Acta Endocrinol (Copenh) 1987. Suppl 281

On the clinical importance of thyroid microsomal and thyroglobulin antibody determination

W. A. Scherbaum

Department of Internal Medicine, University Hospital Ulm, FRG

Abstract. Among the various autoantibody tests applied in research and clinical practice, the determination of thyroid microsomal (TMAb) and thyroglobulin antibodies (TgAb) still retains its strong value in the screening for thyroid autoimmunity. The presence in the serum of TMAb is almost invariably associated with thyroid autoimmune disease or focal thyroiditis. The appearance of TMAb together with elevated serum-TSH in subclinical autoimmune thyroiditis strongly suggests progression to overt hypothyroidism. Pregnant women with positive TMAb and/or TgAb run an increased risk for post-partum painless thyroiditis with transient thyrotoxicosis and subsequent hypothyroidism. After delivery also a relapse of previously unrecognized Graves' thyrotoxicosis may occur. Thyroid antibody determination is not a valuable tool to discriminate autoimmune thyroiditis from thyroid malignancies. TMAb and TgAb determination helps to recognize individuals with thyroid autoimmunity among patients with non-thyroid autoimmune diseases such as Addison's disease and Type I diabetes mellitus.

Autoimmunity plays a key role in the pathogenesis of a number of thyroid disorders, namely Hashimoto's thyroiditis, primary myxoedema, Graves' thyrotoxicosis, and also Graves' ophthalmopathy. The clinical picture, cytological or histological assessment as well as the demonstration of cellular and humoral immune phenomena may lead to the appropriate diagnosis.

A number of autoantibodies have been detected in thyroid autoimmune diseases, and some of them such as thyroid-stimulating antibodies in Graves' thyrotoxicosis and neonatal hyperthyroidism (Zakarija & McKenzie 1983) are now thought to be directly linked with clinical disease. It is the aim of this article to re-evaluate the significance of thyroid microsomal (TMAb) and thyroglobulin antibody (TgAb) determination for the clinical management of patients.

Evidence for a role of TMAb in the pathogenesis of autoimmune thyroid disease

The cytoplasmic autoantigen has been shown to be also represented on the apical surface of human thyroid monolayers and disrupted follicles and is involved in the complement-mediated cytotoxic effect of TMAb-positive sera (Khoury et al. 1984). It has been shown by Hanafusa et al. (1984) that the cell surface antigen, normally localized at the microvillar edge of follicles may be shifted to the vascular pole through reversal of thyroid epithelial polarity thus allowing direct access of circulating autoantibodies to the 'microsomal' antigen.

Prevalence of TMAb and TgAb in thyroid disorders

The presence in the serum of TMAb is almost invariably associated with autoimmune thyroid disease or focal thyroiditis (Yoshida et al. 1978). The prevalence of thyroid antibodies depends on the detection method. With a widely applied commercial haemagglutination test, the prevalence in Graves' disease of TMAb was 63% and TgAb 18%, Hashimoto's thyroiditis 73%/40%, myxoedema 55%/55%.

Regarding an antibody titre of 1:100 as positive, nearly all the Hashimoto or myxoedema cases have TMAb and/or TgAb, but at these titres the normal controls were positive for TMAb and TgAb in 6.8% and 1.3%, respectively, and also 20% of patients with a euthyroid goitre had TMAb (Scherbaum et al. 1979). Titres are usually lower in asymptomatic individuals, in juvenile autoimmune thyroiditis and in severe myxoedema (Doniach et al. 1979). Half the cases with TMAb titre of ≥ 102 400 and TgAb titres of ≥ 6400 are associated with frank hypothyroidism (Scherbaum et al. 1982). In presumably healthy blood donors, TMAb seem to have a far higher predictive value than TgAb for the detection of previously unrecognized hypothyroidism (Björo et al. 1984).

Time course of TMAb and TgAb in autoimmune thyroid disease

Epidemiological studies suggest that both, antibody titres and hypothyroidism progress very slowly in subclinical autoimmune thyroiditis (Aho et al. 1985). Titres of TMAb and TgAb may fluctuate from one investigation to another, and rises after viral infections have been observed. The data on TMAb and TgAb titres after thyroid operation or radioiodine therapy for Graves' disease are highly divergent and the individual course cannot be predicted. However, once present, TMAb and TgAb only rarely disappear in Hashimoto's and Graves' diseases (Hayashi et al. 1985). Low or absent TMAb/TgAb are detected in long-standing myxoedema.

In subclinical autoimmune thyroiditis, thyroid antibodies may also appear transiently and later disappear. This finding seems to have little bearing on the long-term thyroid function. However, the appearance of TMAb together with elevated serum TSH strongly suggests progression to overt hypothyroidism (Tunbridge et al. 1981).

