Pure alpha subunit-secreting pituitary tumors

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The authors describe six patients with pituitary macroadenomas hypersecreting only the alpha subunit of the glycoprotein hormones. These patients had been previously diagnosed as having “non-functioning chromophobe adenomas.” All of the patients had visual field abnormalities and partial hypopituitarism. The elevated serum alpha concentrations showed a variable response to stimulation by thyrotropin-releasing hormone, and could not be suppressed by thyroid hormone administration. Immunological, gel chromatographic, and immunocytochemical studies documented that only the alpha subunit was present. Following pituitary surgery and radiotherapy, serum alpha levels decreased. These patients represent a new subset of functioning pituitary tumors. Determination of alpha subunit concentration is useful in managing some patients with pituitary tumors previously thought to have non-functioning chromophobe adenomas.

KEY WORDS • pituitary tumor • alpha subunit • glycoprotein • hormone • chromophobe adenoma

Hypersecretion of prolactin (PRL), growth hormone, or corticotropin typically occurs in patients with pituitary tumors. The majority of pituitary tumors secrete PRL alone, or in combination with other anterior pituitary hormones. Excess secretion of PRL in these patients produces a range of well described clinical syndromes, including amenorrhea, ovulatory dysfunction, and galactorrhea in women, as well as hypogonadism and impaired sexual function in men. The diagnosis and medical and surgical management of these patients are dependent upon monitoring these specific symptoms and measuring serum pituitary hormone concentrations. Some pituitary tumors are unassociated with hormonal hypersecretion. Because these patients lack a specific tumor marker, the diagnosis of “non-functioning chromophobe adenoma” is usually delayed until these tumors are large enough to produce visual loss and other compressive symptoms. Similarly, assessing the completeness of pituitary surgery and monitoring these patients is difficult after radiotherapy. Their follow-up examination is limited to the evaluation of tumor recurrence producing visual field changes or radiographic abnormalities.

The anterior pituitary gland produces three glycoprotein hormones: thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). These glycoprotein hormones are composed of two subunits, alpha and beta. The isolated subunits are not biologically active; alpha and beta must be combined into the intact hormone to produce a hormonal response. The alpha subunit of all three pituitary glycoprotein hormones is immunologically identical, and can easily be measured in the sera of normal men and women. The beta subunits of these hormones are different, and determine the biological specificity of the intact hormone. Increased amounts of alpha subunit in the serum can be found in hypothyroidism or menopause when TSH or LH and FSH are greatly increased. Pituitary tumors secreting abnormal amounts of alpha subunit together with increased amounts of TSH, LH, PRL, or growth hormone have been described.

We have recently reported two men with pure alpha subunit-secreting pituitary tumors in whom immunological and gel chromatographic studies determined that only the alpha subunit was present. In these two patients, the alpha subunit was the only demonstrable tumor marker and was valuable in the postoperative management of these patients. In this report, we describe a total of six patients with pure alpha-secreting pituitary adenomas.

Clinical Material and Methods

Assays

Serum levels of TSH and alpha subunit were measured as described previously. For alpha subunit, the detection limit of the assay was 0.5 ng/ml. The
cross-reactions of TSH, LH, and FSH in the alpha assay were 2.5% to 3.0% when purified intact hormones were used. The cross-reaction of alpha (National Pituitary Agency (NPA) Parlow 745A) in the TSH assay was 2%. Normal subjects have alpha subunit levels of 0.5 to 2.5 ng/ml; patients with primary hypothyroidism and menopausal women may have levels as high as 5 ng/ml, in association with elevated levels of TSH, LH, or FSH.

