Influence of the age at diagnosis in the disease expression of primary Sjögren syndrome

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Influence of the age at diagnosis in the disease expression of primary Sjögren's syndrome. Analysis of 12,753 patients from the Sjögren Big Data Consortium

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ABSTRACT

Objective. *To analyse how the main components of the disease phenotype (sicca symptoms, diagnostic tests, immunological markers and systemic disease) can be driven by the age at diagnosis of primary Sjögren's syndrome (pSS).*

Methods. *By January 2021, the participant centres had included 12,753 patients from 25 countries that fulfilled the 2002/2016 classification criteria for pSS. The age at diagnosis was defined as the time when the attending physician confirmed fulfilment of the criteria. Patients were clustered according to age at diagnosis. 50 clusters with more than 100 observations (from 27 to 76 years) were used to study the influence of the age at diagnosis in the disease expression.*

Results. *There was a consistent increase in the frequency of oral dryness according to the age at diagnosis, with a frequency of <90% in patients diagnosed at the youngest ages and >95% in those diagnosed at the oldest ages. The smooth curves that best fitted a linear model were the frequency of dry mouth (adjusted R^2 0.87) and the frequency of abnormal oral tests (adjusted R^2 0.72). Therefore, for each 1-year increase in the age at diagnosis, the frequency of dry mouth increased by 0.13%, and the frequency of abnormal oral diagnostic tests by 0.11%. There was a consistent year-by-year decrease in the frequency of all autoantibodies and immunological markers except for cryoglobulins. According to the linear models, for each 1-year increase in the age at diagnosis, the frequency of a positive result decreased by 0.57% (for anti-Ro antibodies), 0.47% (for RF) and 0.42% (for anti-La antibodies). The ESSDAI domains which showed a more consistent decrease were glandular and lymph node involvement (for each 1-year increase in the age at diagnosis, the frequency of activity decreased by 0.18%), and constitutional, cutaneous, and haematological involvements (the frequency decreased by 0.09% for each 1-year increase). In contrast, other domains showed an ascending pattern, especially pulmonary involvement (for each 1-year increase in the age at diagnosis, the frequency of activity increased by 0.22%), and peripheral nerve involvement (the frequency increased by 0.09% for each 1-year increase).*

Conclusion. *The influence of the age at diagnosis on the key phenotypic features of pSS is strong, and should be considered critical not only for designing a personalised diagnostic approach, but also to be carefully considered when analysing the results of diagnostic tests and immunological parameters, and when internal organ involvement is suspected at diagnosis.*

Introduction

Primary Sjögren syndrome (pSS) is a systemic autoimmune disease that mainly affects middle-aged women, and has a frequency ranging between 0.01 and 0.72% (1). Aetiopathogenically, SS targets the exocrine glands, which are infiltrated by lymphocytes (2). More than 95% of patients present with oral and/or ocular dryness, but may also develop a large number of extraglandular (systemic) manifestations, which may be the presenting manifestation (3). The key immunological markers are anti-Ro antibodies (the most specific) and cryoglobulins and hypocomplementaemia (the main prognostic markers) (4).

Understanding how these factors influence the systemic phenotype could aid the identification at diagnosis of patients who may be more prone to a more-complicated disease and, therefore, determine which patients should be followed more closely and/or treated more intensively (5). A significant challenge in diagnosing pSS is recognising that it may occur at any age. Although it is diagnosed predominantly in people aged 30–60 years, the epidemiology of pSS is a continuum and it has been reported in people aged 2 (6) to 97 years (7). Studies in small series of patients have suggested a role for the age at diagnosis in the disease phenotype (4). In these studies, the statistical approach was based on the comparison of the main SS features between a specific epidemiological onset (defined according to the age at diagnosis) and the remaining patients: a young disease onset was defined according to an age at diagnosis of <35–40 years, and an elderly onset by an age at diagnosis >65–70 years. Considering that the definition of "young" or "elderly" disease onset is arbitrary and the statistical limitations of using a dichotomic analysis of a continuous variable such as age, a better methodological approach could be to analyse how the frequency of the main SS features may change year by year, according to the age at diagnosis. This type of analysis is only possible when big data sources are used, including a sufficiently representative number of patients per year of age at diagnosis, as occurs with the Sjögren Big Data Consortium (8). The objective of this study was to analyse how the main components of the disease phenotype (sicca symptoms, diagnostic tests, immunological markers and systemic disease) can be driven by the age at diagnosis in the largest reported international, multi-ethnic cohort of patients with pSS.

