Resistance of Peripheral Tissues and Pituitary to Thyroid Hormone

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Abstract

We describe a 29-year-old male with thyroid hormone resistance. He was first seen because of a goiter, and was considered to have hyperthyroid Graves’ disease. Despite subtotal thyroidectomy followed by radioiodine therapy, serum thyroxine levels were elevated with high serum TSH levels. Baseline thyroid function showed serum thyroxine of 16.6 μg/dl, free thyroxine of 4.60 ng/dl, triiodothyronine of 197 ng/dl, and TSH of 34 μU/ml. Triiodothyronine administration by gradually increased doses of 75, 150, 225, 300, and 375 μg/d over a 25-day period resulted in gradual reduction of serum TSH and T4 levels, but serum TSH still responded to TRH even during this period. The basal metabolic rate was −4% and showed a minimal rise even with large doses of triiodothyronine. The results led to the diagnosis of generalized thyroid hormone resistance including the pituitary gland. Increased pulse rate, finger tremor and emotional lability in the patient suggest that the severity of peripheral refractoriness to the hormone may vary from tissue to tissue. In addition, a reduced thyroidal responsiveness to TSH as a consequence of inappropriate radioiodine therapy was observed in this patient.

Pseudohypoparathyroidism caused by target organ refractoriness to parathyroid hormone was first described by Albright et al. in 1942. Since then, several diseases resulting from insensitivity of peripheral tissue to the hormone have been reported. The syndrome of thyroid hormone resistance was first described by Refetoff et al. (1967). As patients with such a syndrome are being reported with increasing frequency, the heterogeneity in clinical manifestations of the syndrome is now recognized.

The patient described here showed resistance of peripheral tissues and pituitary to thyroid hormone, but presented an increased resting pulse rate and finger tremor. This paper describes the first adult patient with thyroid hormone resistance in Japan, and the clinical features are discussed.

Case Report

A 29-year-old man was first seen in March 1978 at the Kuma Hospital because
of a large goiter. He had been treated with 30 mg of methimazole daily for six months because toxic goiter was considered. There was no history of earlier thyroid disease. His triiodothyronine (T3) resin-uptake was 21.9% with methimazole therapy, and thyroid radioactive iodine uptake (RAIU) was 60% at 24 hr. After administration of 75 μg of exogenous T3 for ten days, his RAIU at 24 hr was not suppressed (44%). He was then considered to have Graves' disease, and underwent subtotal thyroidectomy in April 1978. One hundred-thirty grams of thyroid tissue was resected and 30 g left in the neck.

Two years after surgery, serum levels of thyroxine (T4), T3, TSH and RAIU were 21.1 μg/dl, 193 ng/dl, 10 μU/ml and 35%, respectively. He was considered to have recurrent Graves' disease although the cause of the increase in serum TSH levels was not known, and received 2.5 mCi of radioiodine in June 1980. One year after the radioiodine therapy, serum T4, T3 and TSH levels were 14.5 μg/dl, 184 ng/dl and 53 μU/ml respectively. The inappropriately elevated levels of serum TSH, despite high levels of serum T4 and T3, persisted during the 3-year follow-up period. Therefore, the patient was admitted to the Osaka Medical College Hospital in January 1982 for further evaluation.

His height was 165 cm and weight 58 kg. He was nervous and restless. There was a fine tremor of the fingers. Blood pressure was 138/80 mmHg, and the resting pulse rate was 96/min. The remnant of thyroid gland which seemed to have enlarged symmetrically, was palpable in the neck. There were no signs of Graves' ophthalmopathy. The relaxation period of the achilles tendon reflexes was shortened.

Analytical Methods

Serum T4 and T3 concentrations were measured by RIA (Daiichi Radioisotope Co, Tokyo). Serum free T4 level was measured by RIA (Amersham Medical Limited, Tokyo). Serum T4-binding globulin level was also measured by RIA (Midorijuji Co, Tokyo). Serum TSH level was measured by a double-antibody RIA method (Eiken Co, Tokyo). Serum TSH receptor antibody activity was measured with a radioreceptor assay kit (Clinical Assay Co, Cambridge, MA). BMR was measured upon awakening at 8 AM using a Sanborn-type Metamodulator (Fukuda Denshi Co, Tokyo). All serum samples for an individual hormone were measured at the same time.

Results

Baseline study

The results of baseline thyroid function test are listed in Table 1. No antibodies to thyroglobulin or microsomes were detected. Other routine laboratory findings were within normal ranges.

Table 1. Thyroid study in January 1982

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4, μg/dl</td>
<td>16.6</td>
</tr>
<tr>
<td>Free T4, ng/dl</td>
<td>4.60</td>
</tr>
<tr>
<td>T3, ng/dl</td>
<td>197</td>
</tr>
<tr>
<td>T4-binding globulin, μg/ml</td>
<td>25.2</td>
</tr>
<tr>
<td>TSH, μU/ml</td>
<td>34</td>
</tr>
<tr>
<td>Peak TSH after TRH, μU/ml</td>
<td>210</td>
</tr>
<tr>
<td>TSH receptor antibody activity</td>
<td>negative</td>
</tr>
<tr>
<td>RAIU 24 h, %</td>
<td>25</td>
</tr>
<tr>
<td>BMR, %</td>
<td>−14</td>
</tr>
<tr>
<td>Cholesterol, mg/dl</td>
<td>169</td>
</tr>
<tr>
<td>Alkali Phosphatase, mU/ml</td>
<td>76</td>
</tr>
</tbody>
</table>

Effect of T3 administration

The patient was then placed on increasing doses of T3. As shown in figure 1, serum TSH and T4 decreased with increasing levels of serum T3. RAIU was insufficiently suppressed from 25% to 14% by 75 μg of T3 daily. The BMR failed to increase during the course of T3 administration. A modest decline in serum cho-
Lesterol levels was observed during this period. The resting pulse rate did not increase during the period, and other physical signs including finger tremor and nervousness did not change even at a daily dose of 375 μg.

