Status of antithyroid antibodies in Bangladesh

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Abstract

To study autoimmunity among thyroid diseases, 397 thyroid patients (age 30 (13) years; M/F 75/322) from two referral centres in Bangladesh and 94 healthy controls (age 30 (13) years; M/F 24/70) were studied for antimicrosomal and antithyroglobulin antibodies. Thyroid patients were clinically grouped as suspected autoimmune thyroid disease (AITD), non-autoimmune, or indeterminate groups (where no decision could be reached). Antimicrosomal antibody was strongly positive in 19.4% and weakly positive in 7.3% of patients but only 4.3% and 2.1% respectively in the controls ($\chi^2 = 17.852$; $p = 0.000$) whereas strong and weak positivity were 27.2% and 6.8% in patients compared with 8.5% and 4.3% respectively in the controls ($\chi^2 = 16.916$; $p = 0.000$) for antithyroglobulin antibody. Antibodies were positive in 63.0% with Hashimoto's thyroiditis, 36.4% with Graves' disease, and 44.7% with atrophic thyroiditis among the autoimmune group. In the non-autoimmune group antibodies were positive in 100% with multinodular hypothyroidism, 46.7% with subacute thyroiditis, 40.0% with suspected iodine deficiency goitre, 31.3% with toxic multinodular goitre, 30.8% with non-toxic solitary nodules, and 19.4% with simple diffuse goitre. None was positive for antimicrosomal antibody without being positive for antithyroglobulin antibody. The two antibodies strongly correlated in both patients ($r = 0.977$, $p = 0.000$) and controls ($r = 0.986$, $p = 0.000$). About 9% (36/397) of patients were mismatched with the final diagnosis on antibody measurement; most of them had Hashimoto's thyroiditis (33/36). Prevalence of AITD among thyroid patients was 48.36%. Specificity of antimicrosomal and antithyroglobulin antibodies were 93% and 87%. It was concluded that AITD is not uncommon in Bangladesh; antimicrosomal antibody is a useful marker for AITD and unless antibodies are checked, an appreciable number of patients with AITDs will remain undetected.

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Thyroid diseases are classified into two groups: autoimmune thyroid disease (AITD) and non-autoimmune thyroid disease (NAITD) on the basis of presence of antithyroid antibodies.^{1–4} Iodine deficiency was found to be hyperendemic in Bangladesh in 1993 in the national survey on goitre.⁵ Some subsequent investiga-

tions in the country attributed endemic goitre to widespread iodine deficiency.^{6–8} Classic AITDs are Graves' disease and Hashimoto's, atrophic, silent as well as postpartum thyroiditis; the rest of the thyroid disorders are considered NAITDs. The autoimmune phenomenon has been observed to coexist in some cases of NAITD interfering with the disease process.^{9–12} Although the nature of the disease may be suspected, diagnosis is often difficult, but it is essential for long term management. A few recent studies have observed the frequency of thyroid autoimmunity and cancer to be higher than it was before iodine prophylaxis in some countries.^{1–13} Estimation of antithyroid antibodies has an important role for diagnosis.¹⁴ Absence of antibodies may not exclude autoimmunity, but presence of antibodies almost always confirms it except in a few situations.¹ Antithyroglobulin antibody is a somewhat weaker marker for discriminating between AITD and NAITD,^{15–16} but antimicrosomal antibody is highly specific for AITD.² Antithyroid antibodies may be positive in a limited percentage of healthy controls and in ~11% of NAITDs.³ High iodine intake as well as widely varying concentration of dietary iodine day to day increases vulnerability to development of thyroid autoimmunity.^{1–13–19} Experimental evidence of the autoimmune phenomenon has been observed recently in NAITDs.^{9–20} Thyroid autoimmunity has not been studied by any group in Bangladesh before. We investigated antimicrosomal and antithyroglobulin antibodies to determine the prevalence of autoimmunity among thyroid diseases in Bangladesh.