Material and methods

Patients

The Big Data Sjögren Project Consortium is an international, multicentre registry designed in 2014 to take a "high-definition" picture of the main features of pSS using worldwide data-sharing cooperative merging of pre-existing clinical SS databases from leading centres in clinical research in SS from five continents (see reference 14 for additional methodological details). The centres share a harmonised data infrastructure and conduct cooperative online efforts in order to refine already-collected data in each centre. The codebook containing instructions on the variables and data codification was discussed and approved by the Steering Committee members and was then shared with the consortium partners. Databases from each centre were harmonised into a single database by applying data-cleaning pre-processing techniques. Descriptive statistics and data visualisation methods were used to detect outliers, data errors, missing data and influential observations (9). Double- checking to correct errors and complete missing information was carried out to minimise incomplete and erroneous data. Inclusion criteria were fulfilment of the 2002 or 2016 classification criteria (10, 11). Exclusion criteria for considering SS as a primary disease were chronic HCV/HIV infection, previous lymphoproliferative processes, and associated systemic autoimmune diseases. Diagnostic tests for SS (ocular tests, oral tests and salivary gland biopsy) were carried out according to the recommendations of the European Community Study Group (12). The study was approved by the Ethics Committee of the Coordinating Centre (Hospital Clinic, Barcelona, Spain, registry HCB/2015/0869).

Definition of variables

The age at diagnosis was defined based on the moment that the attending physician confirmed fulfilment of the 2002 or 2016 criteria. The main disease features at this time were retrospectively collected and analysed. The following clinical variables were selected for harmonisation and further refinement: age, sex, ethnicity, country of residence, fulfilment of 2002/2016 criteria items, antinuclear antibodies, rheumatoid factor, C3 and C4 levels, cryoglobulins, and organ-by-organ ESSDAI scores. By January 2021, the participant centres had included 12,753 valid patients from 25 countries. The epidemiological variables included were age at diagnosis (continuous variable), sex and ethnicity according to FDA definitions (5). Systemic involvement at diagnosis was classified and scored according to the ESSDAI (13).

Statistical analysis

Descriptive data are presented as mean and standard deviation (SD) for continuous variables and numbers and percentages (%) for categorical variables. Patients were clustered according to age at diagnosis. Fifty clusters with more than 100 observations (from 27 to 76 years) were used to study the influence of the age at diagnosis in the disease expression. For each cluster, the frequency and percentage of positive diagnostic tests for SS, immunological markers and systemic activity were computed. To represent the main increasing and decreasing patterns, smoothed conditional means were calculated. Generalised additive models were used as the smoothing method. Linear regression models were fitted to smooth curves to identify linear increasing and decreasing trends. Slope (beta) and adjusted R-squared coefficients were computed to interpret models fitting. If the regression beta coefficients for each variable were positive (or negative, respectively) and therefore for every 1-unit increase in the age at diagnosis, the outcome variables will increase (or decrease, respectively) by the corresponding beta coefficient value. Adjusted R-squared values higher than 0.8 were considered as well-fitting. All analyses were con-

ducted using the R v.3.6.0 for Windows statistical software package (https://www.R-project.org/).

