituitary gland directly and indirectly via the hypothalamus, whereas insulin-induced hypoglycemia stimulates the pituitary gland via the hypothalamus alone. The criterion for cortisol in this study is essentially the same as the criterion used by other authors. In addition, we recommend introducing the corticotropin releasing hormone (CRH) test to evaluate ACTH secretion [16-18]. Because CRH stimulates the pituitary gland, we can evaluate pituitary-adrenal function irrespective of hypothalamic dysfunction.

As for endocrinological follow-up for NPA, the present study has resulted in several important findings.

First, it took up to one year to restore anterior pituitary function following surgery, but no function was restored after one year. There are few reports regarding this length of time. Arafah et al. [3, 10] evaluated postoperative anterior pituitary function 3 months after surgery. In the present study, more than 85% of the patients had anterior pituitary function restored within 3 months after surgery, for each hormone, but it took some patients from 6 months to a year to have function restored. If the tumor does not relapse, endocrinologic evaluations at one year postoperation are likely to indicate future pituitary function.

Second, the need for periodic endocrinological follow-up was decided by treatment. There was no difference in tumor size between groups B and C, however, postoperative course was different between them. Therefore, the postoperative course was not decided by the tumor size. In patients with total adenomectomy, the results of the provocative tests one year after surgery indicate their future anterior pituitary function, so that if they do not need hormonal replacement therapy after surgery, they can be exempted from periodic endocrinological check-ups. On the other hand, patients with partial removal of the tumor may exhibit impairment of anterior pituitary function due to tumor regrowth during the follow-up period. Patients with noncurative surgery therefore require periodic radiographic examinations. If the tumor regrows radiographically, the hormonal provocative testing is needed.

It is clinically important that patients receiving irradiation developed impairment of anterior pituitary function many years after irradiation without tumor regrowth. Postoperative radiotherapy is useful in preventing tumor recurrence, and many authors have reported its effects [18-21], but it has been reported that patients receiving irradiation were at higher risk of impairment of anterior pituitary function [19, 22, 23]. According to these reports, many patients developed impairment of function within five years after irradiation and some lost anterior pituitary function 8 or 9 years after irradiation [23]. It has been suggested that radiation-induced hypopituitarism is due to injury to the hypothalamus and/or the pituitary gland [19, 22-24]. The fact that these patients lost their anterior pituitary function long after irradiation suggests that delayed vascular damage could play an important role in the development of radiation-induced hypopituitarism. In the present study, two patients developed new impairment of anterior pituitary function 11 years after irradiation. Patients receiving irradiation therefore require periodic endocrinological examinations.

At present, cortisol or thyroxine replacement is given to patients with hypopituitarism. These hormones are indispensable for life. Currently, other hormonal replacement therapy, such as for sex steroids or GH [25, 26], still under clinical research, can be tried. These hormones are not indispensable for life, but their appropriate administration may improve the quality of life. Because these replacement therapies may be more commonly administered in the future, all of the anterior pituitary hormones should be periodically investigated in follow-up.

In summary, it took three months to one year to restore anterior pituitary function after surgery, but if the patient failed to have function restored within one year after surgery, it was never restored. Patients receiving irradiation were at greater risk of impairment of anterior pituitary function. Based on these results, lifelong endocrinologic follow-up is recommended for patients with postoperative irradiation, and for patients with the potential for tumor regrowth. On the other hand, patients with total adenomectomy may be exempted from periodic endocrinological follow-up if they do not need postoperative hormonal replacement therapy.
References


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