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ASSOCIATION BETWEEN EARLY SJOGREN MARKERS AND SYMPTOMS AND SIGNS OF DRY EYE

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Abstract

PURPOSE: Animal models suggest that early markers of Sjögren's (EMS)— antibodies against salivary protein 1 (SP1), parotid secretory protein (PSP), and carbonic anhydrase 6 (CA6)—are more accurate signals of early Sjögren's when compared to classic markers (anti-Ro and anti-La). To further understand the relationship between EMS and dry eye (DE), we compared symptoms and signs of DE in subjects who tested positive versus negative for EMS.

METHODS: In this cross-sectional study, patients at the Miami Veterans Affairs Eye Clinic who were tested for EMS underwent a standard ocular surface examination. Indications for EMS testing included DE symptoms in combination with dry mouth symptoms, low tear production, corneal staining, or a Sjögren's associated auto-immune disease. Statistical tests performed were the Chi Square test, Fischer's exact test, independent sample t-test, and correlations.

RESULTS: 73% of 44 patients tested positive for one or more EMS. CA6 IgG was most frequently elevated, followed by CA6 IgM and PSP IgG. EMS positive versus negative subjects were more likely to escalate DE treatment past artificial tears to topical cyclosporine (n=32, 100% vs n=9, 75%, p=0.02). There were no demographic or co-morbidity differences between EMS positive and negative subjects, and markers levels did not correlate with more severe tear film measures.

CONCLUSIONS: A majority of individuals with DE tested positive for one or more EMS antibodies, including men and Hispanics. Future studies will be needed to understand how to incorporate EMS data into the care of an individual with DE.

Keywords

dry eye; early markers of Sjögren's; Sjögren's; Sjögren's antibodies

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INTRODUCTION

Sjögren's disease is a common autoimmune disorder that affects up to 4.8% of the American population.[1] This chronic disease initially damages the salivary and lacrimal glands, and results in dry mouth, dry eye (DE), and secondary health problems due to the absence of protective secretions.[2] Additionally, Sjögren's can involve the kidneys, lungs, and eventually can cause lymphoma.[3,4] The most serious complications of Sjögren's are B cell lymphomas of the salivary glands and gastrointestinal tracts.[5] Sjögren's can develop in isolation or in the setting of various autoimmune diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).[2]

Sjögren's is under-diagnosed or diagnosed late in up to 75% of patients.[5,6] Multiple criteria exist to diagnose Sjögren's, including those defined by the American-European Consensus Group (AECG)[7] and the American College of Rheumatology (ACR).[8] Since 2012, the ACR criteria were based on data from the Sjögren's International Collaborative Clinical Alliance (SICCA)[9] and defined Sjögren's by the presence of at least 2 out of the following 3 objective findings:

1. Positive serum anti-SSA (Ro) and/or anti-SSB (La) or [positive rheumatoid factor (RF) and antinuclear antibody (ANA) ≥ 1:320]
2. Ocular staining score ≥ 3
3. Presence of focal lymphocytic sialadenitis with focus score ≥ 1 focus/4mm^2 in labial salivary gland biopsies

A limitation in diagnosing Sjögren's is that salivary gland biopsy is an invasive procedure, and that anti-Ro and anti-La antibodies commonly appear in late stages of the disease, if at all. In fact, a study found that anti-Ro and anti-La are present in the minority of patients who otherwise meet at least 3 criteria for Sjögren's diagnosis (based on the 2002 AECG criteria[7]).[3] Therefore, patients can be misdiagnosed until more serious aspects of the disease develop. Due to the unreliability of classic markers, the ACR joined with the European League Against Rheumatishm (EULAR) and updated its classification standard in 2016 to remove Anti-La from the inclusion criteria for Sjögren's, among other modifications.[10] The new ACR/EULAR criteria diagnose Sjögren's in individuals who score ≥4 on the following items: focal lymphocytic sialadenitis and focus score ≥1 foci/4mm^2 on labial salivary gland biopsy (3 points), anti-Ro positivity (3 points), ocular staining score ≥5 in at least one eye (1 point), Schirmer score ≤5mm/5 minutes in at least one eye (1 point), and unstimulated whole saliva flow rate ≤0.1ml/minute (1 point).[10]

