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Hashimoto thyroiditis may be associated with a subset of patients with systemic sclerosis with pulmonary hypertension

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ABSTRACT

Introduction: Recent studies show an association between autoimmune thyroiditis and systemic sclerosis (SSc) and suggest that this condition may interfere with the ES phenotype. However these studies evaluate the autoimmune thyroiditis as a whole and none of them specifically addresses Hashimoto's thyroiditis (HT) in SSc.
Objective: To investigate the presence of HT in SSc patients and its possible association with disease manifestations.
Methods: Clinical manifestations of hypothyroidism, TSH and anti-thyroid auto antibodies (anti-TPO. anti TBG and TRAb) were studied in 56 patients with SSc. SSc patients with HT were compared with SSc patients without thyroiditis.
Results: HT was observed in 19.64% of patients with SSc. No association was observed between HT and the different forms of disease or profile of autoantibodies. Likewise, there was no difference between the mean modified Rodnan score and presence of Raynaud's phenomenon, scars, digital necrosis, myositis, arthritis, sicca symptoms, esophageal dysmotility and scleroderma renal crisis when the groups were compared. On the other hand, patients with HT had higher frequency of pulmonary hypertension in relation to patients without HT (66.6% *vs* 22.5%, p = 0.016).
Conclusions: In the studied sample patients with ES and HT had higher prevalence of pulmonary hypertension. Long-term follow-up studies with a larger number of TH and SSc patients are needed to confirm these data.

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Tireoidite de Hashimoto pode estar associada a um subgrupo de pacientes de esclerose sistêmica com hipertensão pulmonar

Palavras-chave:
Esclerose sistêmica
Esclerodermia
Tireoidite de Hashimoto
Hipertensão pulmonar

RESUMO

Introdução: Estudos recentes mostram associação entre tireoidites autoimunes e esclerose sistêmica (ES), e sugerem que essa condição pode interferir no fenótipo da ES. Entretanto, esses estudos avaliam as tireoidites autoimunes como um todo e nenhum deles aborda especificamente a tireoidite de Hashimoto (TH) na ES.

Objetivo: Investigar a presença de TH em pacientes com ES e sua possível associação com as manifestações da doença.

Casuística e métodos: Manifestações clínicas de hipotireoidismo, TSH, T4 livre e anticorpos antitireoidanos (anti-TPO, anti TBG e TRAb) foram pesquisados em 56 pacientes com ES. Pacientes com ES e TH foram comparados com pacientes com ES sem tireoidite.

Resultados: TH foi observada em 19,64% dos pacientes com ES. Não foi encontrada associação entre a TH e as diferentes formas de doença ou com o perfil de autoanticorpos. Da mesma forma, não houve diferença entre a média do escore de Rodnan modificado e entre a presença de fenômeno de Raynaud, cicatrizes estelares, necrose digital, miosite, artrite, sintomas *sicca*, dismotilidade esofágica ou crise renal esclerodérmica quando os grupos foram comparados. Por outro lado, pacientes com TH apresentaram maior frequência de hipertensão pulmonar quando comparados a pacientes sem TH (66,6% *vs* 22,5%; p = 0,016).

Conclusões: Na amostra de ES estudada, a TH está associada a uma maior prevalência de hipertensão pulmonar. Estudos de seguimento a longo prazo, englobando um número maior de pacientes com ES e TH, são necessários para confirmar esses dados.

Introduction

The association among autoimmune diseases is common, regardless if they are organ-specific or systemic.[1] Thus, it is necessary that the physician attending these patients be aware of possible associations, not only for an early diagnosis of such entities, but also to understand more completely the clinical manifestations that these patients may have.

Although there is no clear explanation for the association between autoimmune diseases, it is assumed that there is a genetic predisposition to a common immune defect in many of them.[1] Among other possibilities, the exposure to some eventual infectious or environmental agent that acts as a triggering factor of several diseases may be implicated.[1]

Hashimoto's thyroiditis (HT) is the most common autoimmune disease of the thyroid, being considered as a prototype of organ-specific autoimmune diseases.[2] HT presents with varying degrees of glandular dysfunction, presence of antithyroid antibodies and goiter or atrophy of the gland, and a diffuse lymphocytic tissue infiltrate.[2]

