

Espectro Clínico dos Autoanticorpos TH/TO e NOR90 na Esclerose Sistémica

Clinical Spectrum of TH/TO and NOR90 Autoantibodies in Systemic Sclerosis

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Resumo:

Introdução: A esclerose sistémica é uma doença autoimune com amplo espectro clínico. Os autoanticorpos podem indicar sintomas, diagnósticos e orientar para o tratamento mais adequado. A relevância da pesquisa do anti-Th/To e anti-NOR90 é menos conhecida. O objetivo foi avaliar as principais manifestações clínicas e diagnósticos etiológicos associados aos anticorpos Th/To e NOR90.

Material e Métodos: Estudo observacional retrospectivo, envolvendo 61 doentes em seguimento na consulta externa de doenças autoimunes com os anticorpos Th/To ou NOR90 positivos em centro único, entre 2018 e 2020. Foram excluídos os doentes sem informação disponível. Os dados demográficos, manifestações clínicas e diagnósticos foram analisados com recurso a informação dos processos informáticos.

Resultados: Na amostra o género feminino foi o mais prevalente. Verificou-se envolvimento cutâneo, articular, cardiopulmonar e gastrointestinal, sem atingimento renal associado a nenhum dos autoanticorpos. Em ambos os grupos foi estabelecido diagnóstico de esclerose sistémica em 40% dos casos. Não se identificaram outros autoanticorpos concomitantes em 53% e 50% dos doentes com Th/To e NOR90, respetivamente.

Discussão e Conclusão: Este estudo demonstrou envolvimento similar em ambos os autoanticorpos com atingimento cutâneo e articular frequentes, maior envolvimento cardiopulmonar nos doentes com anti-Th/To e gastrointestinal no grupo com anti-NOR90. Apesar de ambos se terem associado à esclerose sistémica numa percentagem não desprezível de doentes, em aproximadamente metade dos casos encontravam-se isolados, sem concomitância com outros autoanticorpos relacionados com esta doença, indiciando a relevância da sua pesquisa ativa aquando a suspeita clínica de esclerose sistémica com intuito diagnóstico.

Palavras-chave: Autoanticorpos; Esclerose Sistémica; Sinais e Sintomas.

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Abstract:

Introduction: Systemic sclerosis is an autoimmune disease with a large spectrum of clinical manifestations. Autoantibodies could indicate symptoms, diagnostics and establish a more appropriate treatment. The relevance of searching Th/To and NOR90 is still unknown. We aim to evaluate major manifestations and disease associations of Th/To and NOR90 autoantibodies.

Material and Methods: Observational retrospective single-centre study, including all patients with Th/To or NOR90 autoantibodies followed in autoimmune consultation from 2018 to 2020. Absence of specific clinical information excluded patients. Demographic, clinical and diagnostic data were analysed.

Results: In this study, female gender was the most prevalent. Cutaneous, articular, cardiopulmonary and gastrointestinal involvements were present in both autoantibodies' groups, with no renal manifestations. In 40% of both groups, systemic sclerosis diagnosis was established. No other concomitant autoantibodies were documented in 53% and 50% of anti-Th/To and anti-NOR90, respectively.

Discussion and Conclusion: This study verified similar involvement in both groups with frequent skin and articular symptoms, more cardiopulmonary involvement in anti-Th/To group and more gastrointestinal association in anti-NOR90. Although, in this study, these autoantibodies were commonly related to systemic sclerosis, in approximately half of cases they were isolated with no other concomitant systemic sclerosis' autoantibodies, enhancing the importance of their active research when this disease is suspected.

Keywords: Antibodies; Scleroderma, Systemic; Signs and Symptoms.