A study of rheumatoid arthritis has shown that there is a window of opportunity to provide disease-modifying treatments during the early course of the disease.[11] Although this has not yet been proven in Sjögren's, the same concept may apply due to the autoimmune nature of both diseases, and as such, missing this window may be detrimental to patients with Sjögren's. Two cases have been reported of patients with chronic DE and dry mouth whose symptoms were dismissed as idiopathic because their anti-Ro and anti-La levels were negative; the diagnosis of Sjögren's was made only once biopsies of salivary glands revealed

salivary gland tumors.[5] The authors emphasize the importance of early recognition of Sjögren's in order to prevent such complications.[5]

Recently, a research group used an interleukin 14 alpha transgenic mouse (IL14αTG) as a model for Sjögren's, and found that autoantibodies to salivary protein 1 (SP1), parotid secretory protein (PSP), and carbonic anhydrase 6 (CA6) were associated with Sjögren's. Furthermore, these antibodies appeared early in the course of disease in animal models and humans, whereas the classic markers, anti-Ro and anti-La, occurred later, if at all.[3] Early antibodies have other advantages over late markers as CA6, SP1, and PSP are specific to the salivary and lacrimal glands, while Ro and La are found in virtually all cells of the body. In addition, antibodies to CA6, SP1, and PSP were often detected before lymphocytic infiltration and destruction of the salivary and lacrimal glands occurred.[3–5,12] One study demonstrated that 60% of patients with no primary cause for their DE expressed either anti-CA6, anti-SP1, or anti-PSP, while only 30% expressed anti-Ro or anti-La.[13] In fact, in patients diagnosed with Sjögren's but lacking anti-Ro and anti-La antibodies, 45% (n=13) had anti-SP1 antibodies and 5% had anti-CA6 antibodies.[3]

While it is known that antibodies against SP1, CA6, and PSP are more likely to appear earlier in the course of Sjögren's, the clinical profile of individuals who test positive for early markers has not been compared to that of individuals who test negative. In order to bridge this knowledge gap, we conducted a cross-sectional study of all individuals who were tested for early markers of Sjögren's (EMS) in their serum. We compared symptoms and signs of DE between individuals who tested positive versus negative for these markers, and correlated different DE measures with EMS levels to evaluate which, if any, were more associated with symptoms and signs of DE.

METHODS

Study Population

A retrospective chart review identified 47 individuals at the Miami Veterans Affairs Medical Center Eye Clinic who had laboratory work for autoantibodies to SP1, PSP, and CA6 between January 2015 and February 2019. Classic markers of Sjögren's (anti-Ro and Anti-La) were also concomitantly assessed and found positive in 3 individuals who were thus removed from the study population. The remaining 44 individuals were all US veterans who presented with complaints of DE symptoms and had a clinical suspicion of Sjögren's based on at least one of the following: (1) dry mouth symptoms, (2) low tear production, (3) significant corneal staining and/or (4) presence of a Sjögren's associated auto-immune disease. The Miami VA Institutional Review Board approved the retrospective evaluation of patient charts for this study.

Data Collection

Chart review—Information obtained from chart reviews included patients' demographics, prior DE therapies [topical cyclosporine (Restasis, Allergan) and lifitegrast (Xiidra, Shire)], reasons for ending specific DE therapies (either due to inability tolerate the medication or due to no effect on symptoms), years of DE symptoms, medications, and medical

comorbidities. Medications and comorbidities were grouped into meaningful categories (e.g., anti-depressants, anti-hypertensive).

Questionnaires—During the visit on which EMS were obtained, a standardized work up was conducted and included the 5-Item Dry Eye Questionnaire [DEQ5][14] and the Ocular Surface Disease Index [OSDI].[15] In addition, individuals were asked to rate their average eye pain over a one week recall period on a numerical rating scale (NRS) anchored at “0” for no pain and “10” for the worst pain imaginable. Subjects also rated the intensity of ocular burning, sensitivity to light, and sensitivity to wind over a 24-hour recall on a similar 0 to 10 rating scale.

Clinical evaluation—Our standard ocular surface examination included, in the order performed, (1) qualitative assessment of ocular surface matrix metallopeptidase 9 (MMP-9) (InflammaDry, Quidel), rated as none, mild, moderate, and severe based on the intensity of the pink stripe; (2) tear break up time (TBUT, seconds); (3) conjunctivochalasis (absent or present) in each area of the lower eyelid (temporal, central, nasal) based on the obliteration of the tear film by conjunctivae in the region of interest[16]; (4) corneal staining graded to the National Eye Institute scale[17]; (5) pain rating 15 seconds after a drop of topical anesthesia (proparicaine) placed in each eye, rated on a 0 to 10 NRS; and (6) anesthetized tear production at 5 minutes (Schirmer test).