On the other hand, SSc is a systemic autoimmune disease characterized by vasculopathy, excessive deposition of collagen in tissues and presence of autoantibodies.[3] The exact role of autoantibodies in SSc is not well defined,[4] but it is known that they can influence the phenotype presented.[4] Indeed, fluctuations in topoisomerase I titles correlate with skin thickening, assessed by the modified Rodnan score, and with disease activity, measured by clinical and laboratory parameters.[5] Interestingly, a subset of patients who developed negativity for this antibody showed less skin thickening, less lung involvement and better survival, when compared to those persistently positive patients.[6]

SSc patients may have antibodies against thyroid antigens, with or without gland dysfunction.[7] A recent meta-analysis showed that thyroid autoimmune disease was the more common organ-specific autoimmunity disease in patients with SSc, with an estimated prevalence of 10.4%.[8] The association of SSc with anti-thyroid peroxidase antibodies is linked to the presence of HLA-DR15.[7] The connection of SSc with other autoimmune diseases also seems to interfere with their phenotype,[4,8] affecting these patients with a milder form of the disease. However, no study has specifically addressed the association of SSc with HT. Thus, the aim of this study was to investigate the presence of HT in SSc patients and its possible association with immunological and clinical profiles of the disease.

Patients and methods

A cross-sectional study evaluating 56 consecutive patients followed-up at an outpatient clinic of systemic sclerosis in a single tertiary care hospital was conducted. Data were collected from June 2012 to June 2013. All patients recruited met the classification criteria for SSc from ACR/EULAR 2013.[9]

The following manifestations of SSc were addressed: Raynaud's phenomenon, stellar scars, digital necrosis, skin thickening according to the modified Rodnan score,[10] arthritis, myositis, esophageal dysmotility, cardiac involvement, interstitial pneumonitis, pulmonary hypertension and scleroderma renal crisis. Arthritis was considered as present when at least one swollen joint was observed.[11] The diagnosis of

myositis was established by the presence of proximal muscle weakness associated with at least one of the following: increased CPK, EMG with myopathic pattern, or biopsy with myositis.[11] Distal dysmotility or aperistalsis was considered present when documented by manometry or seriography.[11] Cardiac involvement was considered as caused by SSc when presented in the form of pericarditis and/or heart failure, or as an arrhythmia not attributed to other causes.[11] Interstitial lung disease was diagnosed when the forced vital capacity was < 70% of the predicted, or ground-glass/fibrosis opacities were observed in thorax high-resolution tomography scans.[12,13] The diagnosis of pulmonary hypertension was established when the systolic pulmonary artery pressure was > 40 mmHg observed in an echocardiogram, or the pulmonary artery mean pressure was > 25 mmHg with pulmonary artery occlusion pressure < 15 mmHg.[4,11]

We evaluated also the presence of ANA, anti-Scl 70, anticentromere, anti-Ro and anti-La. Clinical and laboratory data were considered cumulatively positive. Disease severity was assessed by Medsger index.[14]

The diagnosis of HT was performed in patients who had hypothyroidism or goiter associated with the presence of positive antibodies.[4] To evaluate thyroid function, TSH and free T4 were measured. The dosed antibodies were anti-peroxidase (anti-TPO), anti-thyroglobulin (anti-TBG) and anti-TSH receptor (TRAb). TSH and free T4 levels were obtained by chemiluminescence, and values of 0.5-3.6 IU/mL and 0.70-1.80 ng/dL were considered normal for TSH and free T4, respectively. The anti-thyroid autoantibodies were also investigated by chemiluminescence; and values <35 IU/mL for anti-TBG; 40 IU/mL for anti-TPO; and 1.35 IU/L for TRAb were considered as normal results.

The research protocol was approved by the local ethics committee and all participants gave written informed consent.

The data were presented as median and interquartile range (IQR) if not normal, and as mean with standard deviation (SD) if normal, according to the Kolmogorov-Smirnov test. When some variable showed indications of normal distribution, we used the Student's *t* test for comparison between the means of two continuous variables; when normality was rejected, we used the Mann Whitney test for two continuous variables.

Categorical variables were compared using the chi-squared test or Fisher's exact test, when appropriate. A P-value <0.05 was considered statistically significant. All calculations were made with the aid of MedCalc software version 12.0.

Results

Description of the sample

Fifty-six patients were studied: 52 women (92.8%) and four men (7.1%), aged 19-81 years (median = 56; IQR of 39-61). In this population, 33% were African descents (black and brown), 66% were Caucasians, and 1% had Indian ancestry. Regarding the form of scleroderma, 19/56 (33.9%) patients had the diffuse type, and 37/56 (66.1%) had the limited type. Approximately 39.6% were smokers.