TMAb and TgAb in subacute (de Quervain's) thyroiditis

TgAb and/or TMAb may be transiently detectable in subacute thyroiditis. In contrast to the painful form of diffuse lymphocytic thyroiditis (Doniach et al. 1979), the titres are usually low and TMAb are often absent. The clinical course of the disease and its relation to viral infections have been described in detail by Volpé (1979). Data on our own series of 18 cases are given in Table 1. The initial goitre and the antibodies disappear in most cases.

Table 1.
Clinical data on 18 patients with subacute thyroiditis.

	Time of evaluation		
	Onset of symptoms	4 weeks	6 months
No. of cases	18	16	10
Females/males	13/5	13/3	8/2
Mean age (years)	39 (24–67)	42 (24–67)	47 (32–67)
TMAb ≥ 1/100	2*	1	0
TgAb ≥ 1/20	4*	4	1
Goitre present	18	16	4**

* All patients with thyroid antibodies at onset were available for the follow-up.
** Goitre size decreased in each case.
Range in parentheses.

Role of thyroid autoantibodies in the diagnosis of post-partum painless thyroiditis

'Painless' or 'silent thyroiditis' may attract the attention of physicians by causing thyrotoxicosis, and it has been thought to be an atypical equivalent of subacute (de Quervain's) thyroiditis (Morrison & Caplan 1978). Low radioiodine uptake of the thyroid gland and spontaneous recovery from hyperthyroidism in most cases indeed suggest that this form of thyrotoxicosis is destruction-induced. Needle biopsies performed during the hyperthyroid phase show focal or diffuse lymphocytic infiltration with destruction of follicle cells, but unlike Hashimoto's thyroiditis, the infiltrates decrease in the recovery phase (Inada et al. 1981).

Painless thyroiditis mainly occurs in the post-partum period, affecting up to 5% of women after delivery (Amino et al. 1982). Thyrotoxicosis sets on about 3 months after partuition, it is usually mild and of short duration and is often followed by transient hypothyroidism that may last for months before recovery to euthyroidism. Hyper- and hypothyroidism may be a cause of discomfort in the post-partum period, and it is therefore an important task to find out which women are at increased risk to develop the disease.

TMAb were demonstrable in 80%, and TgAb in 40% of 40 cases of spontaneous or post-partum painless thyroiditis (Amino et al. 1981). In the survey of Jansson et al. (1984), all women who

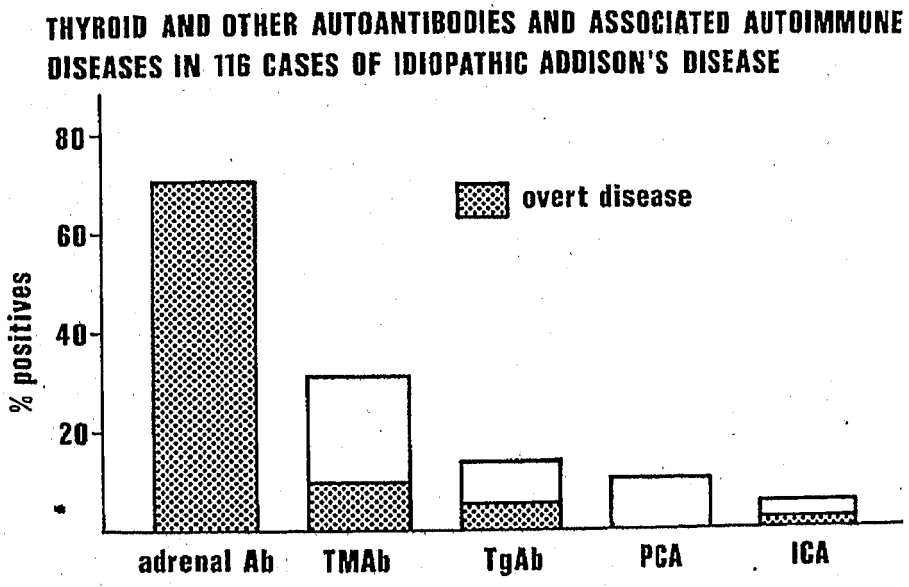

Fig. 1.

The absolute numbers of positive sera were: adrenal antibodies (adrenal Ab) N = 82. Thyroid microsomal antibodies (TMAb) N = 36, 12 of them with overt thyroid autoimmune disease. Thyroglobulin antibodies (TgAb) N = 16, 7 with overt thyroid autoimmune disease. Gastric parietal cell antibodies (PCA) N = 12. Pancreatic islet-cell antibodies (ICA) N = 7, 4 with Type-I diabetes mellitus.

developed post-partum hypothyroidism had circulating TMAb and/or lymphocytic thyroiditis at fine-needle aspiration biopsy. In their studies, a TMAb titre of 1/1600 or above in early pregnancy was associated with a high risk of symptomatic post-partum hypothyroidism. It may therefore be beneficial to include this test in a screening programme in pregnant women.