Laboratory data—A blood sample was sent to Quest Diagnostics through the Miami Veterans Affairs Medical Center. For each early marker, a value of 20 EU/ml or greater was considered as positive and a value of less than 20 EU/ml as negative.

Statistical Analysis

The main outcome measure was a comparison of DE symptoms and signs in subjects who tested positive versus negative for any of the EMS using independent student t tests and Chi square analyses. All statistical analyses were performed using SPSS 22.0 (SPSS Inc, Chicago, IL) statistical package. Spearman correlations were also conducted to examine the relationship between marker levels and DE measures. We opted to give information on all variables being compared as opposed to correcting the p-value (e.g. Bonferroni) since the latter methodology has its own limitations.[18] All statistical tests were 2 sided and a p value <0.05 was considered as statistically significant.

RESULTS

Study population:

Of 47 subjects tested for EMS, 44 were negative for classic markers of Sjögren’s. Of these, 32 (72.7%) had one or more maker elevated at a level of 20 EU/ml. CA6 IgG was the marker most commonly elevated (n=11) followed by and CA6 IgM (n=10) and PSP IgG (n=7). EMS positive versus negative subjects had significantly higher CA6 IgM, CA6 IgG, CA6 IgA, PSP IgM, PSP IgG, and SP1 IgM (Table 1). No significant differences in demographics or co-morbidities were noted between EMS positive versus negative subjects (Table 2).

Participants included 29 men and 15 women. Sixty-three percent of EMS positive subjects were white, 28% were black, 9% were Pacific Islander, and none were Asian.

Sicca symptoms:

While there were no differences between EMS positive versus negative subjects with regards to DE measures, EMS positive subjects were significantly more likely to have received treatment escalation beyond artificial tears to topical cyclosporine (n=32, 100% vs n=9, 75%, p=0.02) (Table 3). There was also a trend for EMS positive versus negative subjects to report worsening, lack of improvement, or only partial improvement of DE symptoms while using cyclosporine (n=21, 65.6% vs n=5, 55.6%, p=0.27), and 11 of the 32 EMS positive subjects on cyclosporine eventually stopped this treatment, compared to 2 out of 9 EMS negative subjects. Our protocol is to prescribe lifitegrast to those with an inadequate response to cyclosporine. Here, a similar trend was noted with more EMS positive subjects having tried lifitegrast than EMS negative subjects (n=13, 40.6% vs n=1, 8.3%, p=0.07).

Correlations between EMS antibodies and DE measures:

Most DE measures did not correlate with EMS antibody levels. Exceptions included a negative relationship between CA6 IgG and pain intensity (rho=−0.4, p=0.03), and positive relationships between SP1 IgM and IgG and TBUT (rho=0.4, p=0.02, and rho=0.4, p=0.01, respectively) and PSP IgM and conjunctivochalasis (rho=0.4, p=0.02) (Supplemental Digital Content 1).

DISCUSSION

In this study, we found that 72.7% of individuals with suspected Sjögren's, including both men and women with a mean age of 54 years, tested positive for at least one EMS antibody. These findings are similar to a study of 65 individuals (mean age 66 years) with a Schirmer score <6 mm, of whom 60% tested positive for at least one EMS.[13] A lower frequency of marker positivity was found in a predominantly white, female population (n=48, mean age 62 years) with "recalcitrant dry eye" not otherwise defined (21%), and in a predominantly white, female population (n=52, mean age 57 years) with Sjögren's diagnosed based on the 2012 ACR criteria (46%).[19,20] It is thus interesting that the higher percentage of EMS positivity in our study was found in a predominantly male veteran population of mixed race and ethnicity.