Table 1 – Clinical and serological profile of 53 patients with scleroderma.

	n	%
Raynaud	56/57	98.2
Stellar ulceration	34/56	60.7%
Digital necrosis	7/56	12.5
Telangiectasias	21/55	38.1
Rodnan (median)	Variation of 0-50 (mean, 15.04 ± 10.19)	
Myositis	8/54	14.8
Arthritis	21/56	14.8
Arthralgia	28/54	51.8
Xerostomia	25/52	48.08
Xerophthalmia	19/53	35.8
Esophageal dysmotility	29/53	54.7%
Interstitial lung disease	20/54	37.04
Pulmonary hypertension	15/49	30.6
Myocarditis	0	
Renal crisis	3/55	5.4%
FAN	50/56	89.2
Anti-Scl70	8/55	14.55
Anti-centromer	12/52	24.08
Anti-Ro	10/56	17.8
Anti-La	4/53	7.5

The autoantibody and clinical profiles of our population are shown in Table 1.

The evaluation of the Medsger severity index was available for 40 patients and ranged from 1 to 15, with a median of 5.0 (IQR, 4.0 to 7.75).

Anti-TPO antibody was present in 32.1%; anti-TBG in 18.8%; and anti-TRAb in 11.4%. The diagnosis of HT was observed in 19.64% of patients with SSc and all of them had hypothyroidism at diagnosis.

Comparison of SSc populations with and without HT

No association between HT and the different forms of the disease or autoantibody profile was observed. Likewise, there was no difference between the mean modified Rodnan score and between the presence of Raynaud's phenomenon, stellar scars, digital necrosis, myositis, arthritis, *sicca* symptoms, esophageal dysmotility and scleroderma renal crisis when the groups were compared, as can be seen in Table 2. On the other hand, patients with HT exhibited a higher frequency of pulmonary hypertension when compared to patients without HT (66.6% vs. 22.5; P = 0.016).

Discussion

There are several mechanisms associated with the occurrence of hypothyroidism in patients with SSc. The sclerosis of the glandular tissue is one of them;[15] the simultaneous occurrence of autoimmune thyroid diseases is another.[1] As previously mentioned, the association among several autoimmune diseases is commonly observed, suggesting the presence of common pathophysiological mechanisms in the scenario of these conditions.[1] Although the true events involved in the pathogenesis of autoimmune diseases are still uncertain, most of these patients have shown a genetic

Table 2 – Comparative analysis of the population of scleroderma with and without Hashimoto's thyroiditis (HT).

	With HT n = 11	Without HT n = 45	P
Ethnicity	Caucasian –63.6% (7/11) African descent – 36.3% (4/11)	Caucasian – 65.9% (29/44) African descent – 31.82% (14/44) Indian descent – 2.28% (1/44)	0.31[a]
Gender Female/Male	10/1	42/3	1.0[b]
Median age of patient	56 (IQI = 25-69)	54 (IQI = 19-81)	0.87[c]
Form of scleroderma	Diffuse – 27.3% (3/11) Limited – 72.7% (8/11)	Diffuse – 35.5% (16/45) Limited – 64.4% (29/45)	1.00[b]
Tabagism	45.5% (5/11)	38.1% (16/42)	0.73[b]
Raynaud	100%(11/11)	97.5% (44/45)	1.0[b]
Stellate ulceration	54.4%(6/11)	62.2% (28/45)	0.73[b]
Digital necrosis	10% (1/10)	13.3% (6/45)	0.62[b]
Teleangiectasias	20% (2/10)	40.9% (18/44)	0.29[b]
Rodnan (median)	11 (IIQ = 0-28)	15 (IIQ = 0-50)	0.22[c]
Myositis	18.2% (2/11)	14% (6/43)	0.66[b]
Arthritis	27.3% (3/11)	12.2% (19/45)	0.17[b]
Arthralgia	27.3% (3/11)	58.1% (25/43)	0.09[b]
Xerostomia	54.5% (6/11)	46.3% (19/41)	0.74[b]
Xerophthalmia	45.5% (5/11)	33.3% (14/42)	0.49[b]
Esophageal dysmotility	70% (7/11)	51.2% (22/43)	0.3[b]
Interstitial lung disease	63.6% (7/11)	30.2% (13/43)	0.07[b]
Pulmonary hypertension	66.7% (6/9)	22.5% (9/40)	0.01[b]
Myocarditis	0	0	-
Renal crisis	9.1% (1/11)	4.5% (2/44)	0.45[b]
Medsger (median)	5.5 (IIQ = 3-12)	5 (IIQ = 1-15)	1[c]
FAN	100% (11/11)	86.7% (39/45)	0.33[b]
Scl-70	0	18.2% (8/44)	0.18[b]
Anti-centromer	40% (4/10)	19% (8/42)	0.21[b]
Anti-Ro	18.2% (2/11)	17.8% (8/45)	1.0[b]
Anti-La	9.1% (1/11)	7.1% (3/42)	1.0[b]

