Distinction Between Autoimmune and Nonautoimmune Hyperthyroidism by Determination of Thyrotropin-Receptor Antibodies in Patients with the Scintigraphic Diagnosis of Disseminated Autonomy

To the Editor:

Graves’ disease (GD) has an estimated incidence of 19.7 or 14.8 patients in 100,000 inhabitants per year in iodine-replete or iodine-deficient areas, respectively, whereas the incidence of toxic multinodular goiter (TMG) is 18 or 1.5 patients in 100,000 inhabitants per year in iodine-deficient or iodine-replete areas, respectively (1). Although TMG is treated by early thyroid ablation, GD is first treated with antithyroid drugs. Because of a 40% remission rate after 1 year of antithyroid drug treatment, distinguishing between GD and TMG is a common clinical problem, especially in iodine-deficient areas.

The presence of thyroid-associated ophthalmopathy, pretibial myxedema, or acropachy is pathognomonic for GD. If these clinical signs of GD are absent, the differential diagnosis may be based on the detection of thyrotropin-receptor antibodies (TRAb). The diagnosis of TMG or toxic adenoma is best made by ultrasound and scintiscan of the thyroid gland. Typically, the ultrasound shows nodules and normal echogenicity of the thyroid. The thyroid scintiscan typically shows single or multiple hot nodules with varying size and functional status with suppression of uptake by the surrounding thyroid tissue. TRAb or thyroperoxidase-antibodies (TPO-Ab) are undetectable. However, in iodine-deficient areas the distinction between GD and TMG is often complicated by findings that do not fulfill these typical diagnostic criteria. The term disseminated autonomy (DISA) is defined by subclinical or manifest hyperthyroidism, homogeneous distribution of the tracer in the thyroid scintiscan in combination with elevated global uptake during endogenous (or exogenous) TSH suppression, and by the lack of evidence of GD. The retrospective study by Meller et al. (2) addresses this clinical problem using the determination of TRAb in patients with DISA to differentiate between autoimmune and nonautoimmune hyperthyroidism. The authors showed that 7 of 32 (22%) of the patients with the clinical diagnosis of DISA were positive in a new TBI assay (Dynotest TRAK human, Brahms, Germany) and therefore most likely had GD and not DISA.

In the Guest Editorial Weetman (3) made three important comments. (1) This was a retrospective study and only 13 of 32 patients had not been treated before. (2) Five of these were TBI negative in the conventional assay but positive in the new TBI assay (Dynotest TRAK human). (3) Ten patients were treated with thionamides. Only two of these pretreated patients showed positive results in the new TBI assay. According to Weetman, these facts suggest a higher frequency of detectable TBI in untreated patients with DISA. This assumption is supported by a previous study that detected thyroid-stimulating antibodies (TSAB) in 11 of 18 (56%) TBI-negative patients not previously treated with antithyroid drugs with TMG who showed a diffuse but uneven technetium distribution in the scintiscan (4) and was thus compatible with the clinical diagnosis of DISA. Moreover, in a recent study (5), we examined 21 consecutive patients with the initial diagnosis of TMG for TSAB (JF26 cell assay) and for TBI with the new TBI assay (Dynotest TRAK human). The initial diagnosis of TMG was based on suppressed TSH and a patchy Tc—uptake > 1% ≡< 7% or TSH ≤ 0.3 mE/L with a patchy Tc—uptake ≥ 1.5% ~< 7% and negative TBI values in a dis-
placement assay using solubilized porcine epithelial cell membranes (TRAK). Only patients with an antithyroid drug pretreatment of less than 3 weeks were included in our study. Eleven of 21 sera showed TSAB activity. Ten of these 11 TSAB-positive sera were also positive in the Dynostet TRAK human assay, whereas 1 serum sample was borderline positive. TSAB activity and inhibition of $^{125}$I-bovine thyrotropin (bTSH) binding in the Dynostet TRAK human assay correlated well ($r = 0.7, p < 0.05$). Therefore, 11 of the 21 (50%) investigated patients initially classified as TMG actually had GD that was undetectable with the porcine TBII assay. Therefore, our recent data support the suggested higher prevalence of TRAb in untreated patients with the diagnosis of TMG or DISA.

The most likely molecular etiology of nonautoimmune hyperthyroidism with the scintigraphical appearance of DISA are small autonomous nodules that are undetectable by conventional ultrasound or thyroid scintiscan (3,6). Constitutively activating TSH-receptor mutations have been established as the most frequent molecular basis for the pathogenesis of hot thyroid nodules (7). Furthermore, somatic TSH-receptor mutations have also been demonstrated in microscopic hot areas in thyroid autoriadiographs of patients with euthyroid goiters from iodine-deficient areas (8). Therefore, we prefer the term TMG for diagnosis in patients with the scintigraphical appearance of DISA without detectable thyroid autoimmunity.

Moreover, activating TSH-receptor germline mutations in patients with nonautoimmune hyperthyroidism might clinically masquerade as GD, as previously shown (9). The increasing number of families and individuals identified with hereditary nonautoimmune hyperthyroidism in both iodine-deficient and iodine-sufficient areas suggest that this condition seems to be more frequent than initially suspected. Therefore, and because hereditary nonautoimmune hyperthyroidism is treated by primary thyroid ablation whereas GD is first treated with antithyroid drugs, hereditary nonautoimmune hyperthyroidism has to be included in the differential diagnosis in patients with hyperthyroidism with the scintigraphical appearance of DISA.

In conclusion, TSAB or TRAb determinations with the Chinese hamster ovary (CHO) bioassay or the second generation TBII assay (Dynostet TRAK human, Brahms, Germany) have the highest diagnostic power to differentiate autoimmune from nonautoimmune hyperthyroidism. One of these assays should be obtained in all patients with nontypical TMG to differentiate GD from nonautoimmune hyperthyroidism in order to select the appropriate therapy for these patients.

References


Address reprint requests to:
Henri Wallaschofski
Christiane Orda
Dagmar Führer
Hans Peter Holzapfel
Knut Krohn
Konstanze Miehle
Susanne Neumann
Peter Georgi
Ralf Paschke

Department of 1Internal Medicine III and
Department of Nuclear Medicine
University of Leipzig
Leipzig, Germany
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