Our study suggests that Sjögren's may be underdiagnosed in men, as 62.5% of individuals with positive EMS were male. In fact, men have a lower frequency of anti- anti-Ro and anti-La antibody positivity than women[21,22], which, likely combined with a lower degree of suspicion of Sjögren's in males, contributes to under-recognition of the disease in this population.[23] In addition, men may have more severe disease, as a Hungarian study of 492 individuals with primary Sjögren's (based on the 2002 AECG criteria[7]) found that men had a higher frequency of polyarthritis and lymphadenopathy compared to women.[21] In an American study, men with primary Sjögren's[7] had more severe ocular involvement, in the form of corneal melt and perforation, than women and were more likely to suffer from vasculitis.[23] Since men are less likely to exhibit classic antibodies of Sjögren's, using EMS

may help identify potential systemic disease in men with DE, and may thus have an impact on the severe disease phenotypes usually present in men at the time of Sjögren's diagnosis.[24]

In terms of ethnicity, we found that 41% of EMS positive individuals were Hispanic or Latino. Knowledge about the epidemiology of Sjögren's is limited, with only minimal published data about multi-ethnic US populations.[25] A French study of over a million subjects with Sjögren's based on the AECG criteria[7] found that anti-SSA/SSB antibody positivity was more frequent in subjects of non-European background.[26] A study of 138 subjects with primary Sjögren's based on modified ACR/EULAR criteria[10] in New York found a higher incidence of Sjögren's in Asians compared to Latinos.[25] Our study is important as it highlights that Hispanics and Latinos also have a high frequency of EMS marker positivity.

With regards to EMS subtypes, we found that the EMS antibodies most often elevated in our population were CA6 IgM and CA6 IgG. This is similar to a study of 37 individuals with long-standing Sjögren's[7] where 38% of subjects tested positive for CA6 IgA, while other EMS were not significantly elevated.[2] In a study of 89 individuals with suspected Sjögren's but no lymphocytic infiltration of the salivary gland (indicating early disease[27]), CA6 antibodies were also the most frequently elevated marker.[4] As such, anti-CA6 antibodies have been found to appear both early and late in the disease.[28] In a retrospective study of 138 individuals with DE, anti-CA6 was also the marker associated with severe aqueous-deficient DE and correlated with increased corneal staining.[29]

With regards to the DE profile, similar to other studies,[20,30] we did not find differences in symptoms and signs between those that tested positive versus negative for EMS. However, we found treatment differences between the groups, with EMS positive subjects being more likely to require treatments beyond artificial tears, such as with cyclosporine and lifitegrast. This has not been reported in prior studies and suggests that the DE profile in EMS positive individuals may be more severe, although this was not detected by the measured tear parameters.

There is biologic plausibility that EMS are involved in the pathophysiology of DE. CA6, SP1, and PSP are enzymes specific to the salivary and lacrimal glands, and thus antibodies to these proteins are more specific to Sjögren's than the classic markers anti-Ro and anti-La, which are found in all nucleated cells.[4] Carbonic anhydrase 6 is an enzyme found in the salivary submandibular and parotid glands, as well as in the lacrimal glands, where it presumably helps maintain a physiologic acid-base balance on the eye surface.[31–33] Salivary protein 1 and parotid secretory protein are highly expressed in both the salivary and lacrimal glands of mice, where they are thought to function as antimicrobial agents that protect tissues from external insults.[3,34–36] In our study population, we found that all EMS were elevated in different frequencies, likely reflecting the heterogeneity of our group, as antibody positivity may change with the course of disease.[28]

As with all studies, our findings need to be considered in light of our study limitations, which included a defined population of US veterans and a retrospective approach. Despite these limitations, this study adds to the literature, as it examines EMS positivity in a

population of men and women with DE, noting that both men and Hispanics have a high frequency of early marker positivity. In our population, antibodies against CA6 were most frequently elevated, but none of the markers correlated with more severe tear film measures. Future studies will need to evaluate other DE signs not measured in our current study, such as tear osmolarity, lipid layer thickness, and tear meniscus height to see if these would better correlate with early markers of Sjögren's. Furthermore, given the novelty of these markers, it is not clear which patients will develop late marker positivity, and which will develop other complications of Sjögren's. Further studies are needed to understand how to incorporate EMS results into the diagnosis Sjögren's and management of DE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