**Gel Chromatography**

A 2-ml serum aliquot from Case 6 was analyzed by chromatography on a Sephadex G-100 column (1.5 × 76 cm).* The column was calibrated with iodine-125 (125I) and labeled thyroglobulin, TSH, LH, and alpha. The columns were equilibrated at 4°C and eluted with 0.01 M sodium phosphate, 0.15 M sodium chloride, and 0.003 M sodium azide (pH 7.4) at a hydrostatic pressure of 15 cm H2O and a flow rate of 7 ml/hr. Fractions of 1 or 2 ml were collected and assayed at various dilutions for alpha, TSH, or LH. Partition coefficients (Kav) were calculated with the formula Kav = Ve - Vo/Vt - Vo, where Ve represents the initial tube of the hormone fraction, Vo the initial tube of the void-volume fraction as determined with labeled thyroglobulin, and Vt the initial tube of the 125I fraction. The initial tube of each fraction was used in the calculation instead of the peak tube because of the broad nature of the hormone peaks.

**Tumor Immunocytochemistry**

Immunocytochemical analysis was performed on tumor tissue obtained during transsphenoidal surgery using specific antibodies to PRL, growth hormone, alpha, TSH-β, LH-β, and FSH-β by previously described techniques.19,20

### Clinical Data

The age, sex, visual fields, therapy, and medications of the six patients are shown in Table 1. Cases 5 and 6 have been described in greater detail in a previous report.17 The patients were 54 to 71 years of age (median 63 years). There were five males and one female. All six patients had visual field abnormalities at the time of initial presentation. All of the patients had radiological studies confirming the presence of a large intrasellar mass with suprasellar extension. Five of the six patients (Cases 1, 2, 4, 5, and 6) underwent transsphenoidal surgery, and one patient (Case 6) had repeat transsphenoidal surgery because of tumor recurrence and the development of a new visual field defect. One patient (Case 3) underwent two craniotomies. All of the six patients received radiotherapy. Four of the six patients were found to be hypothyroid and were receiving thyroid replacement therapy. All of the males with the exception of Case 2 were found to be hypogonadal. Case 1 had received testosterone enanthate, 100 mg intramuscularly every 10 days, since 1964, and Case 5 had received testosterone enanthate, 200 mg intramuscularly every 2 or 3 weeks, since 1979. The serum thyroxine, testosterone, LH, and FSH concentrations, as well as basal and TRH-stimulated TSH and PRL concentrations are shown in Table 2.

### Results

**Serum Alpha Concentrations**

The basal serum alpha concentrations in all six patients were markedly elevated above the upper limits of

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* TABLE 1

**Clinical data in six patients with pituitary tumors**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Visual Fields</th>
<th>Therapy</th>
<th>Medications*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54, M</td>
<td>bitemporal hemianopsia</td>
<td>1964: radiotherapy 1981: transsphenoidal surgery</td>
<td>Synthroid (levothyroxine) 0.2 mg; cortisone acetate 25 mg each a.m., 12.5 mg each p.m.; testosterone enanthate 100 mg IM each 10 days</td>
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<tr>
<td>2</td>
<td>62, M</td>
<td>bitemporal hemianopsia</td>
<td>1980: transsphenoidal surgery</td>
<td>prednisone 5 mg each a.m., 2.5 mg each p.m.</td>
</tr>
<tr>
<td>3</td>
<td>55, F</td>
<td>rt homonymous hemianopsia</td>
<td>1978: left frontotemporal craniotomy 1978: radiotherapy 5000 rads 1979: left temporal craniotomy</td>
<td>Synthroid 0.1 mg</td>
</tr>
<tr>
<td>4</td>
<td>71, M</td>
<td>rt temporal defect</td>
<td>1975: transsphenoidal surgery 1979: radiotherapy 5000 rads 1959: cobalt irradiation 3500 rads</td>
<td>Synthroid 0.05 mg; prednisone 5 mg each a.m., 2.5 mg each p.m.</td>
</tr>
<tr>
<td>5</td>
<td>64, M</td>
<td>bitemporal hemianopsia</td>
<td>1980: transsphenoidal surgery</td>
<td>Synthroid 0.1 mg; testosterone enanthate 200 mg each 3 wks</td>
</tr>
<tr>
<td>6</td>
<td>67, M</td>
<td>right superior temporal defect</td>
<td>1980: radiotherapy 4500 rads</td>
<td>prednisone 5 mg each a.m.</td>
</tr>
</tbody>
</table>

