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ORIGINAL ARTICLE

The spectrum of thyroid disorders in systemic lupus erythematosus

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Abstract To study the spectrum of thyroid disorders in systemic lupus erythematosus (SLE). Hundred SLE patients as per American Rheumatology Association(ARA) classification criteria underwent clinical examination, including assessment of disease activity (SLEDAI) and laboratory evaluation for serum triiodothyronine (T3),free thyroxine (FT4), thyroid stimulating hormone (TSH), antithyroperoxidase (TPO) antibody and antithyroglobulin (TG) antibody. Hundred age- and sex-matched apparently healthy individuals served as control. Thirty-six (36%) lupus patients had thyroid dysfunction when compared to 8 (8%) of controls and all of them were women. Primary hypothyroidism was the commonest dysfunction in 14 (14%), while subclinical hypothyroidism and subclinical hyperthyroidism was seen in 12 (12%) and 2 (2%), respectively. Eight (8%) had isolated low T3 consistent with sick euthyroid syndrome. Eighteen (50%) of thyroid dysfunction were autoimmune in nature (autoantibody positive) and rest 18 (50%) were non-autoimmune. Euthyroid state with the elevation of antibodies alone was seen in 12 (12%) of the lupus patients. In contrast, only 5 (5%) of controls had primary hypothyroidism and 3 (3%) had subclinical hypothyroidism, while none had hyperthyroidism. SLEDAI score and disease duration were compared between lupus patients with thyroid dysfunction to those with normal thyroid function. A statistically significant association was found between SLEDAI and thyroid dysfunction of sick euthyroid type.SLE disease duration had no statistically significant association with thyroid dysfunction. Prevalence of thyroid autoantibodies in lupus patients was 30% when compared to 10% of controls. Ninety-six (96%) of the SLE patients were ANA positive, while 4 (4%) of them were ANA negative but were anti-Sm antibody positive. There were no suggestions of any other autoimmune endocrine diseases like diabetes or Addison's disease (clinically and on baseline investigations) in our lupus cohort and hence no further work up was done for these diseases. Thyroid disorders are frequent in SLE and are multifactorial with a definite higher prevalence of hypothyroidism as well as thyroid autoantibodies.

Keywords SLE · Autoimmune thyroid disorder · Antithyroid antibodies · Sick euthyroid · Subclinical hypothyroidism

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Introduction

The association between systemic lupus erythematosus (SLE) and thyroid abnormalities was first described in 1961 by White et al. [1] and Hijmans et al. [2], who showed that the presence of thyroid dysfunction appeared to be more frequent in SLE patients than in the general population [3]. A number of studies have suggested that thyroid disease is

Table 1 Studies on thyroid function and presence of autoantibodies in patients with SLE (%)

Reference no.	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	Our study
No. of cases	319	332	45	63	300	100	153	524	100
Primary hypothyroidism	0.94	6.6	8.8	9.5	5.7	4	7.8	5.3	14
Subclinical hypothyroidism	0	39	ND	1.6	ND	10	2.6	11.5	12
FT4 low	ND	ND	ND	ND	ND	1	0	ND	0
Hyperthyroidism	2.82	3	ND	3	1.7	0	1.3	ND	0
Subclinical hyperthyroidism	ND	ND	ND	ND	ND	2	0	ND	2
Antithyroid antibodies	ND	20	46.7	27	14	6	13.1	17	30

ND no available data

more common in SLE than in the general population (Table 1) but there is disagreement as to whether both hypothyroidism and hyperthyroidism are more common or whether this finding is restricted to hypothyroidism alone. The underlying mechanism and the non-specific thyroid function abnormalities are also not well defined.

Thyroid involvement being non-life-threatening than other organ involvement in SLE, it is often under looked and goes undetected for long contributing to the morbidity of the illness. Thyroid dysfunction in SLE can have varied underlying pathogenetic mechanisms, autoimmunity being just one of them. Thyroid being one of the common target of autoimmune process, its association with SLE, a systemic autoimmune disease is likely. Autoimmune thyroid disease, marked by the presence of antibodies directed against thyroid antigens, has been associated with a number of non-organ-specific rheumatologic disorders like systemic lupus erythematosus [5–10], Sjögren's syndrome [12], rheumatoid arthritis [10] and giant cell arteritis [13].

Thyroid derangement is more than it can be accounted by autoimmunity in SLE patients. Several other mechanisms of thyroid dysfunction include the effect of underlying systemic illness (sick euthyroid syndrome), drug effects (like corticosteroid, immunosuppressants commonly used in treatment of SLE) or just a mere coincidence due to similar population affected. Both antithyroglobulin and antiperoxidase antibodies have been found with greater frequency in SLE than in the general population, even in lupus patients who do not have clinical thyroid disease (Table 2). It is still a subject of discussion as to whether SLE is an independent risk factor for these thyroid abnormalities or whether this is a coincidental finding because the group most at risk for SLE, young to middle-aged women, is precisely the same group most at risk for autoimmune thyroid disease.

Symptoms of thyroid disease can be confused with those of lupus. Even subclinical dysfunctions can be present in these patients with its antecedent damaging effects and often goes unrecognised. So, it is necessary to identify the thyroid dysfunction in patients with lupus and treat them accordingly.

Materials and methods

The study was an observational cross sectional study involving patients attending Lupus clinic, Department of Rheumatology and Clinical immunology, IPGMER, Kolkata, West Bengal, India. The study was done from January 2008 to December 2009. Hundred consecutive patients (either newly diagnosed or follow up) satisfying American Rheumatology Association's revised criteria for classification as SLE published in 1997, irrespective of disease duration, severity and treatment received (for SLE) were consecutively selected and assessed for SLE disease activity by SLEDAI and investigated for thyroid function test by FT4 (free thyroxine), T3 (tri iodothyronine), TSH (thyroid stimulating hormone) and thyroid autoantibodies (anti-TPO and anti-TG). Hundred age- and sex-matched apparently healthy individuals were taken as control for comparison who also underwent thyroid function assessment (serum T3, FT4, TSH, anti-TPO and anti-TG antibodies).The thyroid hormones were estimated by chemiluminescent immunoassay (CLIA). CLIA is a third-generation assay and can detect TSH up to accuracy of <0.02 μU/ml. It was done using ARCHITECT immunoassay analyzer (Abbott Diagnostics).

Elevated TSH with low T3/FT4 was categorized as primary hypothyroid, while those with high TSH with normal T3/FT4 was considered as subclinical hypothyroid. Similarly, low TSH with raised T3/FT4 and normal T3/FT4 were called primary hyperthyroid and subclinical hyperthyroid, respectively. Any other thyroid function abnormality not fitting with the above pattern was considered non-specific and was included under sick euthyroid pattern (classically isolated low T3), which per se does not require any treatment and the treatment of the underlying disease itself corrects this abnormality.

The nature of study was explained to each patient, and written consent was obtained, according to the Declaration of Helsinki (Br Med J 1996;31:1448-9), from all of them fulfilling the inclusion criteria. The subjects were assessed clinically using a case record format followed by

Table 2 Studies on the prevalence of anti-TPO antibody and anti-TG antibody in patients with SLE

Reference number	Number of lupus patients	Number with anti-TPO Ab	Number with anti-TG Ab	Number with both Ab
Our study	100	12	4	14
[3]	42	7	3	–
[6]	45	21	13	–
[8]	300	36	28	25
[16]	41	16	15	10
[17]	100	19	11	9
[20]	129	43	21	18
[31]	35	7	10	–
[34]	4	4	5	2

TPO thyroperoxidase, *TG* thyroglobulin, *Ab* antibody

above-mentioned laboratory investigations. Data were analyzed by standard statistical methodology and intergroup comparisons were made using unpaired student *t* test. The study was approved by Institutional Ethics Committee, IPGMER, Kolkata (INDIA).

Results

A total of 100 patients and 100 controls (age and sex matched) were enrolled in the study. The mean age of the study group was found to be 26.6 years (±9.42) with minimum of 12 years and maximum of 50 years. Twelve (12%) of our study population were men, while rest 88 (88%) were women consistent with higher prevalence of SLE in female population. Ninety-six (96%) of the SLE patients were ANA positive, while 4 (4%) of them were ANA negative but were anti-Sm antibody positive. There were no suggestions of any other autoimmune endocrine diseases like diabetes or Addison's disease (clinically and on baseline investigations) in our lupus cohort and hence no further work up was done for these diseases.

Thirty-six (36%) of lupus patients had thyroid dysfunction when compared to 8 (8%) of controls and all of them were women. Primary hypothyroidism was the commonest dysfunction in 14 (14%) of them. Subclinical hypothyroidism was seen in 12 (12%). Subclinical hyperthyroidism was seen in 2 (2%). Eight (8%) had isolated low T3 consistent with sick euthyroid syndrome. In contrast, only 5 (5%) of controls had primary hypothyroidism and 3 (3%) of them had subclinical hypothyroidism, while none had hyperthyroidism or any other thyroid dysfunction. Six of these 8 controls having thyroid dysfunction had positive thyroid autoantibodies .