Results

The baseline characteristics of the cohort are summarised in Table I and included 11,918 (93.5%) women with a mean age at diagnosis of pSS of 52.2 (SD 14.6) years. The frequencies of fulfilment of the 2002 classification criteria items (were 91.9% for dry eye (item I), 93.2% for dry mouth (item II), 83.7% for abnormal ocular tests (item III), 82.2% for positive minor salivary gland biopsy (item IV), 79% for abnormal oral diagnostic tests (item V) and 76.9% for positive anti-Ro/La antibodies (item VI). The frequency of other immunological markers at diagnosis was: positive ANA in 80.8% of patients, positive RF in 48.4, low C3 levels in 12.8%, low C4 levels in 13.3% and positive serum cryoglobulins in 7.6% of patients.

Table I. Baseline characteristics of 12,753 patients with primary Sjögren's syndrome.

Variable	Patients with pSS (n=12,753)
Age at diagnosis (n=12,719) (mean ± SD)	52.2 ± 14.6
Sex (female)	11,918 (93.5)
Ethnicity (n=12,747)	
White	9,169 (71.9)
Asian	2,059 (16.2)
Hispanic	734 (5.8)
Black/African-American (AA)	178 (1.4)
Others	607 (4.8)
Geolocation	
Europe	8,844 (69.3)
America	1,760 (13.8)
Asia	1,880 (14.7)
Other	269 (2.1)
Signs and symptoms at presentation	
Dry eye	11,723 (91.9)
Dry mouth	11,891 (93.2)
Diagnostic tests	
Abnormal ocular tests (any) (n=10,834)	9,070 (83.7)
Schirmer's test (n=10,720)	8,391 (78.3)
Rose Bengal score/other ocular dye score (n=5,103)	3,643 (71.4)
Abnormal oral diagnostic tests (any) (n=9,665)	7,637 (79.0)
Unstimulated whole salivary flow (n=7,758)	5,908 (76.2)
Parotid sialography (n=2,416)	1,954 (80.9)
Salivary scintigraphy (n=2,282)	1,846 (80.9)
Positive minor salivary gland biopsy(n=9,045)	7,431 (82.2)
Immunological profile	
ANA-positive (n=12,020)	9,713 (80.8)
RF-positive (n=10,424)	5,047 (48.4)
Positive anti-Ro/La antibodies (n=12,630)	9,714 (76.9)
Anti-Ro antibodies (n=12,624)	9,431 (74.7)
Anti-La antibodies (n=12,564)	5,641 (44.9)
Low C3 levels (n=10,392)	1,332 (12.8)
Low C4 levels (n=10,376)	1,380 (13.3)
Positive cryoglobulins (n=5,614)	428 (7.6)
Systemic activity	
Mean ESSDAI score (n=11,724)	5.9 ± 7.3
DAS (n=11,724)	
No activity (ESSDAI=0)	2,239 (19.1)
Low	4,471 (38.1)
Moderate	3,604 (30.7)
High	1,410 (12.0)
ESSDAI domains (score ≥1) (n=12,152)	
Constitutional	1,200 (9.9)
Lymphadenopathy	1,055 (8.7)
Glandular	2,487 (20.5)
Articular	4,493 (37.0)
Cutaneous	1,115 (9.2)
Pulmonary	1,258 (10.4)
Renal	513 (4.2)
Muscular	262 (2.2)
PNS	693 (5.7)
CNS	220 (1.8)
Haematological	2,619/11,986 (21.9)
Biological	5,817/11,800 (49.3)