Introduction

Systemic sclerosis (SSc) is a chronic inflammatory systemic disease, being the most severe within the scleroderma spectrum, with high case-specific mortality.^{1,2} Although its pathogenesis is shared by other similar autoimmune conditions including immune-inflammatory processes, vasculopathy and fibrosis, its triggers and aetiologies remain unknown.^{2,3} In more

than 80% of the patients, autoantibodies have been identified years before the clinical onset of the disease, and therefore they are essential for an early diagnosis and treatment of these diseases.^{1,4} Traditional classification of SSc defines this as diffuse or limited disease, depending on the extent of skin sclerosis. The clinical association with high-titer SSc patterns of ANA reactivity, generally mutually exclusive, allows to define the risk of specific complications, providing a complementary subgrouping for SSc that could enlighten therapeutic enhancements.²

Anti-Th/To antibodies are directed against subunits of human mitochondrial RNase and RNase P ribonucleoprotein complexes and produce a typical nucleolar staining pattern on IIF.⁵ Anti-Th/To antibodies are considered fairly specific to SSc and may be present in 2–10% of patients.^{1,5} They may also be detected in primary Raynaud's phenomenon, however, they aren't present in systemic lupus erythematosus; polymyositis / dermatomyositis and in undifferentiated connective tissue disease.^{6,7}

Antibodies NOR90 were first identified as a novel 90-kDa protein recognized by autoantibodies that selectively stained the nucleolus organizing region (NOR) of chromosomes 13, 14, 15, 21, and 22. The 90-kDa autoantigen was later proved to be identical to human upstream-binding factor, an RNA polymerase I-specific transcription factor which plays a central role in transcriptional regulation of rRNA.⁴ Based on search, NOR90 is present in ~5% of SSc cases with low specificity, since it's been also associated with other autoimmune conditions such rheumatoid arthritis, systemic lupus erythematosus; Sjögren's syndrome or neoplastic diseases.^{1,5,8}

We examined clinical and etiologic diagnosis associated to Anti-Th/To and NOR90 autoantibodies in a cohort of patients followed in an autoimmune consultation.

Methods

In this observational retrospective study, from a total of 712 patients with follow-up in autoimmune consultation of a single centre, we included all 61 patients with positive anti-Th/To or NOR90 antibodies, from January 2018 to March 2020. Clinical information was obtained from electronic medical records. All patients with loss of follow-up from consultation or absence of specific clinical data were excluded. Demographic characteristics, clinical features and etiologic diagnosis of the selected patients were analysed and compared between anti-Th/To and anti-NOR90 groups. All data were statistically analysed using IBM SPSS Statistics version 26.0®. Categorical variables are presented as number of cases or percentages. Continuous variables are presented as mean and standard deviation. In the bivariate analysis we used chi-square test or fisher-test as appropriated for categorical variables. The Mann Whitney U Test was used for continuous variables. All reported p-values are two-tailed and statistical significance was considered if *p-value* <0.05.

Results

From a total of 712 patients with follow-up in autoimmune consultation of a single centre, we included all 61 patients who tested positive to Th/To and/or NOR90. From those, 36 patients were excluded for insufficient record data or loss of follow-up. A total of 25 patients included, 15 with anti-Th/To and 10 with anti-NOR90 antibody, were analysed in different variables (Fig. 1).

Both autoantibody groups had similar characteristics as shown in Table 1.

In Th/To autoantibody group, female gender was more prevalent with a mean age of 57.27 (\pm 20.74) years and

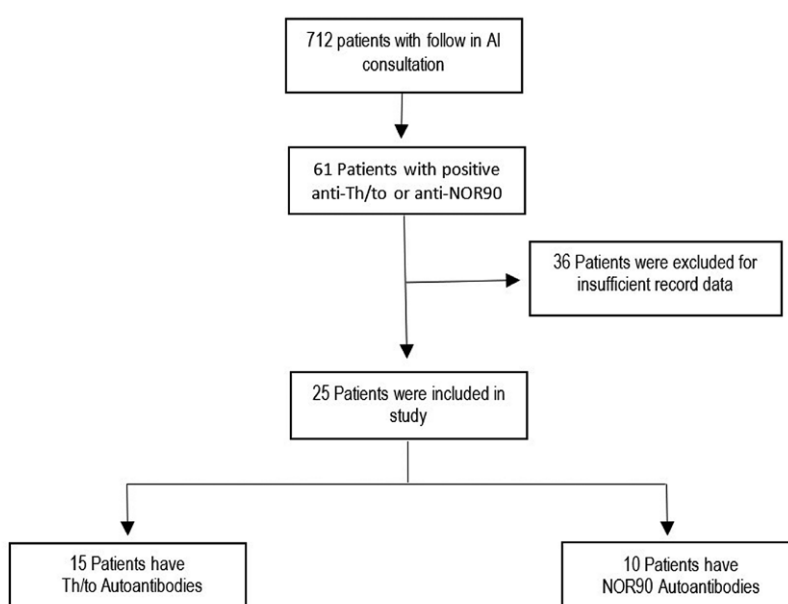


Figure 1: Selection of study sample.

