Normalization of Thyroid Stimulating Hormone Levels in Acromegalic Patients after Selective Adenectomy

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Abstract

Changes in TSH secretion in six acromegalic patients were studied before and after transsphenoidal adenectomy (Hardy's method) and compared to normal subjects and six patients with prolactinoma. Basal serum GH levels ranging from 5 to over 250 ng/ml before adenectomy decreased to below 5 ng/ml after the operation, and the abnormal responses of GH to TRH observed initially in three of the six patients almost disappeared in the post-adenectomy period. The response of serum TSH to TRH in acromegalic patients improved in each of the six patients after the operation. The TRH-stimulated TSH secretion in patients with prolactinoma of a size and grade similar to those in acromegalic patients was not so extremely low as that in the acromegalic subjects. As indicators of thyroid function, serum triiodothyronine (T₃), thyroxine (T₄), T₃-uptake levels and free T₄ indices did not change significantly after adenectomy as compared with those before the operation in five of the six patients tested. Serum T₃, T₄ and T₃-uptake levels and free T₄ indices before adenectomy were normal or subnormal in each patient except for a high serum T₄ level and free T₄ index before the operation in only one patient. Thus, it is difficult to conclude that the function of thyrotrophs was decreased by pressure upon the intact pituitary gland by the tumor, or that the thyroid gland also became hypertrophic secondary to the elevated GH, resulting in a large quantity of thyroid hormone being secreted, which caused a suppression of TSH secretion by negative feedback. The data suggest instead that the secretion of GH and TSH from the intact pituitary gland is inhibited due to the autonomous production of excessive GH from the tumor, which may also suppress growth hormone releasing factor secretion and accelerate SRIF secretion from the hypothalamus.

The response of serum TSH to TRH is diminished in acromegalic patients (Sakoda *et al.*, 1970; Karlberg *et al.*, 1971; Gual *et*

al., 1972; Hall *et al.*, 1972; Irie *et al.*, 1972; Kumahara *et al.*, 1975). Pressure on the normal pituitary gland by a pituitary tumor or the effect on TSH secretion of excessive secretion of GH is considered to be the cause of the decreased TSH secretion in acromegalic patients. In this investigation we report the changes in TSH secretion in acromegalic patients before and after adenomectomy and compared the results with normal subjects and patients with prolactinoma.

Materials and Methods

Subjects

Six patients with acromegaly (patient number 1–6) were studied (Table 1). The tumor in each patient was determined to be an intrasellar microadenoma. None except patient No. 5 had received therapy prior to surgery. Six normal subjects matched in age and sex served as controls, and six women (aged 24–50 yr) with hyperprolactinemia and pituitary microadenomas whose prolactin level ranged from 118 to 325 ng/ml, were examined for the purpose of comparison with the acromegalic patients.

Laboratory Examinations

Insulin tolerance tests (ITT: 0.1 U/kg BW, MC Novo Actrapid, iv) were conducted on each of the acromegalic patients before and approximately two weeks after surgery. TRH tests (500 µg, iv) also were performed before, approximately two weeks after, and three months after their operations. We also performed TRH tests to measure serum TSH in six normal subjects and six patients with prolactinoma. Serum GH, TSH, T₃ and T₄ were measured by radioimmunoassay using commercial kits (GH: Dainabot RI Lab., Tokyo, TSH: Daiichi Radioisotope Lab., Tokyo, T₃, T₄: Eiken Immunochemical Lab., Tokyo), and T₃-uptake was measured by a T₃U-MAA kit (Amersham International).

Table 1. Laboratory data for six acromegalic patients before and after adenomectomy.

Patient number	Age (yr)	Sex	Basal serum GH (ng/ml)		Serum T ₃ (ng/dl)		Serum T ₄ (µg/dl)		T ₃ -uptake (%)		Free T ₄ index		Basal serum TSH (µU/ml)		Peak serum TRH injection (µU/ml)		TSH after before after*	
			before	after	before	after	before	after	before	after	before	after	before	after	before	after	before	after
1	42	F	25.4	2.7	129.0	93.0	8.4	7.3	26.0	31.3	7.5	7.9	2.0	2.4	10.0	13.5		
2	43	F	38.0	3.9	75.0	95.0	4.3	4.1	27.9	28.3	4.1	4.0	<2.2	1.3	4.3	6.0		
3	47	M	231.0	4.8	51.0	115.0	7.2	7.4	27.3	29.2	6.8	7.5	<1.0	3.4	4.6	12.4		
4	52	M	280.0	1.4	85.0	98.0	7.6	7.7	28.7	29.7	7.5	7.8	<1.2	<1.2	4.1	7.4		
5	50	M	8.1	4.5	NM	106.0	NM	6.9	NM	NM	NC	NC	<1.0	NM	5.2	NM		
6	34	M	50.0	<1.2	159.0	178.0	13.0	11.8	28.4	28.8	12.7	11.7	<1.0	2.7	6.1	18.0		
Mean					99.8	114.2	8.1	7.5	27.7	29.5	7.7	7.8						
±SD					±43.5 ^a	±32.3 ^a	±3.1 ^b	±2.5 ^b	±1.1 ^c	±1.2 ^c	±3.1 ^d	±2.7 ^d						

* Three months after adenomectomy.