EMS levels in the study population

	% with value >20 EU/ml	Population Mean (SD)	EMS Positive Mean (SD)	EMS Negative Mean (SD)	P value
CA6 IgA	13.6 %	13.7 (14.5)	15.7 (16.3)	8.3 (5.5)	0.03
CA6 IgM	22.7%	11.0 (11.0)	13.4 (11.8)	4.6 (4.2)	0.001
CA6 IgG	25.0%	17.4 (15.6)	20.3 (17.0)	9.6 (6.2)	0.004
PSP IgA	6.8%	6.8 (7.1)	7.8 (7.7)	4.2 (4.6)	0.07
PSP IgM	6.8%	7.6 (10.2)	9.0 (11.5)	3.7 (3.4)	0.02
PSP IgG	15.9%	8.8 (8.8)	10.4 (9.8)	4.5 (3.0)	0.004
SP1 IgA	11.4%	11.0 (11.1)	12.6 (12.1)	6.9 (6.8)	0.06
SP1 IgM	4.6%	8.8 (17.4)	11.0 (20.1)	3.1 (2.4)	0.04
SP1 IgG	2.3%	6.6 (9.6)	7.5 (11.1)	4.3 (2.7)	0.15

EMS=Early Markers of Sjögren's; CA6= carbonic anhydrase 6; PSP= parotid secretory protein; SP1= salivary protein 1; SD=standard deviation

Table 2:

Demographics and co-morbidities by EMS marker status

	EMS positive	EMS negative	P value
Demographics			
Age, mean (SD) years	54.1 (11.8)	59.6 (15.7)	0.29
Gender, male % (n)	62.5% (20)	75.0% (9)	0.50
Race, White % (n)	62.5% (20)	41.7% (5)	0.11
Ethnicity, Hispanic or Latino % (n)	40.6% (13)	8.3% (1)	0.07
Co-morbidities, % (n)			
Hypertension	21.9% (7)	50.0% (6)	0.07
Diabetes	9.4% (3)	25.0% (3)	0.32
COPD or asthma	15.6% (5)	0.0% (0)	0.30
Depression	62.5% (20)	50.0% (6)	0.45
Systemic autoimmune disease	15.6% (5)	0.0% (0)	0.3
Medications, % (n)			
Anti-hypertensives	21.9% (7)	41.7% (5)	0.26
NSAIDs	40.6% (13)	50.0% (6)	0.74
Anti-histamines	50.0% (16)	41.7% (5)	0.74
Anti-depressants	53.1% (17)	41.7% (5)	0.50
Analgesics	53.1% (15)	50.0% (6)	0.85

EMS=Early Markers of Sjögrens; SD=standard deviation; COPD=chronic obstructive pulmonary disease; NSAIDs=Non-steroidal anti-inflammatory drugs

Table 3:

Sicca symptoms, signs, and treatment by EMS marker status

	EMS positive	EMS negative	P value
Self-reported dry mouth, % (n)	59.4% (19)	58.3% (7)	0.25
DE symptoms, mean (SD)			
Years with DE symptoms	11.5 (12.5)	10.0 (11.8)	0.74
DEQ5 (0–22)	16.3 (3.2)	16.1 (2.3)	0.81
OSDI (0–100)	59.7 (21.2)	57.6 (18.3)	0.80
Pain intensity (0–10) 1 week recall	5.8 (3.0)	5.3 (2.8)	0.70
Burning (0–10)	5.0 (3.2)	5.4 (4.4)	0.83
Sensitivity to wind (0–10)	5.2 (3.1)	5.3 (3.4)	0.98
Sensitivity to light (0–10)	6.4 (2.9)	5.5 (3.5)	0.53
DE signs, mean (SD)			
Inflammadry * (range 0–3)	1.1 (0.1)	1.5 (0.7)	0.21
TBUT * (seconds)	4.2 (2.6)	5.7 (4.6)	0.36
Conjunctivochalasis * (range 0–3)	0.4 (0.4)	0.3 (0.6)	0.61
Corneal staining * (range 0–15)	5.3 (4.3)	4.2 (3.6)	0.43
Persistent pain after anesthesia (range 0–10)	2.0 (2.3)	1.9 (2.8)	0.91
Schirmer score at 5 min * (mm)	5.0 (4.0)	6.5 (5.6)	0.45
Topical medications †, % (n)			
Artificial tears	100.0% (32)	83.3% (10)	0.07
Cyclosporine	100.0% (32)	75.0% (9)	0.02
Lifitegrast	40.6% (13)	8.3% (1)	0.07
Ketotifen	18.8% (6)	8.3% (1)	0.65

* All dry eye signs represent score in the more severely affected eye.

† Current or prior

EMS=Early Markers of Sjögren's; SD=standard deviation; DE=dry eye; DEQ5=Dry Eye Questionnaire 5; OSDI=Ocular Surface Disease Index; TBUT=tear break up time