Patients and methods

Patients with thyroid diseases ($n = 397$, age 30 (13) years; M/F 75/322) were recruited from two referral centres after informed consent. Ninety four age and sex matched healthy subjects (age 30 (13); M/F 24/70) were recruited from hospital visitors only if their thyroid hormones were within the normal range (triiodothyronine 0.8–3.16 nmol/l; thyroxine 64.5–152.0 nmol/l; thyroid stimulating hormone 0.47–5.0 mU/l). None of the subjects was pregnant or had any concurrent illness that could interfere with thyroid function and all were below the age of 60 years. A uniform physical examination was done for all thyroid patients after taking a thorough clinical history. On the basis of clinical findings and laboratory investigations they were classified into three clinical subgroups on consultation with a board of consultants before the estimation of antithyroid antibodies. The clinical subgroups were: AITD, NAITD, and indeterminate (this group included those in whom no decision could be reached about autoimmunity). Thus, AITD

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Table 1 Antibody positivity in suspected autoimmune (AITD), non-autoimmune (NAITD), and indeterminate groups of total thyroid patients

Subjects (clinical suspect)	Weak positive	Strong positive	Negative
Antimicrosomal antibody (%)			
AITD (n=156)	17 (10.9)	43 (27.6)	96 (61.5)
NAITD (n=220)	9 (4.1)	30 (13.6)	181 (82.5)
Indeterminate (n=21)	3 (14.3)	4 (19.0)	14 (66.7)
Total thyroid patients (n=397)	29 (7.3)	77 (19.4)	291 (73.3)
Controls (n=94)	2 (2.1)	4 (4.3)	88 (93.6)
χ^2		17.852	
p Value		0.000	
Antithyroglobulin antibody (%)			
AITD (n=156)	13 (8.3)	62 (39.7)	81 (51.6)
NAITD (n=220)	11 (5.0)	40 (18.2)	169 (76.8)
Indeterminate (n=21)	3 (14.3)	6 (28.1)	12 (57.1)
Total thyroid patients (n=397)	27 (6.8)	108 (27.2)	262 (66.0)
Controls (n=94)	4 (4.3)	8 (8.5)	82 (87.2)
χ^2		16.916	
p Value		0.000	

comprised Graves' disease, Hashimoto's thyroiditis, atrophic thyroiditis, silent thyroiditis and postpartum thyroiditis; the indeterminate group those in whom possibility of these varieties of autoimmunity could not be clearly excluded on clinical grounds; and the rest of the thyroid diseases were classified as NAITD. After the measurement of antibodies was completed, each patient's profile was reviewed by the same board of consultants and final assignment to the AITD or NAITD group and their mismatch with initial clinical suspicion was verified. The study was carried out after approval by the Institutional Review Board and Ethical Committee of BIRDEM.

For measurement of antimicrosomal and antithyroglobulin antibodies, serum from each subject was preserved at -70°C until assay. Antibodies were measured by enzyme linked immunosorbent assay (ELISA) using a commercial kit (INOVA Diagnostics Inc, San Diego, USA) with the help of a computerised program of a Kc3 biograph. Antibody titre ≥ 130 units for antimicrosomal and ≥ 150 units for antithyroglobulin antibody were considered positive whereas values >250 units were

considered as strongly positive for both the antibodies. Interassay coefficient variance for antimicrosomal and antithyroglobulin were 7%–17% and 8%–15% respectively. Coefficient variance for triiodothyronine, thyroxine, and thyroid stimulating hormone measurement for control subjects were 3.7%, 6.3%, and 0.8% respectively. Subjects positive for any of the two antibodies or for both were considered positive for antithyroid antibodies.

Statistical analysis of data was done by Statistical Program for Social Studies (SPSS for Windows, release 6.0). Data are expressed in frequencies or mean (SEM) unless stated otherwise. Comparisons were done by the χ^2 test, McNemar's test, Kruskal-Wallis one way analysis of variance, and Pearson's linear correlation as applicable. Only a p value ≤ 0.05 was considered significant.