Role of thyroid antibodies in the diagnosis of post-partum Graves' thyrotoxicosis

Pregnancy may have a beneficial influence on the course of several autoimmune diseases. Autoimmune thyroiditis and Graves' thyrotoxicosis have been reported to ameliorate in late pregnancy. A decline of thyroid microsomal and thyroglobulin antibodies (Amino et al. 1983) as well as thyroid stimulating antibodies (Zakarija & McKenzie 1983) can be observed in the second and third trimester of pregnancy. After delivery, a relapse of Graves' thyrotoxicosis may occur, and in some cases, Graves' disease may be first diagnosed in this period.

In the absence of typical eye signs or myxoedema, TSH-receptor antibody measurement rather than TMAb and TgAb determination will help to differentiate Graves' thyrotoxicosis from painless thyroiditis. Patients with a history of Graves' disease run an increased risk for post-partual recurrence. However, patients with previously diagnosed Graves' disease may also acquire a self-limiting post-partum painless thyroiditis as evidenced by a low radioiodine uptake test (Check & Avellino 1980).

Thyroid malignancies associated with thyroiditis

The detection in the serum of TMAb or TgAb does not allow to diagnose non-malignant autoimmune thyroid disease. Thyroid antibodies and histological evidence of thyroiditis may be demonstrable in both, patients with thyroid lymphoma (Sirota & Segal 1979) and thyroid carcinoma (Meier et al. 1959). There have been many case reports on an association of Hashimoto's thyroiditis and also Graves' thyrotoxicosis with malignant lymphoma of the thyroid. In a recent epidemiological study, patients with serological and cytological signs of thyroiditis, but not those with colloid goitre, had a greatly increased risk of malignant thyroid lymphoma (Holm et al. 1985).

Thyroid autoantibodies in rheumatic disorders

An association of thyroid autoimmunity with rheumatoid arthritis (RA) was suggested by some case reports, family studies and a few systematic investigations (Walker et al. 1986). These findings may arise from the bias that cases with more than one disease are more likely to be admitted to a

hospital. Other studies failed to show an association between RA and Hashimoto's thyroiditis (Linos et al. 1980). In a combined French and German study, we found TMAb (HA test, Wellcome) in 4.4% of 367 patients with RA, 11.6% with systemic lupus erythematosus, and in 22.5% with Sjögren's syndrome, the latter being significantly increased as compared to normal controls. TgAb were significantly increased in RA, and titres ≥ 80 occurred in as many as 7.4% as compared to 1.3% in controls.

TMAb and TgAb determination in patients at risk for thyroid autoimmune disease

Individuals with a family history of thyroid autoimmune disease run an increased risk to acquire such a syndrome (Doniach & Bottazzo 1981). This is exemplified by family studies that point to an immunogenetic risk of family members who are HLA-identical and haplo-identical with their affected relative. TMAb and TgAb determination is suggested for screening.

Autoimmune diseases may affect several endocrine organs. Adrenal insufficiency is preferentially associated with thyroid autoimmunity (Nerup 1974). In 116 own cases of idiopathic Addison's disease, TMAb and TgAb were detected in 31% and 14%, respectively. 15 (13%) of these patients had overt autoimmune thyroid disease either at presentation or in their history. Another 7 (6%) had evidence of subclinical hypothyroidism. TMAb and TgAb measuring is therefore advisable in patients with idiopathic Addison's disease. In 318 cases of Type I (autoimmune) diabetes mellitus, TMAb and TgAb were present in 18% and 9%, respectively. Associated thyroid autoimmune diseases were found in 3.5% of these cases. Thyroid antibody screening is therefore also suggested in patients with Type I diabetes.

Acknowledgment

Supported by the Deutsche Forschungsgemeinschaft Sche 225/2-2.

References

Aho K, Gordin A, Palosuo T & Takala J (1985): Development of thyroid autoimmunity. Acta Endocrinol (Copenh) 108: 61–64.

Amino N, Yabu Y, Miki T, Morimoto S, Kumahara Y, Mori H, Iwatani Y, Nishi K, Nakatani K & Miyai K (1981): Serum ratio of triiodothyronine to thyroxine, and thyroxine-binding globulin and calcitonin concentrations in Graves' disease and destructive induced thyrotoxicosis. J Clin Endocrinol Metab 53: 113–116.

Amino N, Mori H, Iwatani Y, Tanizawa O, Kawashima M, Tsuge I, Ibaragi K, Kumahara Y & Miyai K (1982): High prevalence of transient post-partum thyrotoxicosis and hypothyroidism. N Engl J Med 306: 849–852.

Amino N, Tanizawa O, Mori H, Iwatani Y, Yamada T, Kurachi K, Kumahara Y & Miyai K (1983): Aggravation of thyrotoxicosis in early pregnancy and after delivery in Graves' disease. J Clin Endocrinol Metab 55: 108–112.