NM, Not measured. NC, Not calculable.

^{a,b,c,d} Statistically not significant in each (by either Student's *t*-test or the paired *t*-test).

Results

The high basal level of serum GH in each acromegalic patient decreased to a level less than 5 ng/ml after adenomectomy. The levels of GH secretion after insulin administration to the patients before and after adenomectomy are shown in Fig. 1. The response of GH to insulin hypoglycemia was not observed in any of the subjects before or after surgery. Fig. 2 shows the GH secretion after TRH administration in

each of the six acromegalic patients before and after adenomectomy. A rise in the GH level after TRH administration was observed in three (patients 3, 5 and 6) of the six patients. The almost complete disappearance of a GH response to TRH in these three patients indicated that their pituitary adenomas were almost completely removed.

Fig. 3 shows the mean TSH levels after TRH administration (mean $\pm$ SD) of the six acromegalic patients before adenomectomy, six patients with prolactinoma before operative therapy and six normal controls. The

Fig. 1. GH secretion before and after adenomectomy during insulin-induced hypoglycemia in six acromegalic patients. The patient number is indicated below each panel. Values before surgery were not obtained in patient No. 2. ●—●, Before surgery; ●---●, two weeks after surgery.

levels of TRH-stimulated TSH were significantly lower in the acromegalic patients than in those of normal subjects ($p < 0.01$) and the patients with prolactinoma ($p < 0.05$). The levels of TRH-stimulated TSH in the six acromegalic patients before, about two weeks after, and three months after adenomectomy are shown in Fig. 4. Each patient showed a stronger response to TRH after, rather than before, adenomectomy. Only patient No. 2 showed a weaker response two weeks after the operation.

In three of five patients studied, the

serum T_3 level before adenomectomy was lower than the lowest limit for those of normal subjects. Serum T_3 concentrations increased after the operation in all patients studied except patient No. 1, whose serum T_3 level was within the normal range initially (Fig. 5). The serum T_4 level and free T_4 index did not change significantly after adenomectomy in each of the five patients studied (Table 1). T_3 -uptake levels were all within the normal range both before and after surgical treatment, although each increased slightly (Fig. 5).

Fig. 2. GH secretion before and after adenomectomy after TRH injection in six acromegalic patients. The patient number is indicated below each panel. ●—●, Before surgery; ●---●, two weeks after surgery.

Fig. 4. TSH secretion before and after adenomectomy after TRH injection in six acromegalic patients. The patient number is indicated below each panel. Values for three months after surgery were not obtained for patient No. 5. ●—●, Before surgery; ●---●, two weeks after surgery; ○—○, three months after surgery.

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Fig. 3. TSH secretion after TRH injection in acromegalic patients, patients with prolactinoma and normal subjects. Each point is represented as mean ± SD. ●—●, Acromegalic patients before surgery (n=6); ●---●, patients with prolactinoma before surgery (n=6); ○—○, normal subjects (n=6). ^ap < 0.05; ^bp < 0.01.

Discussion

Some acromegalic patients with a normal serum GH level continue to show an abnormal GH response to TRH even after surgical therapy (Samaan *et al.*, 1974; Giovanelli *et al.*, 1976). Because the serum GH response to TRH is believed to be mediated by a direct pituitary action of TRH which probably is exerted on abnormal receptors of the adenomatous somatotrophs (Faglia *et al.*, 1973; Giustina *et al.*, 1974; Hoyte and Martin, 1975; De Camilli *et al.*, 1976), the patients who persistently respond abnormally to TRH are not to be regarded as cured. The disappearance of the abnormal GH response to TRH after surgery probably indicates satisfactory treatment of acromegaly (Faglia *et al.*, 1978). In this study, the basal serum GH level dropped to less than 5 ng/ml after surgery and abnormal GH response to TRH disappeared (Fig. 2). These findings indicate that a nearly complete resection of the pituitary adenoma was obtained. Serum GH did not

Fig. 5. Thyroid functions in five acromegalic patients before and three months after adeno-mectomy. Shaded areas indicate normal ranges. ●—●, patient No. 1; ○—○, patient No. 2; ■—■, patient No. 3; □—□, patient No. 4; ▲—▲, patient No. 6.