**Response to TRH**

Five hundred micrograms of TRH was injected serially before and during T3 administration. As shown in Figure 2, serum TSH strikingly increased to 210 μU/ml of the peak value before T3 therapy. This hyperresponse of TSH to TRH was still observed even while he was taking 75 or 150 μg of T3 daily.

**Thyroid Pathology**

Histological examination of the thyroid tissue obtained by surgery revealed enlarged follicles with abundant colloid mimicking diffuse epithelial hyperplasia of Graves' disease. It also showed a papillary proliferation of follicular epithelium (Figure 3).

**Other studies**

Administration of prednisolone, 30 mg per day for one month reduced serum TSH levels of basal and peak after TRH infusion, to 26 and 120 μU/ml, respectively. Administration of 5 mg of bromocriptine per day for one month failed to alter the thyroid function indices. Radiological examination...
results for the sella turcica were normal. All other pituitary hormones including LH, FSH, PRL, GH and ACTH responded normally to LHRH, TRH and insulin hypoglycemia. His parents were the only family members who consented to the study. Both had normal serum T4, T3 and TSH concentrations. None of his three siblings were known to have goiters or thyroid disease.

Discussion

The co-existence of increased serum T4 levels and high serum TSH levels in this patient indicated inappropriate secretion of TSH (Weintraub et al., 1981). The normal radiological findings for the sellar region and positive response of serum TSH to TRH infusion negated the possibility of a TSH-producing pituitary tumor. The minimal metabolic changes with a subnormal level of BMR during T3 administration suggested insensitivity of the target organ to thyroid hormone. These results led to the diagnosis of generalized (peripheral tissues and pituitary) resistance to thyroid hormone.

The patient had tachycardia, finger tremor and nervousness, which mimicked manifestations of thyrotoxicosis. It is intriguing that some of the reported patients with global resistance to thyroid hormone have shown an increasing pulse rate, finger tremor and emotional lability. From our retrospective analysis of 26 cases with this syndrome reported by some investigators (Table 2), tachycardia was present in 12 patients (46%). Also, finger tremor and nervousness was observed in 4 (15%) and 6 (23%) of the patients, respectively. The hypothesis propounded by Murata et al. (1983) seems to be inappropriate to explain the paradoxical clinical features: the severity of peripheral refractoriness varies from tissue to tissue. From our analysis, the myocardium of approximately half the number of the patients who presented tachycardia may be less resistant to the hormone. A similar...
mechanism may be considered in regard to the adrenergic nervous system in patients who had tremulousness or emotional lability. Failure to increase the pulse rate in this patient during administration of T3 may have resulted from most of the myocardial receptors to T3 being bound under baseline thyroid hormone concentrations.

The serum T4 level of 16.6 μ/dl in the patient was approximately twice as great as the mean normal value, while the serum T3 level of 197 ng/dl showed a minimal increase to the higher normal limit. Wortsman et al. (1983) reported a familial syndrome with high serum T4 levels and normal serum T3 levels which was caused by selective T4 resistance. This patient differed from their cases, because he apparently was resistant to T3. A possible pathogenesis is that peripheral metabolism between T4 and T3 is different: T3 is degraded more rapidly than T4. Kinetic studies of T4 and/or T3 have been performed in some cases and showed variable degrees of increased degradation (Refetoff et al., 1972, Lamberg et al., 1973, Schneider et al., 1973, Seif et al., 1978 and Tamagna et al., 1979). Another possibility is that chronic actions of excess TSH may provide preferable T4 secretion, considering the fact that the thyroid gland of this patient was chronically stimulated by TSH due to defective thyroid hormone feedback regulation. Further studies to explain T4-predominance in the patient are required.

Subtotal thyroidectomy and radiiodine therapy administered to this patient were apparently due to lack of recognition of
the syndrome of thyroid hormone resistance. The radioiodine therapy resulted in the drop in the serum T4 level. This change indicated a reduced thyroidal reserve caused by the reduced functioning mass due to radioiodine therapy. Serum T4/TSH ratios ($\mu g/\mu U \times 100$) were calculated to determine the magnitude of thyroidal responsiveness to TSH stimulation. The ratios in this patient, before and after radioiodine therapy were 2.11 and 0.27, respectively. Thus, the response of thyroid to TSH may have been altered by the inappropriate therapy. A similar phenomenon was documented by Refetoff et al. (1983).

The syndrome of thyroid hormone resistance is being reported with increasing frequency. Recognition of the disease is important in avoiding inappropriate treatment due to erroneous diagnosis (Refetoff et al., 1983). Since almost all patients have inappropriate TSH secretion, measurement of serum TSH and, in some cases, a TRH stimulation test are recommended for patients with a diffusely hyperactive thyroid gland to obtain the correct diagnosis.

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