Results

CLINICAL SUSPICION FOR AUTOIMMUNITY AND FREQUENCY OF POSITIVE ANTIBODIES

Among thyroid patients, 19.4% (77/397) were strongly positive, 7.3% (29/397) were weakly positive, and 73.3% (291/397) were negative for antimicrosomal antibody in comparison with only 4.3% (4/94), 2.1% (2/94), and 93.6% (88/94) respectively in the control group ($\chi^2 = 17.852$; $p = 0.000$). For the antithyroglobulin antibody, the frequency for strongly positive, weakly positive, and negative was 27.2% (108/397), 6.8% (27/397), and 66.0% (262/397) respectively among thyroid patients in comparison with 8.5% (8/94), 4.3% (4/94), and 87.2% (82/94) in the control group ($\chi^2 = 16.916$; $p = 0.000$). It was found that 13.6% of suspected NAITD and 19% of the indeterminate group were strongly positive, and 4.1% of NAITD and 14.3% of the indeterminate group were weakly positive for antimicrosomal antibody. For antithyroglobulin antibody 18.2% were strongly and 5.0% were weakly positive

Table 2 Individual impact of antimicrosomal (anti-MIC) and antithyroglobulin (anti-TG) antibodies in autoimmune (AITD) and non-autoimmune (NAITD) groups of thyroid patients and healthy control subjects

Clinical suspect	Positive (%)				Negative (%) both	p Value
	Both	Only anti-TG	Only anti-MIC	Total		
AITD						
Graves' disease	18 (27.3)	6 (9.1)	0	24 (36.4)	42 (63.6)	0.0313
Hashimoto's thyroiditis	30 (55.6)	4 (7.4)	0	34 (63.0)	20 (37.0)	0.1250
Atrophic hypothyroidism	12 (31.6)	5 (13.1)	0	17 (44.7)	21 (55.3)	0.0625
Postpartum thyroiditis	0	0	0	0	1	—
Silent thyroiditis	0	0	0	0	1	—
NAITD						
Simple diffuse goitre	12 (12.9)	6 (6.5)	0	18 (19.4)	75 (80.6)	0.0313
Simple uninodular goitre	1 (3.7)	1 (3.7)	0	2 (7.4)	25 (92.6)	1.0000
Simple multinodular goitre	3 (21.4)	1 (7.1)	0	4 (18.5)	10 (71.5)	1.0000
Iodine deficiency goitre	12 (40.0)	0	0	12 (40.0)	18 (60.0)	1.0000
Multinodular hypothyroidism	5 (100.0)	0	0	5 (100.0)	0	—
Subacute thyroiditis	4 (26.7)	3 (20.0)	0	7 (46.7)	8 (53.3)	0.2500
Toxic multinodular goitre	5 (31.3)	0	0	5 (31.3)	11 (68.7)	1.0000
Toxic adenoma	0	1 (25.0)	0	1 (25.0)	3 (75.0)	1.0000
Non-toxic adenoma	0	1 (11.1)	0	1 (11.1)	8 (88.9)	1.0000
Non-toxic solitary nodule	3 (23.1)	1 (7.7)	0	4 (30.8)	9 (69.2)	1.0000
Thyroid cyst	1 (12.5)	0	0	1 (12.5)	7 (87.5)	1.0000
Cancer	0	0	0	0	2	—
Cretinism	0	0	0	0	1	—
Controls	6 (6.4)	6 (6.4)	0	12 (12.8)	82 (87.2)	0.0313
Total	112 (22.8)	35 (7.1)	0	147 (29.9)	344 (70.1)	0.0000

McNemar's test (for last row): $\chi^2=33.0286$; $p=0.000$.

Among both positive (n=112): both weak positive = 4 (3.6%); weak anti-MIC but strong anti-TG = 27 (24.1%).

Among only anti-TG positive (n=35): weak positive anti-TG = 27 (77.1%); strong positive anti-TG = 8 (22.9%).

Table 3 Diagnostic impact of antithyroid antibodies

Clinical suspicion	No	Matched with final diagnosis	Mismatched (%)
Graves' disease	66	66	0
Hashimoto's thyroiditis	54	53	1 (1.9)
Atrophic hypothyroidism	38	38	0
Simple diffuse goitre	93	81	12 (12.9)
Simple uninodular goitre	27	26	1 (3.7)
Simple multinodular goitre	14	11	3 (21.4)
Iodine deficiency goitre	30	21	9 (30.0)
Multinodular hypothyroidism	5	0	5 (100)
Non-toxic adenoma	9	8	1 (11.1)
Non-toxic solitary nodule	13	9	4 (30.8)
Others	48	48	0
Total	397	361	36 (9.1)

Thirty three out of mismatched 36 fell into the subgroup of Hashimoto's thyroiditis on final diagnosis.

for suspected NAITD and in the indeterminate group 28.1% and 14.3% respectively. However, a good number of those with clinically suspected AITD were negative for antimicrosomal (61.5%) and antithyroglobulin (51.6%) antibodies (table 1).