Glandular involvement

There was a consistent increase in the frequency of oral dryness according to the age at diagnosis, with a frequency of <90% in patients diagnosed at the youngest ages and >95% in those diagnosed at the oldest ages; a similar pattern was found for ocular dryness until an age at diagnosis of 60 years, although in people diagnosed after 60 years, the ascending curve of the frequency of ocular dryness was inverted, showing a sustained decrease. The curves of the age-by-age frequencies corresponding to the results of diagnostic tests showed a similar pattern: a progressive increase in the frequency of abnormal oral results as the age at diagnosis increased, and the same increase for abnormal ocular tests until an age at diagnosis of 60 years and a progressive decline thereafter (Fig. 1). The regression beta coefficients for each variable were positive and, therefore, for every 1-unit increase in the age at diagnosis, the outcome variables increased by the corresponding beta coefficient value. The smooth curves that best fitted a linear model were the frequency of dry mouth (adjusted R^2 0.87) and the frequency of abnormal oral tests (adjusted R^2 0.72). Therefore, for each 1-year increase in the age at diagnosis, the frequency of dry mouth increased by 0.13%, and the frequency of abnormal oral diagnostic tests by 0.11% (Table II).

Autoantibodies and immunological markers

There was a consistent year-by-year decrease in the frequency of all autoantibodies and immunological markers except for cryoglobulins (Fig. 2). For the

four main autoantibodies, the smooth curves of the age-by-age frequencies for positive results showed a progressive decrease as the age at diagnosis increased. The smooth curves that best fitted a linear model were the frequency of anti-Ro antibodies (adjusted R^2 0.97), ANA (adjusted R^2 0.93), anti-La antibodies (adjusted R^2 0.88), RF (adjusted R^2 0.86) and low C3 levels (adjusted R^2 0.85). The regression beta coefficients for these variables were negative, and according to the linear models, for each 1-year increase in the age at diagnosis, the frequency of a positive result decreased by 0.57% (for anti-Ro antibodies), 0.47% (for RF), 0.42% (for anti-La antibodies), 0.36% (for ANA, although the smooth curve broke the progressive decrease after the age of 70 and started to ascend slowly). The regression beta coefficients for complement levels were also negative, especially for low C3 levels (for each 1-year increase in the age at diagnosis, the frequency of low C3 levels decreased by 0.26%) (Table II).

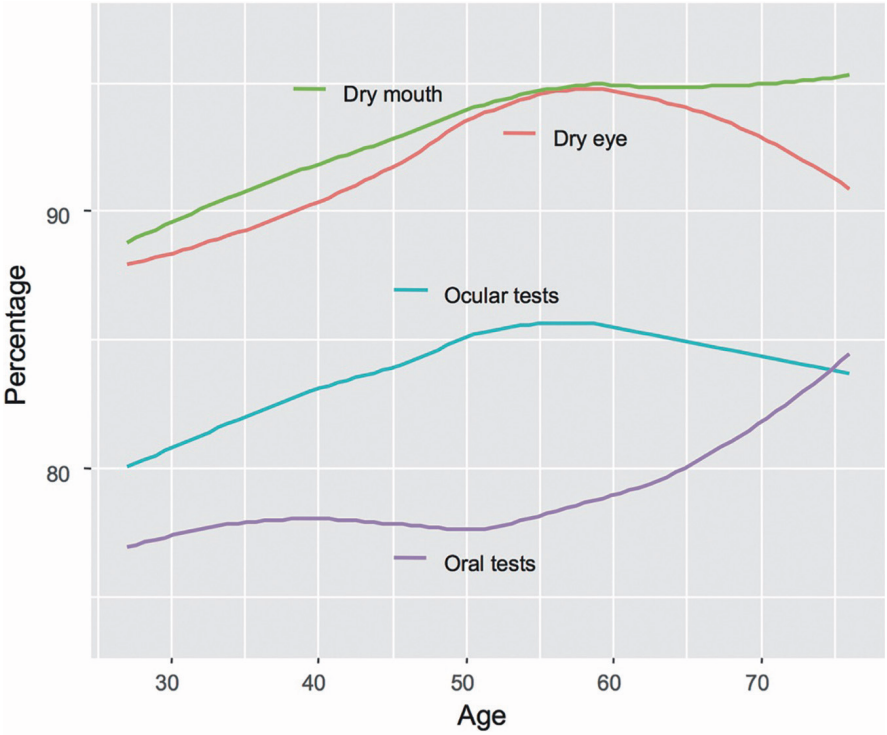

Fig. 1. Smooth curves (with 95% confidence intervals) representing the association between age at diagnosis and the frequency at presentation of the main symptoms and diagnostic tests related to glandular involvement.

