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Factors influencing polyautoimmunity in systemic lupus erythematosus

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ABSTRACT

Objective: Since characterization of the extent to which particular combinations of autoimmune diseases (ADs) occur in excess of that expected by chance may offer new insights into possible common pathophysiological mechanisms, polyautoimmunity (i.e., ADs co-occurring within patients) in systemic lupus erythematosus (SLE) and its associated factors were investigated.
Methods: This was a cross-sectional study in which 335 consecutive patients with SLE and the history of 22 ADs were investigated. A multivariate analysis was performed. A systematic literature review was done and results were grouped by hierarchical cluster procedure analysis.
Results: There were 136 (41%) SLE patients presenting with at least one other AD. A total of 191 ADs were observed, of which the most frequent were autoimmune thyroid disease (AITD), antiphospholipid syndrome (APS) and Sjögren's syndrome (SS), registered in 60 (18%), 48 (14%) and 47 (14%) cases, respectively. Out of a total number of 1515 SLE patients with polyautoimmunity (1379 reported previously and 136 informed here) there were 77 (5.1%) cases with multiple autoimmune syndrome (i.e., two or more ADs in addition to SLE). Female gender, articular involvement, familial autoimmunity, anti-Ro positivity and patient's origin were risk factors for polyautoimmunity while the presence of anti-RNP antibodies was protective. Four clusters of ADs were found. The most hierarchical one was composed of AITD, APS, SS, and systemic sclerosis.
Conclusion: Polyautoimmunity is frequent in SLE, and it is influenced by clinical and immunological features. These findings support that clinically different autoimmune phenotypes might share common susceptibility variants.

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1. Introduction

Systemic lupus erythematosus (SLE) is a prototype of autoimmune diseases (ADs) affecting predominantly women. It is characterized by a multisystem organ involvement because of dysregulation of self-reactive B cells leading to autoantibody production, immune complex deposition and complement activation with tissue damage [1]. Although the etiology of ADs remains poorly understood, common features among them and a plausible common background for autoimmunity are emerging and recognized. The fact that more than one AD may coexist in a single patient (polyautoimmunity) or in the same nuclear family (familial autoimmunity) as well as the characterization of the extent to which particular combinations of ADs occur in excess of that expected by chance may offer new insights into the common origin of ADs [2,3]. Despite SLE association with other ADs has been reported separately in the literature, there is a requirement to group and analyze it highlighting the heterogeneity between SLE and other ADs and remarking the hypothesis of an underlying shared immunogenetic mechanism. Thus, the aim of this study was to investigate the current evidence of polyautoimmunity in SLE and to examine the factors influencing it.

2. Methods

2.1. Study subjects

This was a cross sectional and multicentre study of patients recruited from a cohort of SLE patients followed at four centers in Colombia, the Center for Autoimmune Diseases Research (CREA) at the Rosario University, the Clínica Universitaria Bolivariana-Corporación para Investigaciones Biológicas (CIB) in Medellín, the Rheumatology Unit at the National University and CAYRE-Riesgo de Fractura SA Clinic in Bogotá, and one center in Catalonia, the Department of Autoimmune Diseases at the Hospital Clinic in Barcelona. Patients fulfilled four or more of the American College of Rheumatology (ACR) criteria for the classification of SLE [4]. The institutional review boards at each center approved the study design.

Information on patient demographics and cumulative clinical and laboratory data were obtained by clinical examination and chart review, and were collected in a standardized report form. The variables associated with SLE, including each feature of the revised ACR criteria, were evaluated as described elsewhere [5]. There were 22 ADs evaluated according to the international validated criteria [6] which included Addison's disease (ADD), alopecia areata (AA), autoimmune hepatitis (AIH), autoimmune thyroid disease (AITD), antiphospholipid syndrome (APS), biliary inflammatory disease (BID) including primary sclerosing cholangitis and primary biliary cirrhosis, celiac disease (CD), demyelinating autoimmune diseases (DAD) including transverse myelitis and multiple sclerosis, dermatomyositis, polymyositis (DM/PM), inflammatory bowel disease (IBD) including ulcerative colitis and Crohn's disease, myastenia gravis (MG), pernicious anemia (PA), pemphigus (PF), psoriasis (Pso), rheumatoid arthritis (RA), relapsing polychondritis (RP), sarcoidosis (Sar), Sjogren's Syndrome (SS), scleroderma (SSc) including systemic and CREST Syndrome, type 1 diabetes mellitus (T1DM), vasculitis (Vas) and vitiligo (VIT).

