Thyroid Function During the Spontaneous Course of Subacute Thyroiditis

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A study of changes in serum T4, T3, and Tg as well as of serum TSH response to TRH was done in ten patients with subacute thyroiditis, from the acute phase up to 56 mo. All patients had symptoms of thyrotoxicosis. The mean ± s.e.m. serum T4 (21.6 ± 8.2 μg/dl), T3 (315 ± 191 ng/dl) and Tg (149 ± 52 ng/ml) concentrations were significantly higher than in normal subjects (8.5 ± 1.7 μg/dl, 136 ± 34 ng/dl, and 10.5 ± 1.0 ng/ml, respectively). The basal TSH concentrations failed to increase in response to TRH. Mean serum T3 and serum Tg levels remained higher than in normal subjects until 4 to 5 mo after the acute phase. However, normalization of clinical status and serum thyroid hormone levels did not coincide with the normalization of serum Tg levels. Thyroid autoantibodies were absent during the whole period of study. An exaggerated response of TSH to TRH in six out of seven patients was observed from a 2 to 3 mo period until the end of follow-up. All patients with T3 to T4 ratio above the normal range (7–24 ng/μg) showed also an exaggerated response of TSH to TRH. These data suggest that the spontaneous course of subacute thyroiditis may lead to a low thyroid reserve detectable even 5 yr following the acute phase of the disease.


Subacute thyroiditis has a clinical course, evolving from hyperthyroidism through a temporary hypothyroidism to recovery (1–3). After recovery, subacute thyroiditis almost always achieves the euthyroid state. However, the final outcome of this disease remains unpredictable in some patients. Permanent hypothyroidism infrequently occurs; it has been observed in up to 10% of the cases (4) and in the presence of thyroid autoantibodies (3,5). Some loss of thyroid reserve may occur in about 30% of patients when studied by the thyrotropin-releasing hormone- (TRH) test in a long-term follow-up (6,7). It should be pointed out that in many of these studies, observations were made in the patients receiving medications which interfere with thyroid function tests (8,9) and at a short period of follow-up. To determine the spontaneous course of subacute thyroiditis, changes in serum T4, T3, thyroglobulin (Tg) and TRH-test were studied in patients without any kind of medication from the acute phase up to 56 mo of follow-up.

MATERIALS AND METHODS

Ten consecutive patients, all females, from 26 to 47 yr old, presented typical clinical pictures of subacute thyroiditis: thyroid tenderness, chills, fever, palpitations, fatigue, heat intolerance, etc. The erythrocyte sedimentation rate was elevated in all patients (22–60 mm/hr). TRH-test and radioiodine uptake (RAIU) at the 24th hr (24-hr RAIU) were studied in the acute phase, from 5 to 14 days after the onset of the first clinical signs of the disease, and at monthly intervals for the first 6 mo, at the 12th mo and after 47 to 56 mo of follow-up. None of them received any medication that could interfere with the thyroid-stimulating hormone (TSH) response to TRH (10). Serum TSH was measured by a modified solid-phase microtiter radioimmunoassay (RIA) as previously described (11). Intra and interassay variances were 10.8 and 15%, respectively. Serum T4 and T3 were determined using RIA kits.* The respective
TABLE 1
Thyroid Function Tests During Spontaneous Course of Subacute Thyroiditis

<table>
<thead>
<tr>
<th>Follow-up (mo)</th>
<th>No.</th>
<th>T₄ (μg/dl)</th>
<th>T₃ (ng/dl)</th>
<th>T₃:T₄ ratio</th>
<th>TSH (μU/ml)</th>
<th>Max Δ TSH (μU/ml)</th>
<th>Tg (ng/dl)</th>
<th>24-hr RAIU (%)</th>
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</thead>
<tbody>
<tr>
<td>Acute phase</td>
<td>10</td>
<td>21.6 ± 8.2*</td>
<td>315 ± 91*</td>
<td>16.2 ± 15.3</td>
<td>1.2 ± 0.2</td>
<td>0.97 ± 0.6</td>
<td>149 ± 52*</td>
<td>1.4 ± 0.4*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(12.5-32)</td>
<td>(105-680)</td>
<td>(6.1-30.3)</td>
<td>(1.2-4.0)</td>
<td>(0-18)</td>
<td>(11-480)</td>
<td>(0.5-5.0)</td>
</tr>
<tr>
<td>1st</td>
<td>10</td>
<td>7.8 ± 0.7</td>
<td>159 ± 28</td>
<td>18.7 ± 3.5</td>
<td>3.1 ± 1.5</td>
<td>26.8 ± 12</td>
<td>113 ± 35†</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5.2-12)</td>
<td>(95-320)</td>
<td>(10.1-25)</td>
<td>(&lt;1.2-2.7)</td>
<td>(0-32.4)</td>
<td>(21-360)</td>
<td>—</td>
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<tr>
<td>2–3</td>
<td>9</td>
<td>11.7 ± 2.4</td>
<td>224 ± 41†</td>
<td>18.9 ± 2.5</td>
<td>2.4 ± 1</td>
<td>48.1 ± 17†</td>
<td>82 ± 26</td>
<td>32 ± 5.4</td>
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<tr>
<td></td>
<td></td>
<td>(8-18)</td>
<td>(70-400)</td>
<td>(11.3-30.7)</td>
<td>(&lt;1.2-9.2)</td>
<td>(0-157)</td>
<td>(10-280)</td>
<td>(19-60)</td>
</tr>
<tr>
<td>4–5</td>
<td>8</td>
<td>9 ± 0.7</td>
<td>176 ± 28</td>
<td>20.8 ± 3.5</td>
<td>5.4 ± 2.5</td>
<td>43.1 ± 10.2†</td>
<td>69.2 ± 20.5†</td>
<td>24 ± 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(6.2-11.2)</td>
<td>(96-330)</td>
<td>(8.7-33)</td>
<td>(&lt;1.2-20)</td>
<td>(5.4-103)</td>
<td>(18-195)</td>
<td>(7-37)</td>
</tr>
<tr>
<td>12th</td>
<td>5</td>
<td>9.4 ± 0.8</td>
<td>125 ± 13</td>
<td>13.6 ± 0.5</td>
<td>2.2 ± 0.6</td>
<td>31.2 ± 12.6†</td>
<td>12.7 ± 1.9</td>
<td>24 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(6-12)</td>
<td>(94-165)</td>
<td>(12.5-15.6)</td>
<td>(&lt;1.2-3.7)</td>
<td>(4.9-79.4)</td>
<td>(6.8-17)</td>
<td>(19-28.5)</td>
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<tr>
<td>Controls</td>
<td>13</td>
<td>8.5 ± 0.5</td>
<td>136 ± 9</td>
<td>15.9 ± 0.7</td>
<td>3.4 ± 0.2</td>
<td>11.3 ± 1.1</td>
<td>10.5 ± 1</td>
<td>31 ± 2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(6.6-11)</td>
<td>(80-205)</td>
<td>(7.5-24)</td>
<td>(&lt;1.2-8)</td>
<td>(4.2-19.3)</td>
<td>(3-30)</td>
<td>(18-43)</td>
</tr>
</tbody>
</table>

Values given are mean ± s.e.m., range in parentheses.
* p < 0.001.
† p < 0.02.
‡ p < 0.05 in comparison with controls subjects.

Intra and interassay variances were 4.2 and 9.4% for T₄ and 5.4 and 11.2% for T₃. Serum Tg concentrations were measured by a solid-phase immunoradiometric assay (12). Thyroid autoantibodies were assayed by passive hemagglutination method for thyroglobulin and microsomal antibodies.

After initial blood samples were drawn at -15 and 0 min, synthetic TRH (200 μg) was injected i.v. and an assay of TSH in blood was performed before and at 15, 30, 45, 60, and 120 min after TRH. The maximum increment of serum TSH (max Δ TSH) was the difference between the mean basal values and the highest reached after the TRH injection. TRH-test was defined as exaggerated when max Δ TSH was greater than 23 μU/ml and absent less than 4 μU/ml. The data shown represent mean ± s.e.m. Statistical analysis of data was carried out by the Student's t-test.

RESULTS

In the acute phase of subacute thyroiditis the 24-hr RAIU was below 5% and TSH concentrations failed to increase in response to TRH. Mean serum T₄ and T₃ concentrations were significantly (p < 0.001) higher than in normal subjects. Mean Tg concentrations were significantly (p < 0.05) higher than in normal subjects. Serum T₄ levels decreased to the normal range in all patients at the end of the 1st mo after the acute phase. However, mean T₃ and Tg concentrations were significantly elevated up to 2 to 3 mo and 4 to 5 mo intervals, respectively (Table 1). The T₃ to T₄ ratio was elevated in five out of the nine patients at 2 to 5 mo, and in four out of the seven patients at the end of the follow-up. The serum Tg concentration remained elevated in nine patients in the 1st mo, in seven patients at 2 to 3 mo and in six patients at 4 to 5 mo intervals.

The mean max Δ TSH after administration of TRH was significantly greater than of the controls from 2 to 3 mo to 47 to 56 mo intervals (Fig. 1). An exaggerated response was observed in four patients in the 1st mo, in five out of nine patients at 2 to 3 mo, in five out of eight patients at 4 to 5 mo, in one out of five patients in the 12th mo, and in six out of seven patients at the end of follow-up. Table 2 summarizes the thyroid function tests of the patients 47 to 56 mo after the acute phase of subacute thyroiditis. No correlation was observed between max Δ TSH and serum T₃ (r = 0.227), serum T₄ (r = 0.299), T₃ to T₄ ratio (r = 0.126), 24-hr RAIU (r = 0.256), and serum Tg (r = 0.244). However, all patients with elevated T₃ to T₄ ratio (above 24 ng/μg) showed the max Δ TSH clearly above the normal range.
DISCUSSION