Table 1: Demographic and clinical features in patients with anti-Th/To and NOR90

Characteristics	Anti-Th/To n=15	Anti-NOR 90 n=10	p-value
Demographic			
Female: Male	10:5	7:3	0.861
Mean age, years (\pm SD)	57.27 (\pm 20.74)	63.90 (\pm 18.91)	0.311
Mean time disease manifestation, years	0.93 (0-5)	1.50 (0-4)	0.461
Skin Involvement, n (%)			
Raynaud's phenomenon,	11 (73.3)	8 (80)	1.000 a)
Puffy hands	3 (20)	4 (40)	0.368 a)
Digital ulcers	1 (6.6)	- (0)	1.000 a)
Capillaroscopic changes	5 (33.3)	4 (40)	1.000 a)
Cardiopulmonary involvement, n (%)			
Pericarditis	1 (6.6)	- (0)	1.000 a)
Pulmonary arterial hypertension	6 (40)	2 (20)	0.402
Interstitial lung disease	5 (33.3)	4 (40)	1.000 a)
Low DLCO	2 (13.3)	- (0)	0.500 a)
Gastrointestinal involvement, n (%)			
Gastric dysmotility	1 (6.6)	2 (20)	0.543 a)
Articular involvement, n (%)			
Peripheral arthralgia	3 (20)	6 (60)	0.087 a)
Kidney involvement, n (%)	- (0)	- (0)	1.000 a)
Aethiologic Diagnosis, n (%)			
Systemic sclerosis	6 (40)	4 (40)	1.000 a)
Systemic lupus erythematosus	1 (6.6)	1 (10)	0.549 a)
Secondary Sjogren's syndrome	- (0)	2 (20)	0.157 a)
Primary Raynaud's phenomenon	- (0)	1 (10)	0.407 a)
Still unknown	8 (53.3)	2 (20)	0.109 a).

SD- standard deviation; DLCO – diffusion capacity of carbon monoxide; a) Fisher-test

a mean time of 0.93 years from disease overall manifestations to diagnosis, with maximum period observed of 5 years (Table 1). Skin involvement had Raynaud's phenomenon present in 73% with capillaroscopic changes in 33.3% cases and peripheral arthralgia was identified in 20% of patients (Table 1). Cardiopulmonary manifestations with pulmonary arterial hypertension and interstitial lung disease were documented in 40% and 33.3% of patients, respectively, and pericarditis was diagnosed in 6.6% of patients (Table 1). None had kidney affections (Table 1). Systemic sclerosis was established in 40% of the Th/To autoantibody patients and systemic lupus erythematosus diagnosis was assumed in 1 patient (Table 1). Half of patients of this group still had no diagnosis assumed link to positive Th/To autoantibody (Table 1).

In NOR90 autoantibody group, female gender was also more prevalent with a mean age of 63.90 (\pm 18.91) years and mean time from overall disease manifestation to diagnosis of 1,5 years, with maximum period observed of 4 years (Table 1). Skin involvement had Raynaud's phenomenon present in 80% and was confirmed by capillaroscopic changes in 40% of cases (Table 1). Gastroenterology manifestations were verified in 20% patients (Table 1). Kidney affections were not documented (Table 1). Systemic sclerosis was the diagnosis determined in 40% of the NOR90 autoantibody group and

systemic lupus erythematosus and secondary Sjogren's syndrome diagnosis were concluded in 10% and 20%, respectively (Table 1). None had neoplastic diagnosis.

In both groups there weren't any results with statistical significance (Table 1).