Systemic disease measured according to the ESSDAI

There was a dual pattern of changes in the frequency of activity in the organ-specific ESSDAI domains according to the age at diagnosis, with some manifestations showing a clearly downward trend when people were diagnosed at an older age, and others with an opposite trend (Fig. 3). The domains which showed a more consistent decrease were glandular and lymph node involvement (for each 1-year increase in the age at diagnosis, the frequency of activity decreased by 0.18%), and constitutional, cutaneous, and haematological involvements (the frequency decreased by 0.09% for each 1-year increase). In contrast, other domains showed an ascending pattern, especially pulmonary involvement (for each 1-year increase in the age at diagnosis, the frequency of activity increased by 0.22%), and peripheral nerve involvement (the frequency increased by 0.09% for each 1-year increase). The smooth curves that best fitted a linear model (adjusted R^2 >0.8) were the frequency of the pulmonary, lymphadenopathy, cutaneous, peripheral nerve, renal, glandular, and constitutional domains (Table II).

Discussion

Wide individual variations in the phenotypic expression of systemic autoimmune diseases are a serious handicap in studies designed to identify homogeneous disease patterns that may aid early identification of disease. This is especially complicated in studies including few patients, as there is often a lack of significant between-group differences. Thus, studies that have analysed potential correlations between the age at diagnosis and the disease phenotype have used a dichotomous statistical approach in which a specific arbitrary age limit is set, dividing the population into two subsets which are compared. Despite this simplified statistical approach, most studies have included samples of a few dozen patients as the study group (Supplementary Tables S1 and S2), making it difficult to identify significant age-dependent between-group differences.

This is the first study to analyse the influence of the age at diagnosis on the key phenotypic features of pSS using a statistical approach based on analysis of the year-by-year frequency of each feature according to the age at diagnosis. This is possible due to the size of the Sjögren Big Data Consortium, as the database contains at least 100 patients per year of age at diagnosis. In contrast, the young- or elderly-onset subsets analysed in previous studies included 10–50 participants (Suppl. Tables S1 and S2). We used an innovative statistical approach that permitted confirmation of some age-dependent associations previously described in small studies, and the discovery of new associations that would be impossible to detect using dichotomous comparisons between small samples of patients.

The first result to highlight is the clear correlation between the age at diagnosis and the frequency of self-reported oral and ocular dryness. All previous studies but one (14) found no significant differences in the frequency of oral and ocular dryness, using various dichotomous thresholds (<35, 40 or 50 years to define young-onset SS, or >60 or 65 years to define elderly-onset SS). In contrast, we found that the reported

frequency of dryness is higher as the age at diagnosis increases, although this pattern differed in patients diagnosed after 60 years of age. Likewise, the frequency of dry mouth increased with age, but the frequency of dry eye decreased after 60 years of age. The key factor influencing salivary flow rate was age (15): studies in non-autoimmune populations have shown that the frequency of oral dryness is much higher in older people (16-20). This has been linked to progressive glandular ageing, and especially with the greater use of drugs in older people which has been closely associated with reduced salivary flow rates (19), especially in patients receiving ≥2 hyposalivatory drugs (21) and those with coexisting diabetes mellitus (22). In patients with pSS, we confirmed that the frequency of abnormal diagnostic tests according to the age at diagnosis followed the same pattern as that of the corresponding symptoms, that is, a progressive age-dependent increase in the frequency of abnormal oral tests, and the same pattern of an increase and subsequent decrease of the frequency of abnormal ocular tests in people aged >60 years. Although most studies have reported no significant differences between age of onset subsets in pSS (23-25), the study with the most patients (26) reported a higher frequency of abnormal Schirmer tests in women >50 years. The age-dependent pattern observed for salivary gland biopsy results is less clear, although there was a tendency to a positive result the younger the age at diagnosis.

Our results clearly show that the immunological profile is mostly driven by the age at diagnosis, with a marked, sustained decrease in the percentage of positive results for the four main SS-related autoantibodies the higher the age at diagnosis. The higher immunological positivity in people diagnosed at younger ages has been reported in some (24, 25, 27-29) but not all (14, 23, 26) studies. We were able to evaluate the evolution of the frequency of positivity of each marker year-by-year of the age at diagnosis and to detect hitherto undescribed trends, with a differential age-dependent pattern of positive results for ANA vs Ro, La and RF. The pattern for ANA, in which the frequency of positive results gradually decreases until the age of 65 years, after which the trend reverses and increases progressively with age, suggests this could be related to the higher frequency of ANA positivity in older people (30, 31). The age-dependent frequencies of positive results for Ro, La and RF are very similar, and are practically parallel in the case of La and RF, two closely-related immunological parameters in pSS patients (32-35). Immunologically, patients diagnosed at younger ages form a distinct disease subset (36). In 1998, we reported that young-onset patients had less salivary gland involvement (dry mouth and parotid enlargement) and a higher frequency of immunologic markers (anti-Ro and low C4 levels) (37, 38), likewise Haga *et al*. also reported higher positivity of Ro/La autoantibodies, RF and hypergammaglobulinaemia (39). This was confirmed by Theander *et al*. (36) who reported that patients diagnosed before 40 years had the highest frequencies of positive autoantibodies (ANA, RF, Ro 60/SSA, Ro 52/SSA and La/SSB) together with higher titres and more autoantibody specificities in the same samples. Due to the close association between systemic disease and the seropositive phenotype (RF/Ro/La carriers) (40), it seems that some SS patients are likely to be diagnosed earlier due to the development of systemic disease before glandular dysfunction becomes clinically apparent. Thus, we have recently confirmed that patients carrying RF, anti-Ro and anti-La are diagnosed at a younger mean age (41), and that anti-Ro/SS-A and anti-La/SS-B antibodies are closely associated with global systemic activity, especially anti-Ro/SS-A, whose positivity at diagnosis also correlated with a higher activity score in the articular, cutaneous and renal domains in a Spanish multicentre study (42). A recent study by Quartuccio *et al*. compared Ro/La+ and Ro/La- patients (43) and found a younger

Table II. Linear regression models fitted to smooth curves to identify linear increasing and decreasing trends.

Clusters	β Coefficient	Std. Error	Sig.	Adjusted R-squared*
Glandular component				
Dry mouth	0.129	0.006	<0.001	**0.874**
Abnormal oral diagnostic tests	0.113	0.008	<0.001	0.720
Dry eye	0.110	0.012	<0.001	0.513
Abnormal ocular tests	0.080	0.009	<0.001	0.528
Positive minor salivary gland biopsy	-0.080	0.008	<0.001	0.547
Immunological component				
Anti-Ro antibodies	-0.568	0.011	<0.001	**0.970**
RF-positive	-0.471	0.021	<0.001	**0.861**
Anti-La antibodies	-0.424	0.018	<0.001	**0.877**
ANA-positive	-0.359	0.011	<0.001	**0.927**
C3 low	-0.259	0.012	<0.001	**0.846**
C4 low	-0.104	0.010	<0.001	0.594
Positive cryoglobulins	0.022	0.004	<0.001	0.218
Systemic component (ESSDAI domains)				
Biological (ESSDAI)	-0.435	0.019	<0.001	**0.869**
Glandular	-0.179	0.008	<0.001	**0.857**
Lymphadenopathy	-0.176	0.003	<0.001	**0.977**
Constitutional	-0.093	0.005	<0.001	**0.812**
Cutaneous	-0.093	0.004	<0.001	**0.883**
Haematological	-0.093	0.010	<0.001	0.515
Articular	-0.071	0.028	0.015	0.062
Renal	-0.064	0.003	<0.001	0.876
CNS	-0.002	0.001	<0.001	0.139
Muscular	0.022	0.003	<0.001	0.405
PNS	0.092	0.004	<0.001	**0.881**
Pulmonary	0.219	0.002	<0.001	**0.990**

Std.: standard; Sig.: significance.
*In bold, smooth curves that best fitted a linear model (adjusted R^2 >0.8)

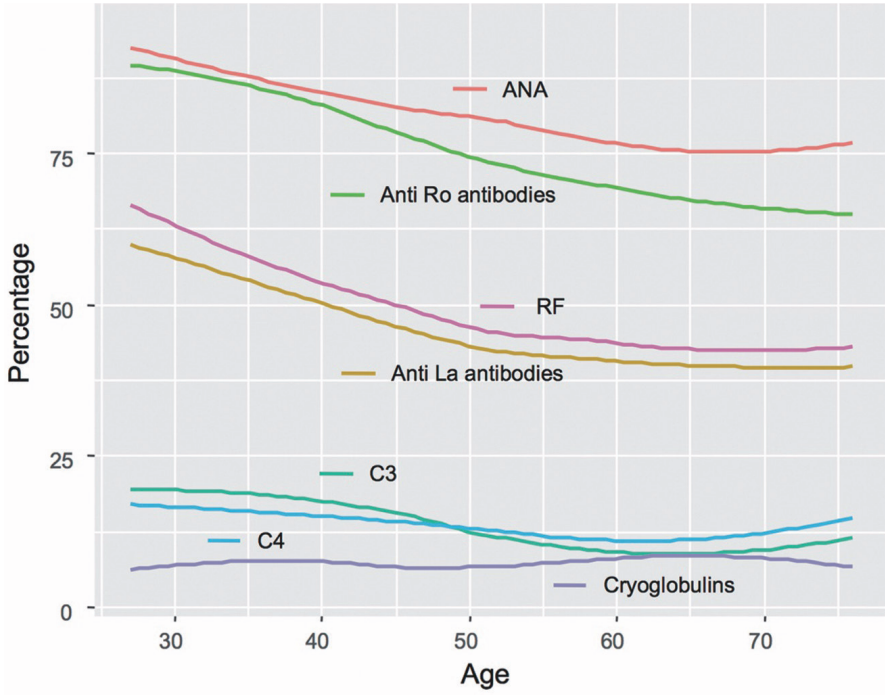

Fig. 2. Smooth curves (with 95% confidence intervals) representing the association between age at diagnosis and the frequency of autoantibodies and immunological markers at the time of diagnosis.

age at diagnosis and a higher frequency of glandular swelling, purpura, leukopenia, lymphoma, low C3, low C4, hypergammaglobulinemia, RF and serum cryoglobulins in Ro/La+ patients. Few studies have analysed the influence of age at diagnosis on the frequency of the main immunological prognostic markers of SS. Our results showed that low C3 levels are the prognostic parameter most influenced by age at diagnosis, with a frequency of alterations that decreases progressively as the age at diagnosis increases; low C4 levels follow a similar pattern although not as clear, while cryoglobulinaemia follows a more oscillating pattern, with a tendency to increase with age.

Analysis of the frequency of people with activity in each of the 12 ESSDAI domains according to the age at diagnosis clearly divides the domains into three differentiated patterns. The first consists of the domains whose frequency is highest among patients diagnosed at a younger age and which decreases with age (glandular, lymphadenopathy, cutaneous, renal and biological domains). The second pattern shows non-linear, undulating frequency curves (articular, general and haematological domains), while the third pattern consists of the domains whose frequency is minimal in patients diagnosed at a younger age and which increases gradually with age (pulmonary, nervous and muscular system domains). Recent studies have reported similar results for some organ involvements, linking a younger age at diagnosis with lymphadenopathy and salivary gland enlargement that have also been identified as risk factors for lymphoma development (44, 45), while an older age was related with pulmonary involvement (46, 47). Although interstitial lung disease (ILD) is often considered a late manifestation of SS (48), a high variability of the time of onset of SS-ILD has been recently reported (49). In some patients with ILD, an underlying SS may be underdiagnosed, especially challenging in seronegative patients with no or mild sicca symptoms, and a SS-specific assessment, including minor salivary glands, is highly recommended (50). Different pathogenetic mechanisms linked to the age at which the disease is diagnosed may be associated with a differentiated organ-specific systemic damage. However, the reasons why the SS phenotype