FREQUENCY OF POSITIVE ANTIBODIES AMONG VARIOUS CLINICAL SUBGROUPS OF THYROID DISORDERS

Table 2 shows the frequencies of positive antibodies among patients of various clinically suspected thyroid diseases. Of the suspected NAITDs, 100% of those with multinodular hypothyroidism, 46.7% with subacute thyroiditis, 40.0% with suspected iodine deficiency goitre, 31.3% with toxic multinodular goitre, 30.8% with non-toxic solitary nodule, 18.5% with simple multinodular goitre, and 19.4% with simple diffuse goitre were positive for antithyroid antibodies. Among the clinically suspected AITDs, 63.0% with Hashimoto's thyroiditis, 36.4% with Graves' disease, and 44.7% with atrophic hypothyroidism were positive for antithyroid antibodies. In the control group, only 12.8% were positive for the antibodies. None of the subjects was positive for antimicrosomal antibody without being positive for antithyroglobulin antibody in the clinically suspected subgroups of thyroid disorders and in the control group. However, in some of the subgroups, antithyroglobulin antibody was positive without being positive for antimicrosomal antibody. Only 3.6% (4/112) were weakly positive for both the antibodies. However, 24.1% (27/112) were weakly positive for antimicrosomal but strongly positive for antithyroglobulin antibody whereas among the subjects who were positive for only antithyroglobulin antibody, most of them (77%;

Table 4 Prevalence of autoimmune thyroid disease; sensitivity, specificity, accuracy, and predictive values of antibody (final diagnosis as gold standard)

Items	All thyroid patients (%)	All subjects (%)
Prevalence	48.36	39.31
Sensitivity	56.25	55.96
Specificity	86.83	86.91
Overall accuracy	72.04	74.75
Positive predictive value	80.00	73.47
Negative predictive value	67.94	75.29

For the thyroid patients—sensitivity: antimicrosomal, 47.67%; antithyroglobulin, 56.25% and specificity: antimicrosomal, 93.14%; antithyroglobulin, 86.83%.

Figure 1 Relationship between antimicrosomal and antithyroglobulin antibodies (○ = thyroid patients; ● = controls; WHO = World Health Organisation).

27/35) were weakly positive for the antibody. Thus there is an overall greater importance of antimicrosomal antibody.

DIAGNOSTIC IMPORTANCE OF ANTIBODIES

As shown in table 3, it was observed that overall 9.1% (36/397) patients were correctly diagnosed by the measurement of antithyroid antibodies. Thirty three out of 36 patients who were incorrectly diagnosed fell into the subgroup of Hashimoto's thyroiditis. Of the clinically suspected subgroups, 100% of those with multinodular goitre, 30.0% with suspected iodine deficiency goitre, 21.4% with simple multinodular goitre, 30.8% with non-toxic solitary nodule, and 12.9% of simple diffuse goitre were found to be mismatched with their final diagnosis. However, in light of the final diagnosis (table 4), prevalence of thyroid autoimmunity among the thyroid patients was 48.36%. Overall sensitivity and specificity of antibody test were 56.25% and 86.83% respectively among patients. On the other hand, sensitivity of antimicrosomal antibody was 47.67% and specificity 93.14%, which was 56.25% and 86.83% respectively for antithyroglobulin antibody.

CORRELATION

Figure 1 shows that the correlation between the two antibodies was highly significant in both thyroid patients ($r = 0.977$; $p = 0.000$) and the control group ($r = 0.986$; $p = 0.000$).

Discussion

Antithyroid antibodies are good markers for the assessment of thyroid autoimmunity. In an attempt to find the frequency of positive antibodies among thyroid diseases, we have observed that prevalence of autoimmunity in the patients with thyroid diseases is quite high in Bangladesh. Moreover, autoimmunity in an appreciable number of thyroid patients may remain undetected unless they are checked for antithyroid antibodies.

