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The Impact of Age on Activity Index and Patient Reported Outcomes in Patients with Sjogren's Syndrome

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Abstract. Sicca symptoms, such as xerostomia and xerophthalmia, are prevalent in geriatric patients and are correlated to exhaustion and low quality of life. Sjögren's syndrome (SS), an autoimmune disorder characterized by lymphocytic infiltration of the exocrine glands, also exhibits xerostomia and xerophthalmia as a main feature. In clinical practice, tools exist to assess disease activity and severity of the symptoms of Sjögren's: the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), respectively. Our objective is to assess the disease activity and complaints in a cohort of Sicca syndrome patients, with an emphasis on senior individuals in particular.

A cross-sectional investigation of 45 adult patients with a clinical diagnosis of Sicca syndrome was conducted, comparing geriatric (>65 years old; $n = 23$) versus nongeriatric ($n = 22$) subgroups with respect to demographic and clinical data, classification criteria fulfillment, disease activity, and symptom burden.

Between the two age groups, no statistically significant differences were found regarding disease duration, immunological and histological features, or disease activity, with overall low ESSDAI values. Symptom burden was relevant, expressed by high ESSPRI values. Drugs that could worsen Sicca symptoms were frequently prescribed, mainly antidepressants.

Symptom burden is significant in our cohort of SS patients. Unexpectedly, ESSPRI values were similar in both groups, despite the higher expected prevalence of Sicca complaints in a geriatric population. Even in people with mild illnesses, management of symptoms may be challenging and special attention is needed in the geriatric population.

Keywords: Sjogren's syndrome, xerostomia, xerophthalmia, geriatrics, aging.

INTRODUCTION

Sicca symptoms, such as xerostomia and xerophthalmia, are present in up to 30% of patients over 65 years old [1, 2]. They are linked to exhaustion and poor quality of life [3]. Many causes can lead to Sicca symptoms, so elderly patients should be carefully evaluated to avoid misdiagnosis [4, 5].

At the same time, Sicca symptoms are a main feature in Sjögren's syndrome (SS). Exocrine glands are characterized by lymphocytic infiltration in SS, a systemic autoimmune disease (AID) in which extraglandular and systemic manifestations are also frequent. The disease mostly affects middle-aged adults. Over the past few decades, different kinds of categorization criteria have been applied, taking into account serology, histology of salivary glands, and functional tests [6–8]. Validated tools exist to assess disease activity and symptoms' burden, respectively: the EULAR Sjögren Syndrome Disease Activity Index (ESSDAI) and the EULAR Sjögren Syndrome Patient Reported Index (ESSPRI) [9, 10].

The geriatric subgroup (those over 65 years old) was of particular interest to the authors, who analyzed a cohort of individuals having a clinical Sjögren's syndrome diagnosis. Because of the aforementioned considerations and the accumulation of causative factors, such as drugs and comorbidities, we hypothesized that the geriatric subgroup of SS patients would have a higher symptom burden than nongeriatric patients.

RESEARCH ELABORATIONS

Patients

We carried out a cross-sectional study over a one-year period. The following inclusion criteria were adopted: (1) The main complaint is Sicca syndrome, and the condition has been clinically diagnosed as SS; (2) no other (AID) is known at the time of inclusion; and (3) at least a one-year follow-up. Antinuclear antibodies (ANA) were detected by indirect immunofluorescence (IIF) using HEp-2 epithelial cells as the substrate (American Type Culture Collection CCL 23). The serum dilution was 1/160, and a titer equal to or greater than 1:160 (20 IU) was considered positive. SSA and SSB were determined by the immunoblot line assay (Euroimmun) [11]. Chisholm and Mason's grading system was used to assign grades to minor salivary gland biopsies [12].

Three different classification criteria were taken into account: The American-European Consensus Group (AECG) 2002 [6], the American College of Rheumatology (ACR) 2012 [7], and the 2016 ACR-EULAR criteria [8]. Retrospective data collection from electronic medical records was used for clinical and demographic data. A Charlson Comorbidity Index was calculated for each patient to assess comorbidities [13].

The 12 organ-specific domains that make up the EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI) are scored from 0 (no activity) to 2 (moderate activity) or 3 (high activity), and the overall score is used to quantify disease activity [9]. The three domains of the EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) are dryness, tiredness, and pain. Each is scored from 0 (none) up to 10 (maximal imaginable) [10]. Patient phone interviews were used to collect the ESSPRI, and each component was examined for analysis.

Statistical Analysis

Patients were divided according to their age, with a cut-off of current age over 65 years for geriatric inclusion. Data was analyzed with mean and standard deviation (SD) if normally distributed and with median and interquartile range (IQR) if non-normally distributed. Geriatric and nongeriatric adults' parameters were compared. For continuous variables, Student's *t*-test was performed. As for dichotomous variables, the chi square test was used if normally distributed and the Wilcoxon Mann–Whitney test for nonparametrically distributed data. Logistic regression was performed for multivariate analysis to account for recorded confounders. A p-value of <0.05 was considered to be statistically significant. Analysis was conducted in Stata (StataCorp. Stata statistical software: release 14. College Station, TX: StataCorp LP). The hospital's institutional review board (Comisso de Ética para a Sade – 326/2016) gave the study its seal of approval.

RESULTS

Forty-five female patients were included; 23 of them were over 65. The median (IQR) age was higher in geriatric patients, 75 (70–80) years versus 60 (51–63) years in the younger group (p-value < 0.0001), and they were also diagnosed at an older age, 60 (51–65) versus 40.5 (32–48) years (p-value < 0.0001), resulting in a similar median disease duration of about 15 years (Table 1).

Regarding the immunological profile, both groups were equivalent regarding antinuclear (86% vs. 100%, p-value $= 0.08$), anti-Ro (36% vs. 59%, p-value $= 0.1$) and anti-La (13% vs. 27%, p-value $= 0.2$) antibody frequencies. A total of 78% of the geriatric patients performed a minor salivary gland biopsy (MSGB), versus 68% in the younger group (p-value = 0.4) (Table 1). MSGB classification was also similar between the two groups, with the following distribution: inconclusive 4% versus 9%, class I 13%, class II 17% versus 27%, class III 30% versus 9%, class IV 13% versus 9% (p-value $= 0.5$) (Table 1).

Both groups behaved similarly as regards to low fulfillment of the several classification criteria (Table 1).

In both groups, the ESSDAI score measuring the severity of the disease was generally modest, with 89% of patients having a score of less than 5. Elderly individuals frequently score lower, albeit statistical significance is not always reached. Two patients, characterized by renal involvement and moderate biological activity, had an ESSDAI of 17, one in the younger and one in the elderly group. If these outliers were excluded from the analysis, ESSDAI was considerably lower in the older group (p-value $= 0.042$). Extraglandular symptoms, particularly articular involvement, which was observed in four younger individuals, were more common in younger patients. Both groups' ESSPRI scores and single component scores were comparable (Table 1). All patients received regular counseling on nonpharmacological measures to relieve xerostomia and xerophthalmia. Artificial tears were used in more than one-third of patients, and pilocarpine in 11%.

The median (IQR) Charlson Comorbidity Index was overall low, slightly higher in the geriatric subgroup as expected as age acts as a variable (Table 1). A high number of patients was treated with drugs that are known to worsen xerostomia, mostly antidepressants, without any difference in geriatric and nongeriatric subgroups.

Table 1. Demographics and disease characteristics of the cohorts (n = 45).

Demographics	NonGeriatric (n = 22)	Geriatric (n = 23)	Total (n =45)	p-values
Gender (female), n (%)	22 (100%)	23 (100%)	45 (100%)	
Age, years, median (IQR)	60 (51–63)	75 (70–80)	66 (60–76)	**<0.0001**
Age at onset, years, median (IQR)	40,5 (32–48)	60 (51–65)	50 (41–61)	**<0.0001**
Disease duration, years, median (IQR)	13.5 (11–22)	17 (11–24)	15 (11–23)	0.18
Charlson Comorbidity Index, median (IQR)	1 (0–2)	3 (2–3)	2 (1–3)	**0.007**
AUTO-ANTIBODIES				
ANA, n (%)	22 (100%)	20 (86%)	42 (93%)	0.08
Anti-Ro, n (%)	13 (59%)	8 (36%)	21 (47%)	0.1
Anti-La, n (%)	6 (27%)	3 (13%)	9 (20%)	0.2
HISTOLOGY				
MSGB performed, n (%)	15 (68%)	18 (78%)	33 (73%)	0.4
Not performed, n (%)	7 (32%)	5 (21%)	12 (26%)	ns
Inconclusive, n (%)	2 (9%)	1 (4%)	3 (6%)	ns
I, n (%)	3 (13%)	3 (13%)	6 (13%)	ns
II, n (%)	6 (27%)	4 (17%)	10 (22%)	ns
III, n (%)	2 (9%)	7 (30%)	9 (20%)	ns
IV, n (%)	2 (9%)	3 (13%)	5 (11%)	ns
CLASSIFICATION CRITERIA				
AECG 2002, n (%)	9 (41%)	9 (39%)	18 (40%)	0.9
ACR 2012, n (%)	3 (13%)	4 (17%)	7 (15%)	0.7
ACR/EULAR 2016, n (%)	7 (32%)	8 (34%)	14 (33%)	0.8
DISEASE SCORES				
Median ESSDAI (IQR)	1 (0–2)	0 (0)	0 (0–2)	**0.05**
Median ESSPRI (IQR)	4.5 (3–6,9)	6 (4.5–6.8)	5.3 (3.5–7.1)	0.26
Dryness, median (IQR)	4 (3–7)	7 (2.5–9)	5 (3–8)	0.65
Fatigue, mdian (IQR)	5 (3.25–6.75)	5 (3–8)	5 (3–7)	0.84
Pain, median (IQR)	4.5 (2.25–7)	7 (5–9)	6 (3–8)	0.07

CONCLUSIONS

In our small cohort, the median age of patients was 65 or older. Overall, they had a long disease duration and follow-up. Only one-third of the patients satisfied the recent classification criteria [8], in both geriatric and non-geriatric subgroups. In fact, these findings could be explained by the fact that MSGB was not performed universally, and inconclusive MSGB were not repeated when the results were thought to have no bearing on clinical management. Additionally, unstimulated whole salivary flow measurement was not performed in our unit. Furthermore, most of the MSGB were performed several years ago and the histology classification used, the Chisholm and Mason grading system, might result in a lower sensibility, compared to the most recent classification proposed by Daniels et al. [14, 15].

We expected an over diagnosis of SS in the elderly subgroup, considering the higher prevalence of Sicca syndrome and age-related antibodies [16]. However, in our cohort, prevalence of autoantibodies was similar between geriatric and nongeriatric patients. Moreover, anti-Ro/SSA is infrequent in healthy elderly subjects [17], and immunology alone is not enough to satisfy the criteria.

Concerning SS disease activity, ESSDAI scores were overall low, with a trend toward lower values in the geriatric group. Late-onset disease is related to a reduction in the severity of a number of autoimmune diseases, including systemic lupus erythematosus [18]. In SS, late-onset forms are described with disease onset of >65 years, with some studies suggesting milder forms of disease in the elderly [19, 20]. In our cohort, elderly patients do not universally fulfill the definition of late onset but have a higher age at diagnosis that could possibly be related to lower disease activity.

The symptom-based ESSPRI score was, however, unexpectedly similar between younger and older patients. Sicca syndrome is a characteristic that is frequently seen in the elderly. It is brought on by a number of reasons, including ageing and lacrimal and salivary gland senescence, polypharmacy, and comorbidities. In elderly patients with SS, it was expected Sicca symptoms would be more intense when compared with a younger group with SS. As shown by the low Charlson Comorbidity Index, comorbidities in older people do not appear to be severe, and this could explain the similar symptom burden. It is also noteworthy that the use of drugs that cause Sicca symptoms, whose effects cannot be overlooked, was similar in both groups. Moreover, we hypothesize that a longer follow-up duration might have improved patients education regarding preventive measures, such as careful oral hygiene.

Furthermore, with regards to polypharmacy, most were antidepressants, and evaluating prescription

appropriateness is beyond the purpose of this work. Nevertheless, we question if the high symptom burden observed could be related to poorer quality of life and depression symptoms. Clinicians will face this "chicken and egg situation" several times, and caution is needed when prescribing new drugs in SS patients to avoid iatrogenesis. Periodic medication review, a practice largely encouraged in geriatric medicine, should be done in SS patients as well, especially in older ones.

In our cohort, it seems that geriatric SS patients are similar to non-geriatric SS patients and, luckily, do not suffer from increased symptom burden. Moreover, disease activity is globally low and extraglandular manifestations are rare in this population. Despite low disease activity, median ESSPRI was still high if we consider an ESSPRI=5 as an unsatisfactory symptom state [21]. Symptom management of SS patients is an ongoing challenge for the clinician, and special attention is required in elderly patients.

AUTHOR CONTRIBUTIONS

Anna V. Taulaigo and Inês R de Figueiredo have contributed equally, participating in all phases from the study's conception to the gathering, analysis, and writing of the article. Each author made a contribution to the study's planning, writing, editing, and final approval of the version that was submitted.

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