IQI, Interquartile interval.
[a] Chi-squared.
[b] Fischer's test.
[c] Mann Whitney.

background on which environmental factors act.[1] Several studies have shown that smoking, deficiency of vitamin D, diet, ultraviolet light, drugs and viral infections can function as environmental triggers for autoimmunity in genetically predisposed subjects.[1]

It was observed in the present study a high prevalence of HT in SSc patients (20%), which confirms the finding of the coexistence of autoimmune diseases. A knowledge of this association is of fundamental importance to the clinician that, in treating an autoimmune disease, remains alert to other ones. Moreover, the symptoms presented by a patient with HT and hypothyroidism and SSc can be confused with each other, especially in the case of those most nonspecific symptoms, such as tiredness, fatigue, muscular weakness, anorexia and arthralgia.[16] These must be properly attributed to the causal element, in order to treat the patient adequately.

Avouac *et al.*,[4] studying patients of European origin, found that SSc patients with other concomitant autoimmune disease appeared to have a milder SSc, associated with the limited form of presentation. In the present analysis, these findings could not be confirmed. However, it is important to note that the authors above included in his work several organ-specific autoimmune diseases, such as Sjögren's syndrome, myositis, systemic lupus erythematosus, and thyroiditis, and not only HT as in our study, which may explain the difference in findings.

Still in the current sample, HT patients had a higher prevalence of pulmonary arterial hypertension (PAH). The association between hypothyroidism and primary pulmonary hypertension had been noted previously.[17–19] Opravil *et al.*[20] also reported an increase in the prevalence of hypothyroidism in patients with HIV and PAH, confirming the possible association between these two entities in another context.

Thyroid dysfunction has been associated with alterations in vasoreactivity, a phenomenon that precedes PAH.[21] Vasospasm causing Raynaud's phenomenon has been found in patients with isolated hypothyroidism and responds to treatment with levothyroxine, which again suggests an intriguing relationship between this hormone and the stabilization of vascular reactivity.[22] Furthermore, in animal models, hypothyroidism has been shown to cause increases in the levels of endothelin-1, a potent vasoconstrictor that contributes to the pathogenesis of PAH,[23,24] and to the pulmonary hypertension of SSc.[25] If this association will prove true, the treatment of hypothyroidism would affect the results obtained in the treatment of pulmonary hypertension, a well-known risk complication, with high potential for morbidity and mortality. Pressure changes in pulmonary artery, secondary to

the thyroid dysfunction, respond to the treatment of the endocrine disease.[26]

In this analysis, we observed a trend of positive association of HT with interstitial lung disease and a trend towards a negative association with arthralgias. Interestingly, the literature describes cases of association of patients with HT and interstitial lung disease, regardless of the existence of SSc.[27,28]

There are limitations to this study: one of them is the small number of SSc patients studied. The second is the fact that not all patients had catheterization in the right side of the heart, and so their pulmonary artery pressures is estimated by echocardiography. However, from a clinical standpoint, the association found is very important and deserves further research with larger numbers of patients.

In conclusion, it can be said that in the present study we found a prevalence of HT in about 20% of the SSc population. Larger studies are needed to clarify the definitive role of this association with PAH.