Compared with healthy controls, thyroid patients were found to be more frequently positive for antithyroid antibodies. Though antithyroid antibodies were more frequently positive among Hashimoto's thyroiditis, atrophic hypothyroidism and Graves' disease,

which are known AITDs, quite a few patients in these subgroups were found to be negative. On the other hand, all the multinodular hypothyroid patients as well as many of those with toxic multinodular goitre, subacute thyroiditis, suspected iodine deficiency goitre, and non-toxic solitary nodule were also positive for antithyroid antibodies. It was interesting to observe that many patients with suspected NAITDs and in the indeterminate group were positive for antibodies. In light of the above facts, it is clear that being negative for antibodies does not necessarily exclude thyroid autoimmunity in many instances; but when antibodies are positive, it strongly indicates the autoimmune nature of the disease. Immunological interference has also been found by some studies abroad in NAITD.^{10-12 21 22} The autoimmune phenomenon should not differ between healthy controls and those with NAITD living under the same environmental conditions; again this would indicate that these antibody positive patients were suffering from AITDs. It is worth mentioning that we have observed positive antithyroid antibodies more frequently among patients with multinodular and diffuse goitre (43% and 36% respectively) as well as among hyperthyroid (37%) and hypothyroid (55%) patients. On the other hand, both mean and median urinary iodine were found higher in multinodular and diffuse goitre as well as in hyperthyroid patients; also both of these were higher among the thyroid patients than controls. However, in none of the groups were these below the cut off value (10 µg/dl) for iodine deficiency (unpublished data).

Antithyroid antibodies are good markers of thyroid autoimmunity.¹⁻⁴ The relationship between the two antibodies was highly significant; this was true for both the thyroid patients and control subjects. Thus, it can be assumed that thyroid autoimmunity involves these two antibodies equally. However, some of the patients and control subjects positive for antithyroglobulin antibody were not positive for antimicrosomal antibody, but none of the subjects were found positive for antimicrosomal antibody without being positive for antithyroglobulin. Many laboratories are now restricting their analysis of thyroid antibodies to the antimicrosomal antibody alone.^{2 23} If this is the case then a small percentage of patients with positive antithyroglobulin antibody will be missed, as has been demonstrated by this study. Therefore, it could be argued that antimicrosomal antibody is not entirely informative in the context of AITD.

About 9% patients would have been incompletely diagnosed unless antithyroid antibodies were assayed. Most of these patients were clinically suspected as having simple diffuse goitre, iodine deficiency goitre, multinodular goitre with hypothyroidism, and non-toxic solitary nodule. Out of the 36 mismatched patients, 33 had Hashimoto's thyroiditis. In the present study, calculated prevalence of autoimmunity among thyroid patients was 48.36%. Sensitivity of antibody tests in identifying AITD was not too high but the

specificity was 87%. Thus tests for antithyroid antibodies can be considered useful in identifying existing thyroid autoimmunity which could not be easily predicted by clinical information only. This is important especially in multinodular hypothyroid, simple diffuse goitre, and iodine deficiency goitre, which are often considered clinically as iodine deficiency related disorders.

In conclusion, prevalence of AITD is quite high in Bangladesh. Antimicrosomal antibody is an important and specific marker for thyroid autoimmunity. An appreciable number of patients with simple diffuse, toxic multinodular, and iodine deficiency goitres were found positive for antithyroid antibodies indicative of coexistent autoimmune phenomenon, which may be missed unless they are investigated for antibodies.

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Medical Anniversary

Benjamin Collins Brodie, 9 June 1783

(Sir) Benjamin Collins Brodie (1783–1862) was born at Winterslow, Wiltshire, son of a parish rector, and educated at St Bartholomew's and Great Windmill Street School of Medicine. He qualified in medicine (1805) and eventually became surgeon at St George's Hospital (1808), FRS (1810), PRS (1858), and first president of the General Medical Council (1858). His textbook on diseases of the joints (1821) includes a good description of Reiter's syndrome, so many refer to the disorder as Reiter-Brodie syndrome. He helped to found the Atheneum. He died in his country home in Surrey on 21 October 1862.—*D G James*