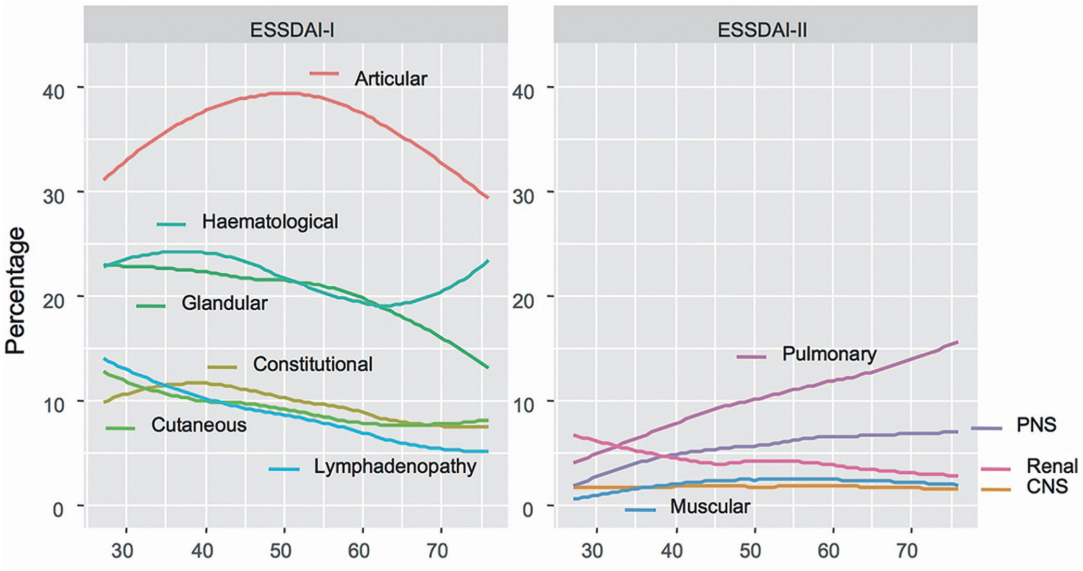

Fig. 3. Smooth curves (with 95% confidence intervals) representing the association between age at diagnosis and the frequency of systemic disease (ESSDAI organ-specific domains) at the time of diagnosis.

varies so widely according to the age at diagnosis is unclear, and factors such as the progressive ageing of the immune system, individual genetic backgrounds or environmental agents may explain the heterogeneous, age-dependent disease phenotype.

In summary, we found that the wide phenotypic variations in the presentation of pSS are strongly linked with the age at diagnosis. The frequency of glandular involvement, immunological markers and the type of organ affected are modulated by age. The best examples are the progressive increase of the frequency of dry mouth with age (1.3% increase per each 10 years) and pulmonary involvement (2.2% increase per each 10 years), and the progressive decrease in the frequency of the main autoantibodies (5.7% decrease for anti-Ro, 4.7% for RF and 4.2% for anti-La, respectively) and some ESSDAI domains (4.4% for the biological domain, 1.8% for the lymphadenopathy and glandular domains, respectively). The age at diagnosis of pSS should be considered critical for the design of a personalised diagnostic approach, and should also be considered when analysing the results of diagnostic tests and immunological parameters or when ruling out potential internal organ involvement at diagnosis.

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