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Original Article

Does systemic sclerosis affect thyroid functions? A study upholding association

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Abstract

Objective To study the association of clinical and subclinical thyroid dysfunction in patients of systemic sclerosis and compare with age and sex matched controls without systemic sclerosis.

Methods This hospital-based study involved 56 patients of systemic sclerosis and 300 age and sex matched controls without systemic sclerosis. Thyroid function tests, such as thyroid-stimulating hormone (TSH), free tri-iodothyronine (T3), free thyroxine (T4), were advised in all cases, and anti thyroid peroxidase (anti-TPO) antibody, thyroid gland ultrasonography and fine needle aspiration cytology in selected patients only.

Results Abnormal thyroid functions were found in 37.5% cases compared to 18.7% in control group, and 26.78% of cases had hypothyroidism compared to 16.7% among the controls. 21.4% patients among cases had subclinical hypothyroidism (SCH) compared to 13.33% among controls.

Conclusion Thyroid dysfunctions are common in systemic sclerosis and the same should be evaluated as routine clinical profiling of patients with systemic sclerosis.

Key words
Systemic sclerosis, thyroid disorders, thyroid function tests.

Introduction

Systemic sclerosis (SS) is a connective tissue disease of unknown etiology, characterized by vascular abnormalities, multi-organ fibrosis and complex immune system alterations.[1,2] The association of autoimmune disorders with each other is a well known phenomenon, and similarly the association of rheumatic diseases particularly systemic sclerosis with thyroid disorders.[3,4] The immunologic basis for this association may be because of predominant Th1 lymphokine profile in target organs of patients with chronic autoimmune thyroid disease[5-7] while both Th1 and Th2 activation is present in SS[8,9] with common Th1 factor, under the combined action of genetic and environmental conditions playing predominant role. [10] Immune reactions in organ-specific autoimmune diseases may be activated to the production of antibodies against both organ, and non-organ specific auto-antigens.[11-14] The association of SS with thyroid fibrosis, hypothyroidism and thyroid autoimmunity has been variably reported by several studies.[15-20] Very few studies from India and none from Kashmir have been conducted regarding this subject. We present our study, the first from our state, in order to uphold the association between systemic sclerosis and thyroid dysfunctions, and review the literature.

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Methods

This hospital-based study was conducted on old and new cases of SS, visiting the dermatology department of our hospital, a tertiary referral centre. After thorough history and examination, details regarding age and sex distribution, duration and type of disease were recorded. Thyroid function tests such as thyroid-stimulating hormone (TSH), free tri-iodothyronine (T3), free thyroxine (T4), were advised in all cases. Normal values for TSH, T3 and T4 were respectively taken as 0.30-5.5 µIU/mL, 60-200ng/dL, 4.5-12 µg/dL. Anti thyroid peroxidase (anti-TPO) antibody and thyroid gland ultrasonography (USG) were advised in selected patients who showed abnormal results in thyroid function tests. Fine needle cytology (FNAC) was done in those with visible or palpable thyroid swellings. The results were compared with age and sex matched controls group with similar status of iodine intake, and having some minor dermatological diseases generally not known to be associated with thyroid dysfunction. At the end of study, the data was compiled and subjected to statistical analysis through computer software SPSS version 16, using chi square (χ^2) test, and taking p value <0.05 as significant for determining differences in the results.

Results

In the SS cases group [total 56 patients], there were 6 males and 50 females with a male to female sex ratio of 1:8.33. The age of patients ranged from minimum 21 years to a maximum of 80 years, with average age 45 years [SD 13.66]. 28 (50%) patients, 4 males and 24 females, were in the age group 41-60, followed by 22 (39.3%), 2 males and 20 females, in age group 21-40 and 6 (10.7%), all females, in the age group >61 years. There was no patient below 20 years of age.

In the 300 age and sex matched control group, there were 34 males and 266 females, with a male to female sex ratio of 1:7.82. The age in controls ranged from minimum 21 years to maximum 78 with average age 44 ± 12.88 years. The age and sex variables in control group were not statistically significant to that of cases, as shown in **Table 1**.

Out of 56 cases of systemic sclerosis, 39 (69.6%), 6 males and 33 females, had limited disease, and 17 (30.4%) patients, all females had diffuse form of the disease. The duration of disease in cases ranged from 6 months to 34 years with average disease duration of 8.76 years (SD 6.73) as shown in **Table 2**.