C Approval of ethics – Opinion 398119 – Research Ethics Committee, Sociedade Evangélica Beneficente de Curitiba.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Nancy AL, Yehuda S. Prediction and prevention of autoimmune disorders. Arch Dermatol Res. 2009;301:57–64.
2. Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. N Engl J Med. 1996;335:99–107.
3. Allanore Y, Avouac J, Kahan A. Systemic sclerosis: an update in 2008. Joint Bone Spine. 2008;75:650–5.
4. Avouac J, Airò P, Dieude P, Caramaschi P, Tiev K, Diot E, et al. Associated autoimmune diseases in systemic sclerosis define a subset of patients with milder disease: results from 2 large cohorts of European Caucasian patients. J Rheumatol. 2010;37:608–14.
5. Hu PQ, Fertig N, Medsger Jr TA, Wright TM. Correlation of serum anti-DNA topoisomerase I antibody levels with disease severity and activity in systemic sclerosis. Arthritis Rheum. 2003;48:1363–73.
6. Kuwana M, Kaburaki J, Mimori T, Kawakami Y, Tojo T. Longitudinal analysis of autoantibody response to topoisomerase I in systemic sclerosis. Arthritis Rheum. 2000;43:1074–84.
7. Molteni M, Barili M, Eisera N, Scrofani S, Mascagni B, Zulian C, et al. Anti-thyroid antibodies in Italian scleroderma patients: association of anti-thyroid peroxidase (anti-TPO) antibodies with HLA-DR15. Clin Exp Rheumatol. 1997;15:529–34.
8. Elhai M, Avouac J, Kahan A, Allanore Y. Systemic sclerosis at the crossroad of polyautoimmunity. Autoimmun Rev. 2013;12:1052–7.
9. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013;72:1747–55.
10. Clements PJ, Lachenbruch P. Siebold. Inter and Intraobsever variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol. 1995;22:1281–5.
11. Poormoghim H, Lucas M, Fertig N, Medsger Jr TA. Systemic sclerosis sine scleroderma: demographic, clinical, and serologic features and survival in forty-eight patients. Arthritis Rheum. 2000;43:444–51.
12. Behr J, Furst DE. Pulmonary function tests. Rheumatology. 2008;47:65–7.
13. Wells AU. High-resolution computed tomography and scleroderma lung disease. Rheumatology. 2008;47:59–61.
14. Medsger Jr TA, Silman AJ, Steen VD, Black CM, Akesson A, Bacon PA, et al. A disease severity scale for systemic sclerosis: development and testing. J Rheumatol. 1999;26:2159–67.
15. Robazzi TCMV, Adan LF. Autoimmune thyroid disease on patients with rheumatic diseases. Rev Bras Reumatol. 2012;52:417–30.
16. Pearce EN, Farwell AP, Braveman M. Thyroiditis. N Eng J Med. 2003;348:2647–55.
17. Sweeney L, Voelker NF. Estrogen exposure, obesity and thyroid disease in severe pulmonary hypertension. Eur J Med Res. 2009;14:433–42.
18. Chu JW, Kao PN, Faul JL, Doyle RL. High prevalence of autoimmune thyroid disease in pulmonary arterial hypertensiom. Chest. 2002;122:1668–73.
19. Curnock A, Raed M, Higgins B, Hussein S, Arroliga AC. High prevalence of hypothyroidism in patients with primary hypertension. Am J Med Sci. 1999;318:289–92.
20. Opravil M, Pechere M, Speich R, Joller-Jemelka H, Jenni R, Russi EW, et al. HIV-associated primary pulmonary hypertension: a case control study. Am J Respir Crit Care Med. 1997;155:990–5.
21. Badesch DB, Wynne KM, Bonvallet S, Voelker NF, Ridgway C, Groves BM. Hypothyroidism and primary pulmonary hypertension: an autoimmune pathogenic link? Ann Intern Med. 1993;119:44–6.
22. Lateiwish AM, Feher J, Baraczka K, Rácz K, Kiss R, Gláz E. Remission of Raynaud's phenomenon after L-thyroxine therapy in a patient with hypothyroidism. J Endocrinol Invest. 1992;15:49–51.
23. Lam HC, Wang JP, Lee JK, Ho LT, Han TM, Chiang HT, et al. Tissue contents of endothelin vary according to thyroid hormone status in rat. J Cardiovasc Pharmacol. 1993;22:S299–302.
24. Stewart DJ, Levy RD, Cernacek P, Langleben D. Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? Ann Intern Med. 1991;114:464–9.
25. Balbir-Gurman A, Braun- Moscovici Y. Scleroderma- new aspects in pathogenesis and treatment. Best Pract Res Clin Rheumatol. 2012;26:13–24.
26. Silva DR, Gazzana MB, John AB, Siqueira DR, Maia AL, Barreto SS. Pulmonary arterial hypertension and thyroid disease. J Bras Pneumol. 2009;35:179–85.
27. Hashizume T1, Numata H, Matsushita K. Interstitial pneumonia associated with chronic thyroiditis. Nihon Kokyuki Gakkai Zasshi. 2002;40:31–4.
28. Khardori R1, Eagleton LE, Soler NG, McConnachie PR. Lymphocytic interstitial pneumonitis in autoimmune thyroid disease. Am J Med. 1991;90:649–52.