Fig. 6. The possible mechanism by which GH and TSH secretion from the intact pituitary gland is suppressed in acromegalic patients.

increase with insulin hypoglycemia even after surgery in these patients (Fig. 1). These results indicate that GH secretion from the intact part of the pituitary gland is impaired in acromegalic patients.

A decrease in TSH has been observed more frequently in acromegalic patients (68%) than in patients with prolactinoma (36%) (Miyai and Uozumi, 1976). Although the response of TSH to TRH was decreased before adenectomy in our patients, the TSH response improved after the operation. The secretion of TSH is regulated mainly by the level of circulating thyroid hormones and by TRH. Somatostatin infusion has been found to suppress TSH secretion in normal subjects (Hall *et al.*, 1973; Siler *et al.*, 1974; Weeke *et al.*, 1974) and in patients with hypothyroidism (Lucke *et al.*, 1975). Elevation of the basal TSH level following administration of somatostatin antiserum has been observed in rats (Arimura *et al.*, 1976; Ferland *et al.*, 1976). These findings indicate that somatostatin has an inhibitory effect on TSH secretion.

The mechanisms by which TSH secretion decreases in acromegaly are not clarified yet. Possible explanations include (i) an adenoma may decrease the function of thyrotrophs by a pressure upon a normal pituitary gland, (ii) the thyroid gland that is often hypertrophic in acromegalic patients may secrete excessive thyroid hormones and result in the suppression of TSH secretion by negative feedback, and (iii) a raised hypothalamic somatostatin level due to increased GH secretion from the pituitary adenoma of acromegalic patients may inhibit TSH secretion, as well as GH secretion from the intact part of the pituitary gland.

If the first hypothesis is correct, the TRH-stimulated TSH concentration in patients with prolactinoma should be as low as in acromegalic patients. However, the patients with prolactinoma showed a stronger TSH response to TRH than the acromegalic patients, as shown in Fig. 3. The second

possibility is unlikely because the serum T_3 and T_4 levels were normal or subnormal in all the patients except patient No. 6 (Fig. 5). The secretion of GH and TSH from the intact pituitary gland may be inhibited by increased somatostatin secretion from the hypothalamus. The excessive GH that is secreted from a tumor may suppress GRF secretion and accelerate somatostatin secretion from the hypothalamus (Fig. 6). It is also possible that the improvement in TSH secretion after surgery, when the GH level dropped to below 5 ng/ml, may be due to a release from the inhibitory effect of somatostatin.

There have been many reports which support the last hypothesis. Berelowitz *et al.* (1981) reported that the somatostatin content in the hypothalamus was distinctly increased and the capability of somatostatin secretion *in vitro* was increased compared with controls when GH was administered to rats. However, the ability to secrete somatostatin from the hypothalamus decreased when an adenectomy was performed or GH antiserum was administered. Furthermore, it has been shown that the somatostatin concentration in pituitary portal blood rises when GH is administered to the third ventricle of the rat (Chihara *et al.*, 1981). These results indicate that at least some of the negative feedback mechanisms involved in GH secretion are caused by a variation in hypothalamic somatostatin.

Lippe *et al.* (1975) reported that in four of six children with idiopathic GH deficiency who became hypothyroid during treatment with exogenous GH, TRH-stimulated TSH concentrations were either absent or reduced.

In this context it has been postulated by Hall *et al.* (1978) that GH may induce the synthesis and release of somatostatin via a short-loop positive feedback, and that the increased endogenous level of somatostatin would in turn suppress both GH and TSH release.

Three of the six patients had a serum

T_3 level lower than normal (Fig. 5). We could not find a correlation between the serum T_3 level and the response of TSH to TRH. Klijn *et al.* (1980) compared the functions of the pituitary-thyroidal axis in acromegalic patients and patients with hyperprolactinemia and a pituitary tumor. They found a positive correlation between the TRH-stimulated TSH concentration and T_3 level but not between the TRH-stimulated TSH concentration and the T_4 level in the patients with prolactinoma, while in the acromegalic patients there was no correlation between TSH reserve and the level of T_3 or T_4 . Serum T_3 , T_4 , T_3 -uptake levels and free T_4 indices did not change significantly after adenomectomy as compared with those before the operation in five of the six patients studied, although all of the patients were almost completely cured by the operation (Table 1 and Fig. 5). Therefore, the impaired TSH secretion may scarcely affect thyroid function in acromegalic patients.

The decreased TSH secretion in acromegalic patients may be due to increased secretion of hypothalamic somatostatin caused by an excess of GH. If one can measure the levels of somatostatin and GRF in the hypothalamus and pituitary portal blood in acromegalic patients, it will be helpful in verifying this.

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