Formulário de acesso a dados do Registo nacional de Doentes Reumáticos (Reuma.pt) da SPR, 2018-2020

1. Title

Frequency of disease-associated autoantibodies in Reuma.pt systemic sclerosis cohort patients and its association with characteristic clinical features.

2. Abstract

The occurrence of different antinuclear antibodies in Systemic Sclerosis has been associated with distinct disease subtypes, guiding the patient's follow-up and treatment plans. However, most of these associations haven't been tested yet in the Portuguese population. The main purpose of this work is to test these immuno-clinical associations in the Portuguese National Registry Reuma.pt.

3. Background

Autoantibodies targeting characteristic nuclear antigens are one of the hallmarks of systemic sclerosis (SSc) [1-3]. The occurrence of different antinuclear antibodies (ANA's) is associated with distinct disease subtypes and with differences in disease severity, including extent of skin involvement, internal organ manifestation and prognosis. Although the current SSc criteria of the American College of Rheumatology [4] do not include the presence of ANAs, the detection of scleroderma-associated antibodies is a valuable tool in the diagnosis of patients with very early SSc or only subtle symptoms [5,6]. For instance, in a recent study of patients with Raynaud's phenomenon, the presence of ANA's (adjusted HR = 5.67) and SSc-associated antibodies (HR = 4.7) was the strongest independent predictor of definite SSc [6]. Some of the autoantibodies in SSc are regarded as disease-specific and can be correlated with genetic, demographic, diagnostic, clinical and prognostic aspects of the disease [1,3]. Therefore, autoantibodies are pivotal tools in the diagnosis of SSc by helping clinicians make decisions whether to perform further, more detailed and efficient diagnostic procedures, as well as decisions addressing disease management [1].

The severity of organ involvement, disease progression, and response to therapies are extremely heterogeneous among patients with systemic sclerosis (SSc). The discovery and validation of biomarkers can help predict disease risk, improve early diagnosis and prognosis, better design clinical trials and assess response to treatment, as well as further elucidate the underlying pathogenic mechanisms of this disease [2].

4. Objectives

Primary objectives

- Associate the expression of systemic sclerosis-associated autoantibodies with characteristic clinical features of Reuma.pt systemic sclerosis cohort patients (i.e., establish associations between clinical features and particular disease-associated autoantibody expression);

Secondary objectives

- Describe the frequency of characteristic clinical features in patients of the Reuma.pt systemic sclerosis cohort;
- Describe the frequency of disease-associated autoantibodies in patients of the Reuma.pt systemic sclerosis cohort;
- Associate the systemic sclerosis cutaneous phenotype with characteristic clinical features expression in patients of the Reuma.pt systemic sclerosis cohort (i.e. establish associations between demographic/clinical features and cutaneous phenotypic expression).

5. Methods

Type of study

Prospective multicentre open cohort study

Inclusion criteria

- Patients that fulfil the ACR/EULAR 2013 classification criteria for systemic sclerosis[3] or patients with very early diagnosis of systemic sclerosis
- Patients registered in Reuma.pt/Scleroderma[4], with both a characterized immunologic profile and a phenotypical description

Variables to be collected

- Age (continuous variable)
- Gender (categorical variable: female; male)
- Age at disease onset (continuous variable)
- ANA (categorical variable: positive; negative)
- Disease-specific auto-antibodies (categorical variables: anti-centromere, anti-topoisomerase I, anti-RNA polymerase III, anti-Th/To, anti-U3 RNP, anti-Pm/Scl, anti-Ku, anti-U1 RNP, anti-U11/U12 RNP, none)
- Phenotype of cutaneous involvement (categorical variables: systemic sclerosis sin scleroderma; very early diagnosis of systemic sclerosis; limited cutaneous systemic sclerosis; diffuse cutaneous systemic sclerosis)
- Overlap syndrome (categorical variables: polymyositis, dermatomyositis, systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, mixed connective tissue disease, none)

- Clinical manifestations (continuous variable: Rodnan skin score; categorical variables: skin thickening, calcinosis, Raynaud's phenomenon, telangiectasia, digital ulcers, oesophageal involvement, gastric involvement, intestinal involvement, cardiac involvement, musculoskeletal involvement (joint contractures, tendon friction rubs, arthralgia, myositis/CK elevation), pulmonary involvement (pulmonary hypertension, pulmonary fibrosis, lung restrictive defect), renal involvement/proteinuria
- Nail fold capillaroscopy pattern (categorical variable)

Statistical analysis

The data will be analysed using SPSS version 25.0 (SPSS, Inc., Chicago, IL, USA).