Among the cases, 21 (37.5%) patients, 1 male and 20 female, had abnormality in thyroid function tests. Subclinical hypothyroidism (SCH) was found in 12 (21.4%) cases, 11 females and the only male patient. Hyperthyroidism was found in 3 (5.4%) patients, clinical hypothyroidism and thyroiditis in 2 (3.6%) each, thyroiditis with colloid goitre and with hypothyroidism in 1 each (1.8%), all found in females only. One patient with thyroiditis on USG showed homogenous texture with multiple nodules in both lobes and isthmus, and anti-TPO antibodies of 482 (normal <50). One patient of thyroiditis with hypothyroidism on thyroid scan showed residual thyroiditis with hypothyroid state. One patient of thyroiditis with colloid goitre showed both lobes enlarged with multiple nodules and hypo-echoic pattern, with areas of cystic dilatation in right lobe. The same patient on FNAC had features of colloid goitre. Rest of the patients had normal USG, anti- TPO antibodies and FNAC.

Among those with thyroid dysfunction, 12/21 (57.1%) had SCH and 3/21 (14.3%) clinical hyperthyroidism. Clinical hypothyroidism and thyroiditis was found in 2/21 (9.5%) each and

Table 1 Age and sex distribution between systemic sclerosis cases and controls.

	Age group	*Males N (%)*	*Females N (%)*	*Total N (%)*	*P value*	*M/F*	*Age range*
Cases	21-40	2(33.33)	20(40)	22(39.3)	0.988		Max 80y
	41-60	4(66.66)	24(48)	28(50)	0.921	1:8.33	Min 21y;
	≥61	0	6(12)	6(10.7)	0.962		Mean 45y
	Total	6(10.71)	50(89.29)	56	0.924		SD= 13.66
Controls	21-40	10(29.41)	105(39.47)	115(38.33)			Max 78y;
	41-60	20(58.82)	129(48.50)	149(49.66)		1:7.82	Min 21y;
	≥61	4(11.76)	32(12.03)	36(12)			Mean 44y
	Total	34(11.33)	266(88.66)	300		0.924 pv	SD= 12.88

Table 2 Disease parameters of systemic sclerosis patients

	Males	*Females*	*Total*	*Duration of disease*
LCSS	6	33	39 (69.6)	Max 34 years; Min 6 months; Mean ±8.7582 years
DCSS	0	17	17 (30.4)	
Total	6	50	56	

DCSS: Diffuse cutaneous systemic sclerosis, LCSS: Limited cutaneous systemic sclerosis

Table 3 Thyroid function status in cases and control group.

	Cases			*Control*			
	Males (n=6)	*Females (n=50)*	*Total (n=56)*	*Male (n=34)*	*Females (n=266)*	*Total (n=300)*	*p valve*
Normal	5	30	35 (62.5%)	29	215	244 (81.3%)	0.003 (S)
Abnormal							
SCH	1	11	12	3	37	40	0.171
Clinical hyperthyroidism	0	3	3	1	5	6	0.315
Clinical hypothyroidism	0	2	2	1	9	10	0.755
Thyroiditis	0	2	2	0	0	0	0.021 (S)
Thyroiditis with colloid goitre	0	1	1	0	0	0	0.346
Thyroiditis with hypothyroidism	0	1	1	0	0	0	0.346
Thyroiditis with hyperthyroidism	0	0	0	0	0	0	
Total	1	20	21 (37.5%)	5	51	56 (18.7%)	0.003 (S)

SCH: Subclinical hypothyroidism.

Table 3 Thyroid function status in each type of systemic sclerosis.

	DCSS (n=17)	*LCSS (n=39)*	*Total (n=56)*	*p valve (DCSS vs. LCSS)*
Normal	9	26	35 (62.5%)	0.499
Abnormal				
SCH	3	9	12	0.331
Clinical hyperthyroidism	1	2	3	0.647
Clinical hypothyroidism	1	1	2	0.688
Thyroiditis	1	1	2	0.688
Thyroiditis with colloid goitre	1	0	1	0.802
Thyroiditis with hypothyroidism	1	0	1	0.802
Thyroiditis with hyperthyroidism	0	0	0	
Total	8	13	21 (37.5%)	0.499

DCSS: Diffuse cutaneous systemic sclerosis, LCSS: limited cutaneous systemic sclerosis, SCH: subclinical hypothyroidism

1/21 (4.8%) each had thyroiditis with colloid goitre and thyroiditis with hypothyroidism. No patient had thyroiditis with hyperthyroidism.

In the control group, 56 (18.7%) patients, 5 males and 51 females, had abnormal thyroid function tests. SCH was found in 40 (13.3%) patients, 3 males and 37 females. Clinical hypothyroidism was found in 10 (3.3%), 1 male and 9 female, and hyperthyroidism in 6 (2%), 1 male and 5 female patients. Among the abnormal thyroid functions, SCH was found in 40/56 (71.4%), clinical hypothyroidism in 10/56 (17.9%), and 6/51 (10.7%) had hyperthyroidism. No patient in the control group had thyroiditis of any type. The status of thyroid functions and the significance of difference between cases and controls are summarized in **Table 3**.

Out of 35 (62.5%) patients with normal thyroid functions, 9 (16.1%) had diffuse cutaneous systemic sclerosis (DCSS) and 26 (46.4%) had limited cutaneous systemic sclerosis (LCSS). Among the 21 (37.5%) cases with abnormal thyroid function, 8/21 (38.1%) had DCSS and 13/21 (61.9%) had LCSS. Out of 12 patients with SCH, 9 had LCSS and 3 had DCSS. Similarly out of 3 patients with hyperthyroidism, and 2 each with hypothyroidism and thyroiditis, LCSS was respectively found in 2, 1, 1, and DCSS in 1 patient each. Thyroiditis with colloid goitre and with hypothyroidism found in 1 patient each had DCSS. These results were statistically insignificant. This is summarized in **Table 4**.

Discussion

Association between rheumatic and autoimmune thyroid diseases has been well accepted, and thyroid abnormalities [hypothyroidism, hyperthyroidism, nodular goiter] have been frequently described along with SS.[4] SS is an autoimmune disease and expected to be associated with other autoimmune phenomena, and also thyroid immune dysfunction. Thyroid dysfunction in SS may be explained on many lines such as production of auto-antibodies and cell-mediated immune response with consequent thyroid gland involvement, and cannot be limited only to gland fibrosis.[21,22]

In the present study, there was a male to female ratio of 1:8.33, with 89.3% females as compared to 10.7% males. The female predominance of SS is in accordance with the findings in literature.[3,23] Most of the patients (89.3%) were in the age range 21-60 years, and no patient below 20 years, in accordance with that described in literature.[24]

The 56 cases were compared with 300 age and sex matched control group. The age and sex variables between the two groups were not statistically significant, thereby removing any confounding factors.

Scleroderma may occur in a localized form or as a systemic disease. Systemic scleroderma is subdivided by the extent of the skin involvement into diffuse cutaneous systemic sclerosis (DCSS) and limited cutaneous systemic sclerosis (LCSS).[25] Majority of patients in our study had limited disease (69.6%). 37.5% cases had abnormal thyroid functions as compared to 18.7% in controls, which was statistically significant. This thyroid dysfunction was found in many previous studies as well.[3,20,23]

Hypothyroidism has been frequently reported in SS, but whether SS itself increases the risk of thyroid dysfunction, or it is an incidental finding is still controversial.[23] In our study, a total of 15/56 (26.8%) patients among cases had hypothyroidism, compared to 50/300 (16.7%) patients among the controls. This included 12 SCH, 2 with clinical hypothyroidism and 1 hypothyroidism associated with thyroiditis

among the cases, and 40 SCH and 10 clinical hypothyroids in controls. This is similar to, but higher than 21% in study by Antenolli *et al*.[3] and 20% by Marasini *et al*.[23] and contrasts with that of Innocencio *et al*.[20] who found no significant difference in hypothyroidism. The significant difference regarding thyroid functions but no statistically significant difference with respect to hypothyroidism may be because of less sample size of cases than controls. These results are similar to a study by Innocencio *et al*.[20] who also found no significant difference in hypothyroidism, and in contrast to Antenolli *et al*.[3] who found more hypothyroidism (clinical and subclinical) in cases than controls.

12/56 (21.4%) patients among cases had SCH compared to 40/300 (13.3%) patients among controls, almost comparable to 17% by Antenolli *et al*.[3] and 17.7% by Marasini *et al*.[23] and contrasts with others.[26] 13.3% controls in our study had hypothyroidism, compared to 6% controls in study by Antonelli *et al*.[3] and 5.8-8% in other studies.[20,27]

Clinical hyperthyroidism was found in 3/56 (5.36%), compared to 6/300 (2%) in controls. Low prevalence of hyperthyroidism was also found in other studies[23,28] and in contrast to others.[3] Thyroiditis, with or without colloid goiter and/ or hypothyroidism was found in cases only. This may be because of autoimmune nature of the thyroid dysfunction found in systemic sclerosis.

Among the 37.5% with abnormal thyroid function, 8/21 (38.1%) had DCSS and 13/21 (61.9%) had LCSS, and similarly 9 LCSS and 3 DCSS patients had SCH. Also, clinical hyperthyroidism, hypothyroidism and thyroiditis was respectively found in 2, 1, 1 patients with LCSS, and 1 each with DCSS. Reports of more thyroid dysfunction in limited SS was also found in the literature.[22] These results were not statistically significant and may be because of more number of LCSS than DCSS. Only DCSS showed thyroiditis with colloid goitre and with hypothyroidism (1 patient each].

Conclusion

In conclusion, evaluation for thyroid dysfunction in SS and its timely diagnosis is important, as also looking for associated systemic sclerosis in patients of thyroid dysfunction. This has a bearing on the clinical manifestations of SS; for example, Raynaud's phenomenon is more difficult to control in hypothyroid individuals, and pulmonary hypertension can be seriously influenced by hemodynamic changes of hypothyroidism. Thus, various evaluation methods for detecting thyroid abnormalities should be considered important in the clinical profiling of SS patients.

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