2.2. Search strategy

Publications were identified through a systematic search made by three independent experts in Pubmed, Medline, EMBASE, SciELO and LILACS electronic databases up to February 2009. The following search terms were used in English, Spanish French and Italian: [Majr] terms were, “Lupus”, “Rhupus”, “Sjögren's”, “Multiple Autoimmune Diseases”, “Multiple Autoimmune Syndrome”, “Multiple Autoimmune Disease”, “co-occurrent Autoimmune Diseases” and [Mesh] terms were: “SLE”, “Systemic Lupus Erythematosus”, “Thyroiditis”, “Hypothyroidism”, “Hyperthyroidism”, “Antiphospholipid”, “Antiphospholipid Antibodies Syndrome”, “Antiphospholipid Syndrome”, “Scleroderma”, “Celiac Disease” “Myasthenia”, “Diabetes”, “Autoimmune Hepatitis”, “Psoriasis”, “Crohn's”, “Ulcerative Colitis”, “Pernicious”, “Vitiligo”, “Primary Biliary”, “Addison's”, “Areata”, “Cryoglobulinemia”, “Polyangiitis”, “Giant Cell”, “Cutaneous Vasculitis”, “Relapsing Polychondritis”, “Penphigus”, “Hemolytic Anemia”, “Transverse Myelitis”, “Multiple Sclerosis”, with limits: title, humans, English, French, Italian, Spanish and Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Review and Case Reports.

2.3. Cluster ADs analysis

A hierarchical cluster procedure analysis was done to identify relatively homogeneous subgroups of variables based on selected ADs in SLE cases with multiple autoimmune syndrome (MAS) reported through the literature systematic review. The objective of this analysis was to find which ADs cluster more frequently in SLE patients. The cluster method implemented was between-group linkage and the measure was Squared Euclidean distance. After the analysis a dendrogram using average Linkage (Between Groups) was plotted.

2.4. Statistical analysis

Descriptive statistics were used to summarize the main characteristics of the patients. The prevalence of coexisting ADs was counted separately by individual. The familial rates of ADs were computed by individual, however, if a patient reported several ADs in the same family member this was counted separately as different cases corresponding to each AD. Family pedigrees were constructed evaluating ADs in all degree relatives. A multivariate analysis was done to identify predictors of polyautoimmunity using logistic regressions models adjusting for age, gender, country and duration of SLE. Adjusted odds ratios (AORs) were calculated with 95% confidence intervals (CIs). A p value of less than 0.05 was considered significant. The Statistical Package for the Social Sciences (SPSS) (V15 for Windows, Chicago, IL) was used for all analyses.

3. Results

3.1. Individual characteristics and polyautoimmunity

There were 335 patients included of whom 200 were included in Barcelona, Spain and 135 in Colombia. Most of them were women (88%), with a mean duration of disease of 10.2 ± 8.3 years, being 12.6 ± 8 years in Barcelona cohort and 6.3 ± 7.2 years in the Colombian patients. 136 (41%) of patients had at least one other AD. A total of 191 ADs were observed, of which the most frequent were AITD, APS and SS, registered in 60 (18%), 48 (14%) and 47 (14%) cases, respectively. There were 40 (12%) with MAS (i.e., two or more ADs in addition to SLE). Risk factors of polyautoimmunity are depicted in the Table 1.

Table 1
Risk factors associated with polyautoimmunity in SLE (multivariate analysis).

	AOR	95%CI		p
Gender (female)	2.30	1.03	5.15	0.043
Current age	1.03	1.01	1.04	0.0001
Articular involvement	2.02	1.26	3.23	0.003
Familial autoimmunity	1.61	1.14	2.28	0.007
Anti Ro	1.54	1.10	2.16	0.013
Anti RNP	0.61	0.42	0.89	0.011
Origin (Colombia)	1.78	1.40	2.27	<0.0001

AOR: adjusted odds ratio by gender, and duration of disease; CI: confidence interval.

3.2. Search strategy

The following items were collected: title of the article, journal, place of publication, type of article, number of cases, ADs reported associated to SLE. The systematic search yielded 1785 articles, out of them 479 articles were entered in the analysis. Main reasons for exclusion were review publications which do not include case reports, citations which were in other languages different to the limits, those whose full text could not be found to determine the number of cases or citations in which cases do not have an association of ADs reported with SLE simultaneously.

A total of 1379 cases were found with polyautoimmunity associated with SLE (Table 2). The most frequent ADs were APS, SS and AITD found in 35% (484 cases); 13% (179 cases); 9.3% (129 Cases), respectively. Additional 477 references concerning the diseases displayed in Table 2 can be found in supplementary material at this link: http://www.urosario.edu.co/medicina/images/crea/SLE_polyAI_article_Supplementary_references.xls. Out of a total number of 1515 SLE cases with polyautoimmunity (1379 reported and 136 informed here) there were 77 with MAS corresponding to 5.1% (see detailed cases in supplementary material http://www.urosario.edu.co/medicina/images/crea/SLE_polyAI_article_Supplementary_references.xls).