Our data in patients without any kind of medication showed that after the acute phase of subacute thyroiditis, normalization of clinical status and serum T\textsubscript{4} and T\textsubscript{3} levels did not coincide with the normalization of the serum Tg levels (13,14). Persistent Tg hypersecretion may be caused by an increased intraglandular Tg turnover as a consequence of Tg hypiodination (15). These data suggest that after the acute phase of subacute thyroiditis the thyroid gland shows a reduced iodine content. In fact, recently Fragu et al. (9) showed that in this disease the thyroid iodine content is lower than normal, and that its restoration appears to be a slow progressive phenomenon. In spite of normal TSH values, in most patients we found an exaggerated response of TSH to TRH. Similar evidence of thyroid dysfunction was seen in endemic goiter regions. Some goitrous subjects have T\textsubscript{4}, T\textsubscript{3}, and basal TSH levels within the normal range but with an exaggerated response of TSH to TRH (16). However, these subjects also have a high thyroid uptake. In contrast, our patients had normal thyroid uptake. The cause of this discrepancy is not clear but our patients have been living in an urban nonendemic area where the urinary excretion of iodide is about 200 \textmu g of iodide/g of creatinine daily.

It is generally accepted that TSH secretion is normally sensitive to small changes in thyroid hormone concentrations (17). Although we did not measure the free thyroid hormone concentrations, the mechanisms behind the observed exaggerated response of TSH to TRH with normal levels of serum T\textsubscript{4} and T\textsubscript{3} might reflect a low thyroid reserve (18). The T\textsubscript{3} to T\textsubscript{4} ratio may be elevated in patients from iodine deficiency region (16) and in mild hypothyroidism, showing thyroid gland hypofunction compensated by relative hyperconversion (19). During a long follow-up, the majority of our patients with subacute thyroiditis showed a T\textsubscript{3} to T\textsubscript{4} ratio higher than normal which coincides with an exaggerated response of TSH to TRH. However, the 24-hr RAIU was always within the normal values by the 2nd mo and one can only speculate that iodide depletion observed in this disease (9) has provoked a shift from T\textsubscript{4} to T\textsubscript{3} production (16).

Lymphocytic thyroiditis was ruled out in all patients because thyroid autoantibodies were absent during the whole period of study (5). Thus, the present findings suggest that the spontaneous course of subacute thy-

### TABLE 2

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Mo of follow-up</th>
<th>T\textsubscript{4} (\textmu g/dl)</th>
<th>T\textsubscript{3} (ng/dl)</th>
<th>T\textsubscript{3}:T\textsubscript{4} ratio</th>
<th>Basal (\mu U/ml)</th>
<th>Max Δ TSH (\mu U/ml)</th>
<th>Tg (ng/dl)</th>
<th>24-hr RAIU (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>6.7</td>
<td>130</td>
<td>22.8</td>
<td>2.0</td>
<td>38.0*</td>
<td>3.0</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>6.3</td>
<td>140</td>
<td>22.2</td>
<td>2.8</td>
<td>25.7*</td>
<td>3.0</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>6.7</td>
<td>90</td>
<td>15.8</td>
<td>4.2</td>
<td>12.8†</td>
<td>24.0</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>6.8</td>
<td>40</td>
<td>5.9</td>
<td>5.4</td>
<td>44.6*</td>
<td>9.0</td>
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<tr>
<td>7</td>
<td>51</td>
<td>6.3</td>
<td>150</td>
<td>23.8</td>
<td>7.0</td>
<td>43.0*</td>
<td>32.0</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>7.3</td>
<td>130</td>
<td>17.8</td>
<td>7.6</td>
<td>60.4*</td>
<td>13.0</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>47</td>
<td>8.5</td>
<td>130</td>
<td>15.6</td>
<td>5.4</td>
<td>58.6*</td>
<td>6.0</td>
<td>29</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>6.9</td>
<td>115.7</td>
<td>17.7</td>
<td>4.9</td>
<td>40.4†</td>
<td>12.5</td>
<td>21.7</td>
</tr>
<tr>
<td>± s.e.m.</td>
<td></td>
<td>± 0.2</td>
<td>± 14</td>
<td>± 24</td>
<td>± 0.7</td>
<td>± 6.4</td>
<td>± 11.5</td>
<td>± 2.2</td>
</tr>
</tbody>
</table>

* Exaggerated response.
† Normal response. Max Δ TSH in normal controls: 11.3 ± 1.1 \mu U/ml

p < 0.001, difference significant from controls.
Thyroiditis may lead to a low thyroid reserve detectable even 5 yr after the acute phase of the disease. Recently Lio et al. (20) found an increased incidence of hypothyroidism during the course of subacute thyroiditis. We have also observed that the basal TSH was not useful and the TRH stimulation was the most appropriate test for the diagnosis of these patients. Among several explanations for these findings could be the fibrosis of thyroid gland, which is a feature in patients whose thyroiditis has been apparently healed (6, 21).

FOOTNOTES
* Immunophase-T4, Corning-Medical, Medfield, MA and Seralute-T3, Ames Co., Elkhart, IN.
† Sorin Biomedica S.P.A., Saluggia, Italy.
‡ Sera-Tek, Ames Co., Elkhart, IN.

REFERENCES
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