Thyroid hypoechogenic pattern at ultrasonography as a tool for predicting recurrence of hyperthyroidism after medical treatment in patients with Graves’ disease

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Thyroid ultrasonography is a diagnostic procedure widely utilized in the evaluation of thyroid disorders, mainly for the identification of solid or cystic lesions (1, 2). Recently, an abnormal thyroid pattern at ultrasonography, characterized by a diffuse low echogenicity, has been described in Hashimoto’s thyroiditis and Graves’ disease (6). In particular, we have reported a strict association between thyroid hypoechogenicity and hypothyroidism in patients with Hashimoto’s thyroiditis (7). In that study thyroid hypoechogenicity was also found in 59/90 (65%) patients with Graves’ disease whether treated or untreated.

Since antithyroid drugs for Graves’ disease were introduced for the therapy of the hyperthyroidism, several parameters have been evaluated for the prediction of relapse of hyperthyroidism after discontinuation of treatment. Among these, the most sensitive and specific have been considered the measurement of TSH receptor antibodies (TR-ab) by a radioreceptor assay (8), HLA-DR typing (9) or the association with ophthalmopathy or large goiter were also used as clinical parameters, but these criteria lack sensitivity and specificity (8). In previous studies from our laboratory (7) and others (6) it has been shown that thyroid ultrasonography allows distinguishing of patients with Graves’ disease into two groups, depending on the presence or absence of thyroid hypoechogenicity. In this paper the relationship between thyroid hypoechogenicity and the outcome of antithyroid drug treatment for hyperthyroidism of Graves’ disease was evaluated.

Materials and methods

Patients

One hundred and five consecutive patients with hyperthyroid Graves’ disease (77F, 28M, age 35 ± 13 years) selected for antithyroid drug treatment were included in the study. The diagnosis of Graves’ disease was made according to common clinical and laboratory criteria, which included high levels of circulating thyroid hormones, undetectable TSH by an ultrasensitive method.
high values of thyroid 131-I uptake with a diffuse distribution of the isotope at thyroid scintiscan; thyroid peroxidase and thyroglobulin antibodies were found in 89 (84%) and 50 (47%) out of 105 patients, respectively. Sixty-eight/105 (65%) had various degrees of Graves' ophthalmopathy. In particular, 46 had a mild degree of ophthalmopathy classified as class 1 or 2 (10), while 22 had more severe eye manifestations (classes 3 to 5).

Methimazole treatment was administered for 12 (25 patients) up to 18 or more months (80 patients) and patients were kept euthyroid under treatment by adjusting the dose of methimazole. The follow-up period after methimazole withdrawal was 6–60 months (mean 13 months).

**Thyroid ultrasound examination**

Thyroid ultrasonography was carried out by two of us (P.V., C.M.) independently in all patients before methimazole therapy was started. A real-time instrument (Aloka SSD 121, Aloka Co., Ltd., Tokyo, Japan) with a 7.5 MHz transducer was used, care being taken to keep the operating conditions constant. The overall gain was adjusted to produce a relatively echo-free appearance of the lumen of the internal jugular veins and neck strap muscles. In these conditions, a healthy thyroid gland has a medium-grey scale homogeneous echo pattern and the level of echogenicity is higher than that of surrounding muscles. Patients were included in the group of thyroid hypoechogenic when their gland had an echo density that was clearly lower than normal and ranged from mild to moderate and marked, according to previously described criteria (7). Discrepancy in the judgment of echogenicity was found in five patients, who were further examined simultaneously by the two examiners and agreement reached for their classification. Thyroid ultrasound examination was performed also during and after treatment. No significant modifications were observed in most of the patients.

**Measurement of TSH receptor antibodies**

TR-ab measurement was performed on whole serum by a radioreceptor assay (TRAk-assay, Henning Berlin) at the end of methimazole treatment. Results were expressed in U/l and values ≥ 5 U/l were considered positive for the presence of TR-ab.

**Statistic evaluation**

Statistical differences between relapsing or euthyroid patients according to thyroid echogenicity or positive TR-ab values were analysed using the $\chi^2$ test; prognostic evaluation was performed according to the Galen and Gambino predictive model (11).

**Results**

Thyroid hypoechogenicity was found in 76/105 (72%) patients. The degree of thyroid hypoechogenicity was mild in 17 patients, moderate in 36 and marked in 23. The echographic pattern of thyroid hypoechogenicity was not associated with the presence or severity of Graves' ophthalmopathy, the size of goiter, the level of circulating thyroid hormones and titer of thyroid peroxidase antibodies (data not shown).

During the follow-up after methimazole treatment 87/105 (83%) patients had relapse of hyperthyroidism: remission of hyperthyroidism was observed in 4/25 (16%) patients treated for 12 months and in 14/80 (17.5%) of those treated for 18 or more months. Recurrence of hyperthyroidism occurred in 71/76 (93%) patients with thyroid hypoechogenicity and in 16/29 (55%) of those with normal thyroid echogenicity ($\chi^2 = 19.0; \ p < 0.0001$) (Table 1). Thus 71/87 (82%) patients who relapsed and only 5 of the 18 (27%) who were in remission had thyroid hypoechogenicity ($\chi^2 = 19.0; \ p < 0.0001$). Positive TR-ab values at the end of methimazole therapy were found in 59/76 (78%) patients with thyroid hypoechogenicity and in 12/29 (45%) patients with normal thyroid echogenicity ($\chi^2 = 10.9; \ p < 0.0001$). Sixty-five/87 (72%) patients with relapse of hyperthyroidism and 6/18 (33%) of those who remained euthyroid (four with normal thyroid echogenicity and two with hypoechogenicity) were TR-ab-positive at the end of methimazole treatment ($\chi^2 = 9.8; \ p < 0.002$) (Table 1).

The evaluation of the thyroid echographic pattern at diagnosis and TR-ab measurement at the end of methi-

<table>
<thead>
<tr>
<th>TR-ab +</th>
<th>TR-ab -</th>
<th>HypoEc</th>
<th>NormoEc</th>
<th>HypoEc</th>
<th>NormoEc</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse</td>
<td>57</td>
<td>8</td>
<td>14</td>
<td>8</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>9</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Outcome of antithyroid drug treatment according to the thyroid echographic pattern at diagnosis: (HypoEc: patients with normal thyroid echogenicity, N = 76; NormoEc: patients with normal thyroid echogenicity, N = 29) and TR-ab measurement (TR-ab +: positive TR-ab value at the end of methimazole treatment; TR-ab -: negative TR-ab value at the end of methimazole treatment).

<table>
<thead>
<tr>
<th>Thyroid ultrasound examination</th>
<th>TR-ab measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive</td>
<td>71/87</td>
</tr>
<tr>
<td>True negative</td>
<td>13/18</td>
</tr>
</tbody>
</table>

$\chi^2$ test: $p < 0.0001$.

*Patients who relapsed and had thyroid hypoechogenicity at diagnosis.

*Patients who relapsed and had TR-ab-positive results at the end of methimazole treatment.

$\chi^2$ test: $p < 0.0001$.

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Hashimoto's genicity patients associated sensitivity specificity but course hyperthyroidism more associated diffuse echogenicity suggested antibodies. surgery echogenicity Hashimoto's zole Galen been reported in patients with Hashimoto's thyroiditis (3–5). In a previous study performed in patients with Hashimoto's thyroiditis (7) we found that thyroid hypoechochogenicity was associated with hypothyroidism in 20% of goitrous patients with circulating thyroid autoantibodies. Thyroid histology of patients who underwent surgery for tracheal decompression showed a diffuse lymphocytic infiltration in patients with thyroid hypoechochogenicity and only focal thyroiditis in those with normal thyroid echographic pattern. These data suggested that thyroid hypoechochogenicity was due to a diffuse thyroiditis and was correlated with hypothyroidism. In that study we showed that thyroid hypoechogenicity was also present in patients with Graves' disease. In this paper we evaluated whether in Graves' disease the pattern of thyroid hypoechogenicity was associated with the relapse of hyperthyroidism after a course of methimazole treatment.

It is well known that hyperthyroidism may relapse in more than 50% of patients with Graves' disease after a course of antithyroid drug therapy (8). Measurement of TSH receptor antibodies during treatment is believed to be the most reliable index for predicting relapse of hyperthyroidism (12, 13). Indeed, in a multicenter European study on 451 patients the positivity of TSH receptor antibodies at the end of drug treatment was significantly correlated with the relapse of hyperthyroidism (8). The sensitivity of this test was 0.49 and the specificity 0.79. Other parameters, such as circulating thyroperoxidase or thyroglobulin antibodies, or the presence of the HLA-DR3 haplotype, had a lower sensitivity with respect to TR-ab measurement. The TRH test at the end of treatment had a good sensitivity (0.89) but low specificity (0.30). The T4 suppression test was slightly more specific than other parameters (0.66), but it has the disadvantage of being time expensive and often associated with side effects.

In the present study we showed that about 70% of patients with Graves' disease have a low thyroid echogenicity at ultrasound. While a diffuse lymphocytic infiltration accounts for thyroid hypoechogenicity in Hashimoto's thyroiditis, in Graves' disease the hypo-echogenic pattern may be due to reduced colloid content with increased cellularity and reduction of the cell/colloid interface (6). In this paper we have shown that the pattern of thyroid hypoechogenicity in Graves' patients is significantly associated with a higher frequency of TR-ab positivity and with the relapse of hyperthyroidism. The finding of thyroid hypoechogenicity at diagnosis had a higher sensitivity and specificity with respect to TR-ab positivity at the end of methimazole treatment for the prediction of relapse of hyperthyroidism.

In conclusion, a diffuse low thyroid echogenicity was present in the majority of patients with Graves' disease. This echographic pattern was correlated with hyperthyroidism and in particular with the relapse of thyrotoxicosis after antithyroid drug treatment. As a prognostic index, the finding of thyroid hypoechogenicity is superimposable or slightly better than TR-ab measurement, having the advantage of being readily feasible and cheap. Thus, the evaluation of thyroid echogenicity before medical treatment can be considered a useful method for the evaluation of patients with Graves' disease and may help in determining the type of treatment for these patients.

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References


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