3.3. Cluster ADs analysis

The smallest average distance between all group pairs was computed and then a combination between the closer groups was done. A proximity matrix was displayed, presenting the information for the distances between the ADs and the clusters (Fig. 1), showing a tree graph in which each node represents a stage from the clustering process. This tree gave additional information about the magnitude of the distance between the clusters. There were four clusters demonstrating that the most hierarchical was composed of four ADs based on the frequency of presentation in the 77 MAS cases: AITD, APS, SS, and SSc.

Table 2
Polyautoimmunity in SLE patients (review of literature).

SLE	No cases
APS	484
SS	179
AITD	129
DAD	96
Vas	74
RA	55
SSc	54
MG	47
CV	44
MAS	37
AIH	31
MC	31
Pso	23
PF	19
BID	14
CD	13
DM/PM	12
IBD	11
VIT	8
PA	7
RP	5
T1DM	2
AA	1
ADD	1
GCA	1
MP	1

International validated criteria described elsewhere [6] SLE: Systemic Lupus Erythematosus; AA: Alopecia Areata; ADD: Addison's disease; AIH: Autoimmune Hepatitis; AITD: Autoimmune Thyroid Disease; APS: Antiphospholipid Syndrome; BID: Biliary inflamatory disease (Including Primary sclerosing cholangitis and Primary Biliary Cirrhosis); CD: Celiac Disease; CV: Cutaneous vasculitis; DAD: Demyelinating autoimmune diseases (including Transverse Myelitis and Multiple Sclerosis); DM/PM: Dermatomyositis, Polymyositis; GCA: Giant cell arteritis; IBD: Inflamatory Bowel Disease (including Ulcerative colitis and Crohn's disease); MAS: Multiple autoimmune syndrome; MC: Mixed cryoglobulinemia; MG: Myastenia Gravis; MP: Microscopic polyagiitis; PA: Pernicious Anemia; PF: Pemphigus; Pso: Psoriasis; RA: Rheumatoid Arthritis; RP: Relapsing Polychondritis; SS: Sjögren's Syndrome; SSc: Scleroderma (Including systemic and CREST Syndrome); T1DM: Type 1 Diabetes Mellitus; Vas: Vasculitis; VIT: Vitiligo. See literature references from this table at this link: http://www.urosario.edu.co/medicina/images/crea/SLE_polyAI_article_Supplementary_references.xls.

4. Discussion

The present study emphasizes that there is a high prevalence of polyautoimmunity in patients with SLE (41%) and that among patients with SLE- polyautoimmunity 5.1% presented with MAS. These findings strongly support that clinically different autoimmune phenotypes might share common susceptibility variants. As previously mentioned [2] the importance of the MAS concept focuses on the probability of having three or more ADs simultaneously in one patient which goes beyond epidemiologic inferences or statistical chance, and is an argument favoring the common pathophysiological mechanisms of ADs.

It is not uncommon that SLE aggregate with other ADs. It has been indicated that SLE as well as AITD and SS should be considered as the "chaperones" of the ADs because having one of these entities is a risk for developing polyautoimmunity [2]. AITD and SS are the most frequent autoimmune conditions associated to SLE-MAS patients. In addition to these diseases APS is the other more prevalent autoimmune condition associated with SLE.

Risk factors were found to be associated with polyautoimmunity in SLE (Table 1). In this study we confirmed that familial autoimmunity is a risk for polyautoimmunity in SLE, as has been shown in RA [7] and SSc [8], SS [6] and T1DM [9]. As a complex trait autoimmunity tend to cluster in families (i.e. familial autoimmunity), and this fact is an important risk factor for polyautoimmunity.

Articular involvement was another risk factor significantly associated with polyautoimmunity. It is well known that the differentiation between lupus arthritis and RA may be sometimes difficult, particularly at the beginning of SLE when patients have joint manifestations without systemic compromise [10]. According to our multivariate analysis, it could be predicted that SLE individuals with articular involvement have 2 fold the probability to develop polyautoimmunity as compared with SLE patients without it. As a corollary, SLE patients with articular compromise should be followed for the risk to develop another AD in addition to SLE. They could present with two entities separately and not an overlapping syndrome. RA was the four more frequent AD associated with SLE.