Thirty of 100 lupus patients (30%) were positive for thyroid autoantibodies (anti-TPO or anti-TG or Both). Twelve (12%) had anti-TPO antibody, while 4 (4%) had anti-TG antibody and 14 (14%) had both antibodies. Of 36 patients with thyroid dysfunction, only 18 (50%) were positive for antibodies and hence autoimmune in nature. Rest 18 (50%) were non-autoimmune in nature. This non-autoimmune group included patients with low T3 (sick euthyroid) and all these patients were on high-dose corticosteroid and other immunosuppressives owing to their higher disease activity. Twelve (12%) of the SLE patients had no thyroid dysfunction but they had antibodies when compared to 4% of controls. Distribution of thyroid dysfunction against their antibody status in SLE patients and control group is shown in (Table 3).

The mean disease duration of SLE was 40.8 (±45.83) months with maximum duration of 216 months (18 years) and minimum of just 2 months. The average of SLE disease duration was 41 months (SD 41.09) in patients with thyroid dysfunction and 40.68 months (SD 48.62) in patients with normal thyroid function.

Our study population had a mean SLEDAI of 7.9 (±6.8) with a range from 0 to 29. The mean of SLEDAI score was 6.69 (SD 6.68) in patients with normal thyroid function and 10.11 (SD 6.58) in patients with abnormalities. Primary hypothyroid group had mean SLEDAI of 8.71, while it was 9.5 in subclinical hypothyroid group and 15 in low T3 (Sick euthyroid) group. SLEDAI score and disease duration were compared between lupus patients with thyroid dysfunction to those with normal thyroid function. Using unpaired student *t* test, a statistically significant association was found between SLEDAI and thyroid dysfunction of sick euthyroid type ($P = 0.03$), while there was no statistically significant association between SLE disease duration and thyroid dysfunction ($P = 0.97$). Other subgroups of thyroid dysfunction had no statistically significant association to SLEDAI.

Discussion

Autoimmune diseases can occur concomitantly in the same patient in various forms of association. In 1956, Roitt et al. [14] described three patients with rheumatoid arthritis and

Table 3 Distribution of thyroid antibodies and dysfunction in our study and control group

	SLE patients ($n = 100$)		Control group ($n = 100$)	
	ATA positive	ATA negative	ATA positive	ATA negative
Primary hypothyroidism	12	2	4	1
Subclinical hypothyroidism	6	6	2	1
Primary hyperthyroidism	–	–	–	–
Subclinical hyperthyroidism	–	2	–	–
Sick euthyroid	–	8	–	–
No thyroid dysfunction	12	52	4	88

ATA antithyroid antibody

Hashimoto's thyroiditis. In 1961, the first cases of SLE and Hashimoto's thyroiditis were reported [1, 2]. Since these initial studies, the association between systemic and organ-specific autoimmune diseases has been investigated. Although the presence of autoimmune thyroid alterations occurs more frequently in SLE patients as shown by previous studies (Table 1) than in the general population (where the incidence of hypothyroidism is estimated to be of 1% [3] in western population, while it is 5.4% in Indian population [15]), this subject is still a matter of controversy. The results of these studies show discrepancies in relation to the thyroid dysfunction types more commonly encountered.

In agreement with most other studies [5, 7, 8], primary hypothyroidism (14%) and subclinical hypothyroidism (12%) were the most common alterations among our SLE patients, which was significantly higher when compared to control group (5 and 3%, respectively). A much higher prevalence of hypothyroidism in our lupus patients when compared to lupus cohort of other studies (Table 1) may be attributed to higher prevalence of thyroid disorders in Asians than western population with SLE further raising the risk over and above the ethnic predisposition. However, in two patients, the diagnosis of subclinical hyperthyroidism was made. Supporting this conclusion is the fact that the association between SLE and Graves' disease has rarely been described [18, 19]. The frequency of hyperthyroidism in the normal population is approximately 1.9% [3]. Larger studies [8, 17, 20], including our own, suggest there is no increase in the prevalence of hyperthyroidism in patients with SLE when compared to general population. Two studies have suggested that there is no statistically significant difference in the prevalence of thyroid disease in SLE compared with age- and sex-matched controls [6, 17] despite a higher prevalence of antithyroglobulin antibodies being found in the SLE group [17]. Contrary to these two studies, our study clearly shows a significant higher prevalence of thyroid disease in SLE cohort when compared to age- and sex-matched control (36 vs. 8%).

