Frequency of Biochemical Hypothyroidism in Sera Referred for Autoantibody Testing

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We examined sera submitted for autoantibody testing for thyroid microsome antibodies (TMA), elevated thyroid-stimulating hormone (TSH), and free thyroxine concentrations. The frequency of TMA in antinuclear antibody-positive sera was higher (19%) than that in antinuclear antibody-negative sera (12%). Elevated TSH concentrations in serum and subnormal thyroxine concentrations in serum were associated with the presence of TMA; TMA titer and the frequency of elevated TSH concentrations were also associated with the presence of TMA.

The presence of thyroid microsome autoantibodies (TMA) is highly specific for and predictive of Hashimoto thyroiditis (autoimmune thyroid disease) (2, 9); Hashimoto thyroiditis is the most commonly recognized cause of subclinical and overt hypothyroidism (1, 5). TMA are found in about 6 to 7% of healthy adult Caucasians (10, 11), and their presence has been said to be predictive of the development of hypothyroidism at a rate of 5% per year (18). The increased prevalence and frequency of both overt and incipient hypothyroidism in patients with rheumatic diseases are well documented (3, 4, 6–8, 12–14, 16, 17, 19, 20). A case-control study revealed that patients with autoimmune thyroid disease do not exhibit a higher frequency of rheumatologic symptoms; however, the majority of those patients were biochemically euthyroid (15). We revisited this issue by examining sera from patients with suspected rheumatic diseases for the prevalence of TMA and the association of TMA with elevated thyroid-stimulating hormone (TSH) concentrations (>4 μIU/ml) and subnormal free thyroxine (FT4) concentrations (<0.8 ng/dl).

Sera from 7,942 consecutive patients referred for autoantibody testing were categorized as positive (>7.5 IU/ml) or negative (<7.5 IU/ml) for antinuclear antibody (ANA); by immunofluorescence and were tested for the presence of TMA. TMA were measured by an indirect enzyme immunoassay with purified thyroid microsomes antigen (Cortex Biochem, San Leandro, Calif.). The frequency of TMA in ANA-negative sera was 12% (361 of 2,892 serum specimens), whereas the frequency of TMA in ANA-positive sera was 19% (877 of 4,700 serum specimens) (χ² = 89; P < 0.0001).

Analysis of a cohort of 95 TMA-positive serum specimens revealed that there was an association between TMA titer and the frequency of elevated serum TSH concentrations (measured by using a third-generation TSH assay kit [Immulite; Diagnostic Products Corporation, Los Angeles, Calif.]) and that in TMA-positive patients there is a high frequency of hypothyroidism. The frequency of elevated serum TSH concentrations in these patients ranged from 12% (2 of 17) in patients with low-titer (1:100) TMA-positive sera to 65% (11 of 17) in patients with high-titer (≥1:25,600) TMA-positive sera. The frequency of biochemical hypothyroidism (subnormal FT4 concentration, measured by enzyme immunoassay) in the TMA-positive sera with elevated TSH concentrations (36 of 95) was as high as 45% (5 of 11) in high-titer TMA-positive sera.

We then conducted a study of 114 TMA-negative, ANA-positive serum specimens, 136 TMA-positive, ANA-positive serum specimens, 110 TMA-positive, ANA-negative serum specimens, and 103 serum specimens from healthy individuals to determine whether the increased prevalence of elevated serum TSH concentrations and subnormal FT4 concentrations in patients with suspected rheumatic diseases is associated with the presence of TMA. All sera were selected to be negative for double-stranded DNA, small nuclear ribonucleoprotein, Smith, SS-A, SS-B, Scl-70, centromere, mitochondrial, parietal, reticulin, striational, smooth muscle, and myocardial autoantibody specificities and had normal C4 complement concentrations. The frequency of elevated TSH concentrations (Table 1) in the TMA-negative, ANA-positive group of sera was 7% (8 of 114 serum specimens); 13% (1 of 8) of TMA-negative, ANA-positive serum specimens with elevated TSH concentrations also had subnormal FT4 concentrations. In contrast, the frequency of elevated TSH concentrations in the TMA-positive, ANA-positive group of sera was 27% (37 of 136 serum specimens); 22% (8 of 37 serum specimens) of TMA-positive, ANA-positive sera with elevated TSH concentrations also had subnormal FT4 concentrations. A total of 32% (35 of 110 serum specimens) of the TMA-positive, ANA-negative sera had elevated TSH concentrations; 34% (12 of 35 serum specimens) of these serum specimens also had subnormal FT4 concentrations. Five of 103 (5%) serum specimens from healthy individuals were positive for TMA; 1 (20%) of these 5 TMA-positive serum specimens had elevated TSH but normal FT4 concentrations, and this individual was also ANA positive. Five of 98 (5%) TMA-negative, ANA-negative serum specimens had elevated TSH concentrations; 1 of these serum specimens also had a subnormal FT4 concentration (0.29 ng/dl), and the serum from this individual also had a greatly elevated TSH concentration (90 μIU/ml).

The data in Table 1 confirm that TMA are common in the population at large and suggest a greatly increased frequency of Hashimoto thyroiditis and subsequent hypothyroidism in patients with suspected rheumatic diseases.

The impact of this biochemical hypothyroidism, and presumably subclinical or clinical hypothyroidism, on the signs and symptoms of patients presenting with suspected rheumatic diseases is unknown. We suspect that undiagnosed hypothyroidism contributes to the clinical picture in a substantial number of these patients. It remains to be determined how many of these patients actually have rheumatic diseases as...
opposed to the number with symptoms attributed to rheumatic diseases which, in fact, are due to hypothyroidism and, hence, are readily amenable to treatment. However, it is clear that TMA have predictive value in patients with suspected rheumatic diseases. Screening for TMA (which costs less than third-generation TSH determination) in patients presenting with symptoms of rheumatic diseases identifies a subset of patients that should be subsequently evaluated and monitored for the development of hypothyroidism (by TSH and/or FT4 concentration determinations) and has a >99% negative predictive value for hypothyroidism in such patients. Prospective studies are needed to determine what proportion of TMA-positive patients with normal TSH concentrations will develop subclinical or overt hypothyroidism over time. Whether screening for autoimmune thyroid disease in the adult population at large (by either TMA or TSH determinations) is useful or cost-effective also requires further evaluation.

REFERENCES


### Table 1. Frequency of elevated TSH concentrations in various groups of sera

<table>
<thead>
<tr>
<th>Serum specimen group</th>
<th>% (no. of individuals with the indicated result/total no. tested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMA negative, ANA negative</td>
<td>5 (5/98) / 20 (1/5)</td>
</tr>
<tr>
<td>TMA negative, ANA positive</td>
<td>7 (8/114) / 13 (1/8)</td>
</tr>
<tr>
<td>TMA positive, ANA negative</td>
<td>32 (35/110) / 34 (12/35)</td>
</tr>
<tr>
<td>TMA positive, ANA negative</td>
<td>27 (37/136) / 22 (8/37)</td>
</tr>
</tbody>
</table>

*Sensitivity = 20/21 × 100 = 95%; specificity = 113/339 = 33%; positive predictive value = 20/246 = 8%; negative predictive value = 113/114 > 99% in patients with suspected rheumatic diseases.*