* IM = intramuscularly.
## TABLE 2

Endocrine studies in six patients with pituitary tumors

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Time of Test</th>
<th>Thyroxine (μg/dl)</th>
<th>Testosterone (ng/dl)</th>
<th>TRH Stimulation</th>
<th>LH (mIU/ml)</th>
<th>FSH (mIU/ml)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alpha (ng/ml)</td>
<td>Basal Peak</td>
<td>Basal Peak</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TSH (μU/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PRL (ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>postoperative (1 mo)</td>
<td>6.6</td>
<td>--</td>
<td>4.5</td>
<td>8.7</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>preoperative</td>
<td>5.9</td>
<td>403</td>
<td>4.1</td>
<td>6.5</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>postoperative (1 mo)</td>
<td>7.6</td>
<td>489</td>
<td>1.8</td>
<td>2.1</td>
<td>0.7</td>
</tr>
<tr>
<td>4</td>
<td>before 1st operation</td>
<td>6.7</td>
<td>--</td>
<td>7.5</td>
<td>11.2</td>
<td>5.3</td>
</tr>
<tr>
<td>5</td>
<td>after 1st operation (6 mos)</td>
<td>11.0†</td>
<td>--</td>
<td>&lt;0.8</td>
<td>--</td>
<td>4.0</td>
</tr>
<tr>
<td>6</td>
<td>after 2nd operation (1 mo)</td>
<td>18.6†</td>
<td>--</td>
<td>1.4</td>
<td>--</td>
<td>--</td>
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<tr>
<td>4</td>
<td>postoperative (6 yrs)</td>
<td>6.6</td>
<td>430</td>
<td>5.4</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>preoperative</td>
<td>1.9</td>
<td>111</td>
<td>9.6</td>
<td>10.0</td>
<td>7.1</td>
</tr>
<tr>
<td>6</td>
<td>postoperative (1 yr)</td>
<td>1.6</td>
<td>94</td>
<td>4.3</td>
<td>4.8</td>
<td>3.6</td>
</tr>
<tr>
<td></td>
<td>before 2nd operation</td>
<td>7.7†</td>
<td>111</td>
<td>5.0</td>
<td>5.6</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td></td>
<td>after 2nd operation</td>
<td>5.4</td>
<td>57</td>
<td>5.7</td>
<td>5.5</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td></td>
<td>normal levels</td>
<td>4.5</td>
<td>14</td>
<td>2.4</td>
<td>3.6</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td></td>
<td>300-1100</td>
<td>0.5-2.5</td>
<td>0.5-2.1</td>
<td>0.5-3.5</td>
<td>5.5-18.3</td>
<td>&lt;10</td>
</tr>
<tr>
<td></td>
<td>0.5-5.0†</td>
<td>2.0-5.0†</td>
<td>30-250†</td>
<td>40-250†</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* TRH = thyroid-releasing hormone; TSH = thyroid-stimulating hormone; PRL = prolactin; LH = luteinizing hormone; FSH = follicle-stimulating hormone.
† Patient receiving L-thyroxine therapy.
‡ Normal values for postmenopausal therapy.

Normal for control men and women (2.5 ng/ml). Basal and TRH-stimulated serum alpha concentrations are shown in Table 2. The preoperative alpha level in the only female patient (Case 3) was above the upper limit of normal for menopausal women (5 ng/ml). Basal serum alpha concentrations in the male patients ranged from 4.1 to 9.6 ng/ml (median 5.6 ng/ml). Following transsphenoidal surgery, serum alpha concentrations decreased from 4.1 to 1.8 ng/ml, 9.6 to 4.3 ng/ml, and 5.7 to 2.4 ng/ml in Cases 2, 5, and 6, respectively. Case 3 was treated with both a craniotomy and postoperative radiotherapy, and the serum alpha concentration decreased from 7.5 to 1.4 ng/ml after 2 years.