Anti-Ro (SS-A) autoantibodies have been described as serological marker for SS but are also found in patients with other systemic autoimmune diseases [11]. Anti-Ro antibodies are associated with cutaneous, hematological and congenital compromise in SLE [12]. Previous studies have shown that SLE patients who develop SS had significantly frequent anti-Ro antibodies [13] and that patients with SLE and anti-Ro antibodies can also develop AITD [13,14]. These reports together with the current results confirm that SS is one of the more prevalent associated AD with SLE.

Anti-RNP antibodies are identified as part of an autoantibody profile in mixed connective tissue disease (MCTD) [12] and as a marker of early lupus [15–17]. There was an unexpected opposite association between anti-RNP antibodies and polyautoimmunity in SLE. This effect could be related with the high specificity and sensibility of these antibodies in MCTD. This condition was not present in any of the evaluated patients. In addition, there was no association between anti-RNP antibodies and any of the ADs associated with SLE, reinforcing the specificity of these antibodies in SLE patients with no other AD. Small nuclear RNPs are common targets of autoantibodies in SLE and other ADs. The etiology and progression of autoimmune responses directed against these antigens are not well understood [15], and further studies are necessary to

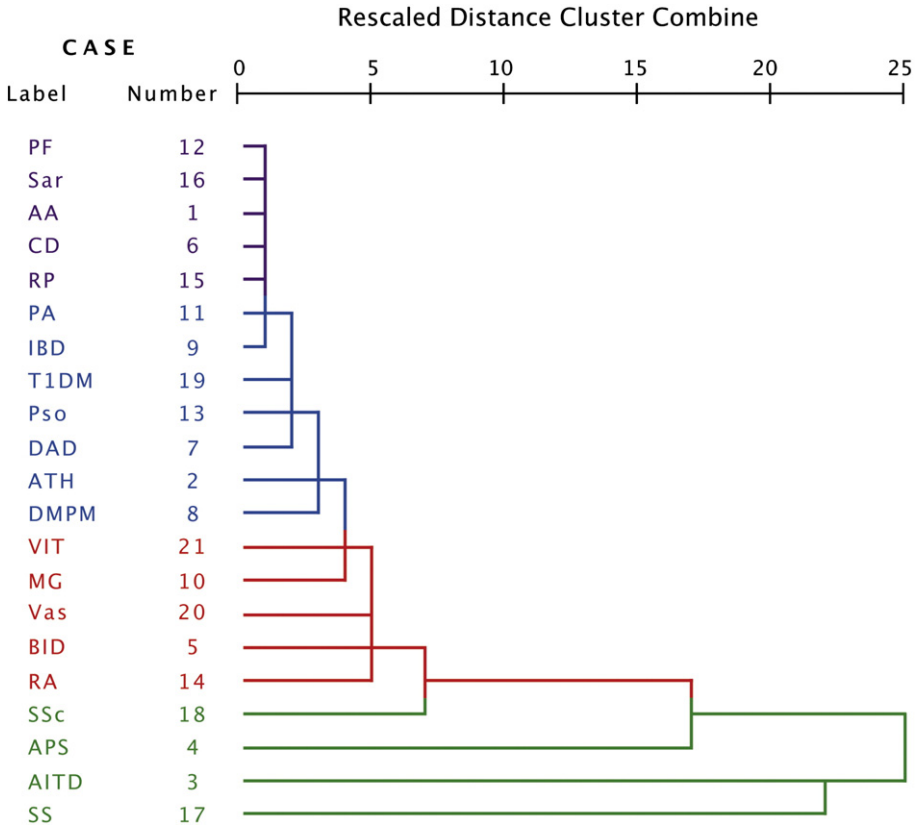

Fig. 1. Cluster analysis dendrogram using average linkage between groups of 77 multiple autoimmune syndrome cases reported in the literature, including the current report.

search for the protective role of these antibodies in the development of polyautoimmunity in SLE.

Complex traits such as polyautoimmunity may vary according to populations. Some ethnic differences could be related to a significant association between Colombian cohort and polyautoimmunity in SLE. This phenomenon should be associated with some different environmental and ethnic backgrounds between the two populations, being the admixture in Latin American patients (i.e. Amerindian, European and African) one of the most important [18].

In conclusion, our study indicates that polyautoimmunity is frequent in SLE and that SLE patients with familial autoimmunity, articular involvement, and anti-Ro antibodies must be carefully followed for the development of polyautoimmunity.

Take-home messages

- Polyautoimmunity is frequent in SLE, and it is influenced by clinical and immunological features.
- Familial autoimmunity (i.e., diverse autoimmune diseases co-occurring in patients relatives) and geography (i.e., environmental vs. genetic factors) are important characteristics to be considered.
- ADs share common susceptibility variants.

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