Björo T, Gaarder P I, Smeland E B & Kornstad L (1984): Thyroid antibodies in blood donors: prevalence and clinical significance. Acta Endocrinol (Copenh) 105: 324–329.

Check J H & Avellino J (1980): Painless thyroiditis and transient thyrotoxicosis after Graves' disease. J Am Med Ass 244: 1361.

Doniach D, Bottazzo G F & Russell R C G (1979): Goitrous autoimmune thyroiditis (Hashimoto's disease). Clin Endocrinol Metab 8: 63–80.

Doniach D & Bottazzo G F (1981): Polyendocrine autoimmunity. In: Franklin E C (ed). Clinical Immunology Update. Rev Physicians, p 95–121. Elsevier, New York.

Hanafusa T, Pujol-Borrell, Chiovato L, Doniach D & Bottazzo G F (1984): In vitro and in vivo reversal of thyroid epithelial polarity: its relevance for autoimmune thyroid disease. Clin Exp Immunol 58: 639–646.

Hayashi Y, Tamai H, Fukata S, Hirota Y, Katayama S, Kuma K, Kumagai L F & Nagataki S (1985): A long term clinical, immunological, and histological follow-up study of patients with goitrous chronic lymphocytic thyroiditis. J Clin Endocrinol Metab 61: 1172–1178.

Holm L-E, Blomgren H & Löwhagen T (1985): Cancer risks in patients with chronic lymphocytic thyroiditis. N Engl J Med 312: 601–604.

Inada M, Nishikawa M, Naito K, Ishii H, Tanaka K & Imura H (1981): Reversible changes of the histological abnormalities of the thyroid in patients with painless thyroiditis. J Clin Endocrinol Metab 52: 431–435.

Jansson R, Bernander S, Karlsson A, Levin K & Nilsson G (1984): Autoimmune thyroid dysfunction in the postpartum period. J Clin Endocrinol Metab 58: 681–687.

Khoury E L, Bottazzo G F & Roitt I M (1984): The thyroid microsomal antibody revisited. J Exp Med 159: 577–591.

Linos A, Worthington J W, Palumbo P J, O'Fallon W M & Kurland L T (1980): Occurrence of Hashimoto's thyroiditis and diabetes mellitus in patients with rheumatoid arthritis. J Chron Dis 33: 73–77.

Meier D W, Woolner L B, Beahrs O H & McConahey W M (1959): Parenchymal findings in the thyroidal carcinoma: pathologic study of 256 cases. J Clin Endocrinol Metab 19: 162–171.

Morrison J & Caplan R H (1978): Typical and atypical (silent) subacure thyroiditis in a wife and husband. Arch Int Med 138: 45–48.

Nerup J (1974a): Addison's disease – clinical studies. A report of 108 cases. Acta Endocrinol (Copenh) 76: 127–141.

Scherbaum W A, Rosenau K O & Seif F J (1979): Antikörper gegen Schilddrüsenmikrosomen und Thyreoglobulin beim Morbus Basedow und anderen Erkrankungen. Med Welt 30: 1401–1406.

Scherbaum W A, Stöckle G, Wichmann J & Berg P A (1982): Immunological and clinical characterization of patients with untreated euthyroid and hypothyroid autoimmune thyroiditis. Antibody spectrum, response to TRH and clinical study. Acta Endocrinol (Copenh) 100: 373–381.

Sirota D K & Segal R L (1979): Primary lymphomas of the thyroid gland. JAMA 242: 1743–1746.

Tunbridge W M G, Evered D C, Hall R, Appleton D, Brewis M, Clark F, Grimley-Evans J, Hall R, Smith P, Stephenson J & Young E (1981): Natural history of autoimmune thyroiditis. Br Med J 282: 258–262.

Volpé R (1979): Subacute (de Quervain's) thyroiditis. Clin Endocrinol Metab 8: 81–95.

Walker D J, Griffith M & Griffith I D (1986): Occurrence of autoimmune diseases and autoantibodies in multicase rheumatoid arthritis families. Ann Rheum Dis 45: 323–326.

Yoshida H, Amino N, Yagawa K, Uemura K, Satoh M, Miyai K & Kumahara Y (1978): Association of serum antithyroid antibodies with lymphocytic infiltration of the thyroid gland: studies of seventy autopsied cases. J Clin Endocrinol Metab 46: 859–862.

Zakarija M & McKenzie J M (1983): Pregnancy-associated changes in the thyroid-stimulating antibody of Graves' disease and the relationship to neonatal hyperthyroidism. J Clin Endocrinol Metab 57: 1036–1040.

W. A. Scherbaum,
Department of Internal Medicine I,
University Hospital,
D-7900 Ulm,
FRG.