There was a variable response of alpha subunit in these patients following TRH stimulation. Case 1 showed an increase in serum alpha levels from 4.5 to 8.7 ng/ml, despite complete suppression of the serum TSH concentration on thyroid hormone therapy. In the preoperative period, Case 2 had a rise in serum alpha levels from 4.1 to 6.5 ng/ml following TRH stimulation, without a response in TSH. Postoperatively, TSH showed a response to the alpha peak; however, alpha was unresponsive. Case 3 showed an increase in alpha subunit from 7.5 to 11.2 ng/ml in association with a hyper-response of TSH. Cases 5 and 6 were unresponsive to TRH stimulation.

### Serum Gel Chromatography

The results of the gel chromatographic analysis of 2 ml of serum from Case 5 are shown in Fig. 1. Immunoactive alpha (Kav, 0.43 to 0.47) co-migrated with labeled alpha (Kav, 0.43; range 0.40 to 0.47). Immunoactive TSH was detectable in the serum fractions (Kav, 0.31; serum TSH 7.1 μU/ml) in a peak distinct from the alpha response, and the immunoactive TSH co-eluted with standard labeled TSH (Kav, 0.27). Immunoactive LH (Kav, 0.50) corresponded to the alpha peak.

### Tumor Immunocytochemistry

Immunocytochemical analysis was performed on the tumor tissue previously obtained at transsphenoidal surgery from Cases 1, 2, 5, and 6. In all four cases, the tumor tissue stained for alpha subunit. Immunocytochemical staining on the tumor tissue from Case 6 is shown in Fig. 2. The tumor tissue reacted positively for alpha, but not for prolactin, growth hormone, LH-β, FSH-β, or TSH-β.

### Discussion

Pituitary tumors secreting the intact glycoprotein hormones, TSH, LH, and FSH are rare but well described. These patients, who were previously thought to have "non-functioning chromophobe adenomas," hypersecreted only the alpha subunit of the glycoprotein hormones. Characteristically, all the patients had large pituitary adenomas with suprasellar extension producing visual field defects. Five of the six patients were male. All of the patients had evidence of partial hypopituitarism, and four of the five men had evidence of hypogonadism. All of the male patients underwent pituitary surgery, and all six in this series had a course of radiotherapy. In all of the patients an elevation of the serum alpha subunit level was the only tumor marker present, and measurement of postoperative serum alpha concentra-

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tion was helpful in their management. The presence of alpha in the serum and tumor tissue was confirmed by gel chromatography, and the alpha subunit present in the tumor specimen was immunologically identical to that found in the patient's serum. Analysis of a patient's serum in this report by gel chromatography revealed that the immunoactive alpha co-migrated with labeled alpha, which was distinct from both immunoactive TSH and labeled LH. Furthermore, immunocytochemical staining of the tumor tissue from four patients was consistent with secretion of alpha by the tumor.

Pituitary tumors hypersecreting the alpha subunit together with other pituitary hormones have also been reported in approximately 10% of patients with demonstrable pituitary tumors. Typically, alpha subunit secretion in these patients is autonomous and unresponsive to stimulation by TRH or suppression by thyroid hormone. In contrast to this, increased alpha concentrations associated with an increase in TSH and gonadotropins in primary hypothyroidism or menopause are stimulated by hypothalamic-releasing hormones or suppressed by thyroid or sex-steroid hormones.

In our patients, who were secreting high levels of alpha subunit alone, there were variable responses of the alpha subunit to TRH stimulation. Two of the patients demonstrated alpha stimulation by TRH unaccompanied by an increase in TSH. However, alpha secretion could not be suppressed in those patients receiving replacement doses of thyroid hormone. This suggests that in the tumor patients described, alpha subunit secretion is increased and relatively autonomous to normal hormonal regulation.

The diagnostic evaluation of patients with prolactin-secreting pituitary tumors, acromegaly, and Cushing's disease is dependent upon typical clinical presentations associated with characteristic hormone measurements. Patients with "non-functioning adenomas" who do not produce known biologically active hormones have been difficult to diagnose since they lack well defined clinical syndromes. Alpha subunit secretion may be abnormal in some of these patients. Determination of serum alpha concentrations will help to identify these patients and thereby contribute to a rational program of management.

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References

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