As shown in Table 2, there were not any other autoantibodies associations in 53.3% of Th/To group. In 4 of these patients, there were documented SSc diagnosis. In this study, 5 autoantibody type associations were documented, with anti-Ro52 (3 cases) and anti-Ku (2 cases) being the most frequent (Table 2).

As shown in Table 3, there were not any other autoantibodies associations in half of the cases of NOR90 group and of these, one patient had SSc diagnosis. In the NOR90 group 5 different autoantibody type associations were also registered and the most prevailing one was with anti-Ku (4 cases with different combinations).

Discussion

In this study, anti-Th/To and anti-NOR 90 groups were similar in respect to clinical manifestations and etiologic diagnosis.

According to literature, anti-Th/To is associated with shorter onset disease.⁵ In this group, the mean time from clinical manifestations to diagnosis was less than a year and skin

Table 2: Autoantibodies associations in anti-Th/To group

SSc Autoantibodies Positive Associations	Anti-Th/To n=15	Diagnosis
Anti-Ku	2	Still unknown
Anti-PM Scl75	1	Still unknown
Anti-Ro52	3	1 case SLE, 1 case SSc, 1 case still unknown
Anti-RNA polymerase III; Anti-Centromere B	1	SSc
No associations	8	4 cases SSc, 4 cases still unknown

SLE- systemic lupus erythematosus

symptoms were the earlier ones, with particular focus on Raynaud's phenomenon. Peripheral arthralgia was described in a considerable percentage of this group. Cardiopulmonary features are frequently documented with pulmonary hypertension; interstitial lung disease and inflammatory muscle disease related.^{5,7,9} In our study, cardiopulmonary involvement was more prevalent in comparison with the NOR90 group and pulmonary arterial hypertension was the most common manifestation. Our data confirm the absence established between anti-Th/To antibodies and renal impairment, since no patient had kidney involvement.^{5,7} Only 1 patient was diagnosed with systemic lupus erythematosus which could be justified by an overlap of autoimmune pathologies as this autoantibody wasn't previously related to this disease.^{6,7}

NOR90 autoantibodies have been considered as a marker of limited cutaneous SSc and mild involvement of internal organs.⁵ In this study we disclose higher prevalence of skin manifestations comparing with other symptoms and with anti-Th/To group. Our data also confirm gastrointestinal involvement with gastric dysmotility demonstrated in a considerable percentage of these patients. No case of pericarditis, low DLCO or kidney involvement were identified in patients with anti-NOR90. Systemic lupus erythematosus and Sjögren's

syndrome were other etiological diagnosis identified in this population, validating its low systemic sclerosis specificity.⁵

Although rare, in this study, 4 patients with anti-Th/To and 1 patient with anti-NOR90, with established SSc diagnosis, did not have any association with other more common SSc's autoantibodies, revealing the importance of their active search when SSc is suspected, especially for Th/To.

Results are limited, influenced by the reduced number of cases, partially due to limited search on these two autoantibodies. Clinical prospective trials with a larger population are needed for more conclusive results.

Conclusion

In this study, anti-Th/To and anti-NOR 90 groups were similar in respect to clinical manifestations and etiologic diagnosis. Both groups had more frequent skin and articular manifestations with more cardiopulmonary involvement in anti-Th/to and gastrointestinal symptoms in anti-NOR90 group.

Active search of Th/To and NOR 90 autoantibodies could be beneficial when systemic sclerosis disease is suspected, since in this study they were singly positive in 20% of these cases. A larger population study is needed to strive for more conclusive results. ■

Table 3: Autoantibodies associations in anti-NOR90 group

SSc Autoantibodies Positive Associations	Anti-NOR90 n=10	Diagnosis
Anti-Ku	1	SLE
Anti-Scl70	1	SSc
Anti-Ku, Anti-PM Scl100	1	SSc
Anti-Ku, Ant-Ro52, Anti-PMScl75	1	Still unknown
Anti-Ku, Anti-Centromere	1	SSc
No Associations	5	1 case SSc, 2 cases SSs, 1 case PRp, 1 case still unknown

SLE- systemic lupus erythematosus; SSs- secondary sjogren's syndrome; PRp- primary raynaud's phenomenon

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

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