The study of thyroid function in patients with SLE comes up against some factors of interference, such as the state of lupus activity, the age of patients and the use of immunosuppressive drugs. Acute and chronic systemic conditions are associated with a significant decrease in the serum concentration of total triiodothyronine (T3) and free triiodothyronine (fT3) [21]. This condition, variously known as "Low-T3 syndrome", "Euthyroid sick syndrome" or "Nonthyroidal illness syndrome(NTIS)'', has been described in patients with various medical and surgical conditions [22–27] and after ingestion of drugs like amiodarone[28], corticosteroids[29], propranolol [30] and even in SLE [7].Drugs and factors like renal failure, liver disease etc. may have an impact on thyroid function in the form of sick euthyroid syndrome in SLE patients. Consistent with this concept, we also got a subgroup of patients with isolated low T3 levels (8%) usually considered commonest abnormality of sick euthyroid syndrome. This subgroup had statistically significant difference of SLEDAI than those without thyroid dysfunction, implying a role of lupus disease activity on this type of thyroid abnormality in SLE patients. All these patients were also on high-dose corticosteroids and other immunosuppressives owing to their higher disease activity, indicating a possible role of these drugs on such type of thyroid dysfunctions. This is the group which have a non-specific thyroid dysfunction, requiring treatment for the underlying disease but not for the thyroid abnormality. However, the study by Park et al. [7], which used the European Consensus Lupus Activity Measurement (ECLAM), and study by Adriana [9] using SLEDAI failed to show any significant relation between thyroid dysfunction and lupus disease activity, possibly because of absence of such non-specific thyroid derangement in their lupus cohort.

In our study, 30 patients (30%) were positive for antibodies against the thyroid when compared to only 10% positivity in the control group. Hence, a significant higher prevalence of thyroid autoantibodies occur in lupus patients, easily explainable on the basis of underlying systemic autoimmunity in these patients. Twelve (12%) of SLE patients had no thyroid function abnormality (euthyroid with positive antibodies) in comparison with 4% in the control group, again a significant higher prevalence. This subgroup of patients can be closely followed up for the development of clinical thyroid disease. An incidence of

43% of positivity for autoantibodies against the thyroid has been described in children with lupus [31], while in the studies of Kausman et al. [32], Magaro et al. [33] and Weetman and Walport [16], a positivity of 21, 45.5 and 51% was described, respectively. Both anti-TG and anti-TPO antibodies were detected in our study. Overall, there was a trend toward TPO antibodies being found more frequently. This trend has been observed in earlier studies as shown in (Table 2).

Disease duration had no statistically significant effect on thyroid function abnormalities, suggesting that the course of the two diseases, although interlinked, may be independent.

A great variety of symptoms and signs are possible manifestations that could be described as thyroid dysfunction or could be exclusively related to lupus. It is interesting to note that rheumatic manifestations are also frequently found in thyroid disease, suggesting the possible role of the underlying autoimmune imbalance [35]. Clinically, both overlap and thyroid are often missed in this setting. Hence, the presence of non-specific suggestive symptoms in a lupus patient inspite of a lower disease activity may be a clinical pointer to the underlying thyroid disorder requiring laboratory evaluation and treatment for it rather than increasing immunosuppression as against higher disease activity–associated thyroid derangements that are usually non-specific and require no treatment per se for itself, and upgrading immunosuppression may resolve symptoms in them.

Conclusion

Thyroid disorders are frequent in SLE. Thyroid dysfunction in SLE is multifactorial and there is a definite higher prevalence of hypothyroidism as well as thyroid autoantibodies in SLE cohorts. Non-autoimmune thyroid dysfunctions are almost equally prevalent as autoimmune thyroid dysfunctions. Sick euthyroid occur in SLE patients especially with those having higher disease activity and on high-dose corticosteroid and immunosuppressives. Thyroid disease can occur at any part of the illness and the course of the two diseases, although interlinked, may be independent. Clinical and laboratory discordance occurs possibly due to multifactorial causation of thyroid disease in this cohort and significant overlap of symptoms between the two.

All this should be taken into consideration when evaluating these patients. However, larger prospective case–control studies are needed to further establish the relation between SLE and thyroid disease so that standard guidelines may be formulated, regarding routine thyroid screening in SLE patients, as for other organ involvement.

Conflict of interest The authors do not have any conflict of interest.

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