Descriptive statistics will be presented as mean ± standard deviation (continuous variables) or as absolute and relative frequencies (categorical variables).

The associations between disease-specific antibody expression, cutaneous phenotype and clinical manifestations will be tested using Chi Square Tests or Fischer's Exact Test, as appropriate. For statistically significant associations, the odds ratio will be calculated as a measure of the effect size of the association.

Differences of Rodnan skin score, age and age of onset between patients with different disease-specific antibodies and between patients with different cutaneous phenotypes will be tested using Student's t-Test or Mann-Whitney Test, as appropriate (normality and variance homogeneity will be calculated). Cohen's D will be used as a measure of the effect size of the differences.

6.1. Expected results

The main objective of this study is to clinically characterize patients of the Reuma.pt systemic sclerosis cohort who express specific systemic sclerosis-associated autoantibodies, in an attempt to validate findings obtained in other systemic sclerosis cohorts, such as the *German network for systemic scleroderma* (GNfSSc) [1]. In terms of autoantibody prevalence, we expect our cohort to be similar to GNfSSc and *European League Against Rheumatism Scleroderma Trials and Research* (EUSTAR) [3].

6.2. Possible limitations

Internal and external validity

This study will focus on a specific cohort and its objectives focus on that same target population. Most patients of the target population can be included in the study. In order to get maximum internal and external validity, we expect not only tertiary but also secondary centres to participate in this project. Centres who actively collaborate in the project may designate project co-authors, irrespective of the number of eligible patients.

Sample size

Systemic sclerosis is a rare disease, and therefore data sets tend to be small. To maximize our sample size, we will try to appeal to as much centres as possible. Besides, we will use measures of effect size to better interpret statistically non-significant results.

Missing data

To overcome this problem, we will ask all participating centres to complete the missing information with data from patients' medical records, whenever such information is available.

Typing errors

To minimize the influence of typing errors, we will make an exploratory evaluation of the data extracted from Reuma.pt. Outlier cases will be individually analysed.

Publication bias

We expect to publish the results of our study, irrespective of the significance of our results.

7. Calendar of tasks

- Literature review, study design and elaboration of research protocol: July - September 2019
- Submission of research protocol to Reuma.pt and Ethics Commission: October 2019
- Invite all national centres to participate in the project: November 2019
- Data completion by all participating centres: November - December 2019
- Data extraction: January 2020
- Data analysis: February - June 2020
- Final report and abstract submissions for presentation at national/international congresses as well as publication: July - Dec 2020

8. Ethical considerations

The study will be conducted according to the principles of the Declaration of Helsinki (revised in Fortaleza – 2013) [6] and will be submitted for evaluation and approval to the Ethics Committee of *Centro Hospitalar e Univeristário Lisboa Norte*.

All patients must have signed the Reuma.pt informed consent.

9.1. Proponent

Eduardo Dourado, resident at *Serviço de Reumatologia e Doenças Ósseas Metabólicas, Hospital de Santa Maria, CHULN*.

9.2. Research team

Eduardo Dourado, Patrícia Martins, João Eurico Fonseca, Inês Cordeiro - *Serviço de Reumatologia e Doenças Ósseas Metabólicas, Hospital de Santa Maria, CHULN*.

9.3. Institutions

The project is open to all national centres willing to participate.

9.4 Co-authorship

Clinicians who actively collaborate in the project will be co-authors, according to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (Vancouver Convention) [5], with a maximum of 2 co-authors per participating centre (+1 author for each 50 patients included without missing data).

10.1. Budget

Reuma.pt data exportation (to be defined).

10.2. Conflicts of interest

There are no conflicts of interest to be declared.

References

1. Mierau, R. *et al.* Frequency of disease-associated and other nuclear autoantibodies in patients of the German network for systemic scleroderma: correlation with characteristic clinical features. *Arthritis Res. Ther.* **13,** R172 (2011).
2. Manetti, M. Emerging biomarkers in systemic sclerosis. *Curr. Opin. Rheumatol.* **28,** 606–612 (2016).
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4. Canhão, H., Faustino, A. & Fonseca, J. E. REGISTO NACIONAL DE DOENTES REUMÁTICOS, REUMA. PT.
5. ICMJE | Recommendations. Available at: http://www.icmje.org/recommendations/. (Accessed: 20th June 2018)
6. WMA - The World Medical Association-WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects.