The clinical phenotype of isolated ocular or oral dryness in Sjögren's disease

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Abstract

Objective

To assess if isolated mouth or eye dryness constitutes distinct clinical phenotypes in Sjögren's disease (SjD).

Methods

We analysed 1765 patients meeting the 2016 ACR-EULAR SjD criteria, followed up at four centres in Greece and Italy (Universities of Pisa, Italy, and Athens, Harokopion, and Ioannina, Greece). Patients with isolated mouth or eye dryness were identified and matched 1:2 with those experiencing both symptoms, according to age at SjD diagnosis, gender, and disease duration. We defined two study groups: a) patients with ocular dryness only, and b) patients with oral dryness only, based on the AECG validated questionnaires for dryness. We compared glandular and extra-glandular manifestations, serology, and histologic features between each study and their matched controls.

Results

Seventy-two patients with isolated ocular dryness and 74 with isolated oral dryness were compared with 144 and 148 matched controls, respectively. Both groups had a median disease duration of 3 years. Patients with isolated eye dryness had lower frequency of salivary gland enlargement (35.4% vs. 28.7%, p=0.05) and lymphoma (0% vs. 11.3%, p=0.001). Conversely, those with isolated oral dryness had lower rates of arthralgias (39.1% vs. 65.5%, p=0.0003) and arthritis (8.6% vs. 20.3%, p=0.05). Isolated oral dryness was associated with older age at SjD diagnosis (median 53.5 vs. 46, p=0.005) and a higher likelihood of lymphoma (9.4% vs. 0%, p=0.01) compared to isolated ocular dryness.

Conclusion

Isolated ocular or oral dryness occurs in 8% of the general SjD population. Patients with isolated dry eyes have a lower prevalence of lymphoma compared to those with isolated dry mouth.

Key words

Sjögren's disease, Sjögren's syndrome, oral dryness, ocular dryness, patient-reported outcomes

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Introduction

Sjögren's disease (SjD) is a systemic autoimmune disorder, predominantly affecting perimenopausal women. The clinical signature of the disease is the presence of glandular dryness, particularly of mouth and eyes, constituting a constellation of symptoms known as sicca symptoms (1, 2). Despite the fact that almost any organ or tissue can be involved and that SjD patients are at risk of MALT lymphomas, sicca manifestations represent the main burden of the disease affecting adversely patients' quality of life including both personal and social status (3, 4).

Dryness in SjD is a subjective symptom reported by patients, but it can be documented by objective tests. To systematically assess the presence of symptomatic dryness, a validated 6-item questionnaire is used, consisting of three questions each for dry mouth and dry eyes (5, 6). On the other hand, objective assessment of dryness include evaluation of hyposalivation and lacrimal gland hypofunction with tests measuring either tear (Schirmer's test) and saliva production (stimulated or unstimulated saliva production) or by examining the damaged epithelial surface (lissamine green or Rose Bengal staining) (7). Several studies though, have shown weak correlation between subjective dryness reported directly by patients and the objective justification of dryness (8, 9). Thus, the subjective and personal perception of dryness rather than the objective measurements, really define patients' reported outcome and therefore reflect the impact on quality of life.

Since the recognition of the disease, symptoms of oral and ocular dryness have often been grouped together in clinical practice and research. Several large cohort studies have reported a frequency of 75–95% for both oral and ocular dryness (10-12). On the other hand, presence of either oral or eye dryness defining patients with sicca manifestations accompanies approximately 98% of patients as opposed to SjD patients without any type of dryness (13). Indeed, not all patients with SjD experience both oral and ocular dryness during their disease course and capturing this discrepancy could be of clinical importance. It remains unclear whether isolated symptoms of mouth or eye dryness represent distinct clinical phenotypes that may provide additional meaningful clinical information. The purpose of this study was to explore the phenotypic characteristics of SjD patients with isolated oral or ocular dryness based on the subjective definition of dryness as reflected by the specific validated questionnaires.

Methods

From a total population of 1765 consecutive patients fulfilling the 2016 ACR-EULAR criteria for SjD, who were followed-up in 4 centres from Greece and Italy (Universities of Pisa, Italy, and Athens, Harokopio and Ioannina, Greece) (PAHI group), those with isolated mouth or eye dryness, were identified and matched according to age at SjD diagnosis, gender and disease duration from SS diagnosis to last follow up in a 1:2 ratio with SjD patients exhibiting both oral and ocular dryness. The differing characteristics of the two study groups necessitated the use of two distinct control groups. The 2 study groups of isolated dryness were defined as follows: a) patients with subjective ocular dryness in the absence of oral dryness and b) patients with subjective oral dryness without ocular dryness. Isolated oral dryness was defined as a negative response to all 3 of the following ocular dryness questions: 1) "Have you had daily, persistent, troublesome dry eyes for more than 3 months?", 2) "Do you experience a recurrent sensation of sand or gravel in your eyes?", 3) "Do you use tear substitutes more than three times a day?" Additionally, patients had to provide at least one positive response to the following oral dryness questions: 1) "Have you had a daily feeling of dry mouth for more than 3 months?", 2) "Do you frequently drink liquids to aid in swallowing dry food?" Isolated ocular dryness was defined conversely, using at least one positive response to the ocular dryness questions and negative responses to all 3 oral dryness questions (14). Objective measurements were not included in the definition of the study groups. Cumulative data regarding glandular

(dry mouth, dry eyes, parotid gland enlargement), extra-glandular manifestations (Raynaud's phenomenon, lymphadenopathy, arthralgias/arthritis, palpable purpura, liver involvement, kidney involvement, lymphoma), serology (anti Ro/SSA, anti La/SSB, rheumatoid factor, cryoglobulinaemia, low C4 complement levels) and histologic features (focus score) were recorded and compared between each study group with their matched SS controls and between the 2 study groups as well. Systemic organ involvement was based on EULAR Sjögren's syndrome disease activity index (ESSDAI) definitions. Statistical analysis for categorical data was performed by Fisher exact test or χ^2 square test accordingly and numerical data with Man Whitney test after implementing the Shapiro-Wilk normality test. A p-value <0.05 was considered as statistically significant.

Results

Among 1765 SjD patients, 72 (4%) were presented with isolated ocular dryness and 74 (4.1%) with isolated oral dryness. The median duration of disease for both study groups was 3 years [range: 0-23 (ocular dryness only group) and 0-21 (oral dryness only group)]. The median age at SjD diagnosis was 46 (range: 21–68) years old for the ocular dryness group and 53.5 (range: 16–79) years old for the oral dryness group. Both study groups were comprised predominantly by female patients with only 3 males in each group (4.1% in the ocular dryness group and 4% in the oral dryness group).

Patients presenting with isolated ocular dryness had a significant higher prevalence of antinuclear antibodies (ANA) positivity (94.1% *vs*. 83.5%, p=0.03), a lower frequency of salivary gland enlargement (SGE) (35.4% *vs*. 28.7%, p=0.05) and a significant lower prevalence of lymphoma (0% *vs*. 11.3%, p=0.001) (Table I). Among the control group, lymphoma involved the parotid glands in 12 out of 16 patients (75%). In contrast, patients with isolated oral dryness showed a lower frequency of arthralgias (39.1% *vs*. 65.5%, p=0.0003) and arthritis (8.6% *vs*. 20.3%, p=0.05), compared to SjD controls with both types of dryness (Table II). Schirmer's test positivity was also found to be significantly increased in the control group (47.2 *vs*. 81.2, p=0.002). No difference in the lymphoma prevalence was revealed in this analysis (9.4% *vs*. 12.1%, p=0.7) (Table II). Among those with isolated dryness, 57% (4/7) of lymphoma cases involved the parotid glands, in comparison to 33% (6/18) in the control group. No significant differences in the focus score were observed in either comparison.

Comparing the isolated ocular dryness group to the isolated oral dryness group, those with exclusive oral dryness were diagnosed at an older age (median age: 53.5 *vs*. 46, p=0.005). Additionally, patients with isolated oral dryness had a higher propensity for developing lymphoma (9.4% *vs*. 0%, p=0.01), despite displaying no significant difference in classical lymphoma predictors, such as the focus score, cryoglobulinaemia or low C4 values (Table III).

Table I. Comparison of clinical and laboratory features between patients experiencing dry eyes without mouth dryness and controls.

Demographics	Dry eyes n=72	Controls n=144	p-value
Median age at disease diagnosis, (range)	46 (21-68)	46, (19-69)	0.89
Median disease duration from SjD diagnosis to last follow up, (range)	3 (0-23)	4, (0-24)	0.98
Glandular and non-specific manifestations			
Salivary gland enlargement	15.4% (11/71)	28,7% (40/139)	**0.05**
Raynaud's phenomenon	26,1% (17/65)	35,2% (43/122)	0.27
Arthralgias	51.3% (37/72)	58,8% (83/141)	0.37
Arthritis	11.6% (7/60)	13.1% (17/129)	0.95
Schirmer's test positivity	80.0% (32/40)	78.9% (60/76)	1
Extraepithelial manifestations			
Glomerulonephritis	1.8% (1/53)	0.9% (1/102)	1
Interstitial lung disease	0% (0/68)	3.7% (5/133)	0.17
Autoimmune hepatitis	0% (0/56)	2.6% (3/115)	0.55
Peripheral nervous disease	1.6% (1/61)	1,7% (2/118)	1
Palpable purpura	12.5% (9/72)	12.0% (17/141)	0.89
Persistent lymphadenopathy	20.6% (11/61)	10% (18/118)	0.79
Periepithelial manifestations			
Tubulointerstitial nephritis	0% (0/69)	1.4% (2/138)	0.55
Small airway disease	9.6% (6/62)	5.7% (7/121)	0.50
Primary biliary cholangitis	0% (0/72)	2.1% (3/142)	0.55
Autoimmune thyroiditis	30.0% (12/40)	27.8% (22/79)	0.97
Focus score	1.86	1.58	0.47
Serology			
Rheumatoid factor	50.7% (33/65)	57.1% (72/126)	0.49
Anti-Ro	86.9% (56/72)	65.7% (105/139)	0.84
Anti-La	31.9% (23/72)	35.9% (50/139)	0.66
LOW C4	40.3% (25/62)	41.3% (50/121)	0.97
Monoclonality	7.8% (5/64)	8.1% (10/122)	0.84
Cryoglobulinaemia	8.1% (3/37)	11.5% (9/78)	0.74
ANA antibodies	94.1% (80/85)	84.5% (149/176)	**0.03**
Lymphoma	0% (0/72)	11.3% (16/141)	**0.001**

Discussion

The hallmark clinical symptom of SjD is dryness of the oral and ocular surfaces, with very few patients lacking sicca manifestations. Most SjD patients report dryness in both epithelial surfaces when consulting their healthcare providers. However, our study revealed that approximately 8% of the total cohort experienced dryness exclusively in either the eyes or the mouth. From the early stages of the disease until now, no differentiation in diagnostic approach or clinical follow-up has been related to whether dryness predominates in the eyes or mouth. Thus, defining distinct clinical phenotypes of the disease may facilitate patient stratification, uncover simple clinically relevant biomarkers and offer the opportunity to study potentially distinct underlying pathogenetic mechanisms and disease endotypes (15). The present study indicates that patients with isolated eye dryness tend to exhibit a

Table II. Comparison of clinical and laboratory features between patients experiencing dry mouth without eye dryness and controls.

Demographics	Dry mouth n=74	Controls n=148	*p*-value
Median age at disease diagnosis, (range)	53.5, (16-79)	53, (14-79)	0.90
Median disease duration from SjD diagnosis to last follow up, (range)	3, (0-21)	3, (0-20)	0.74
Glandular and non-specific manifestations			
Salivary gland enlargement	29,7% (22/74)	27.3% (40/146)	0.83
Raynaud's phenomenon	23.4% (15/64)	30.1% (41/136)	0.41
Arthralgias	39.1% (29/74)	65.5% (97/148)	**0.0003**
Arthritis	8.6% (6/69)	20.3% (27/133)	**0.05**
Schirmer's test positivity	47.2% (17/36)	81.2% (78/96)	**0.0002**
Extraepithelial manifestations			
Glomerulonephritis	0% (0/61)	1.6% (2/124)	1
Interstitial lung disease	5.6% (4/71)	6.2% (9/145)	1
Autoimmune hepatitis	0% (0/59)	1.6% (2/120)	1
Peripheral nervous disease	4.8% (3/62)	3.0% (4/133)	0.68
Palpable purpura	4.0% (3/74)	10.8% (16/148)	0.12
Persistent lymphadenopathy	17.7% (11/62)	10.4% (14/134)	0.23
Periepithelial manifestations			
Tubulointerstitial nephritis	5.4% (4/74)	1.3% (2/146)	0.18
Small airway disease	4.8% (3/62)	0.7% (1/135)	0.09
Primary biliary cholangitis	0% (0/74)	2.7% (4/148)	0.30
Autoimmune thyroiditis	37.8% (14/37)	29.1% (21/72)	0.48
Focus score	1.87	2.22	0.44
Serology			
Rheumatoid factor	54.5% (36/66)	58.3% (80/137)	0.71
Anti-Ro	82.1% (60/73)	76.8% (113/147)	0.46
Anti-La	40.2% (29/72)	35.6% (52/146)	0.60
LOW C4	30.5% (18/59)	36% (44/122)	0.56
Monoclonality	8.3% (5/60)	6.6% (8/120)	0.91
Cryoglobulinaemia	2.7% (1/36)	8.1% (6/74)	0.42
ANA antibodies	93.0% (67/72)	87.5% (127/145)	0.31
Lymphoma	9.4% (7/74)	12.1% (18/148)	0.70

milder clinical course, characterised by a lower frequency of salivary gland enlargement and lymphoma, while those with isolated oral dryness present with reduced articular involvement. These specific phenotypes, although rare, are described here for the first time in the literature, and clinicians evaluating patients with systemic autoimmune diseases should be aware of these subsets of SjD patients.

The fact that the vast majority of SjD patients present with both ocular and oral dryness, clearly implies that these patients with ocular or oral dryness only, may possess a distinct place regarding disease pathogenesis. Our finding that the absence of subjective oral dryness is almost invariably associated with a significantly lower frequency of lymphoma development and parotid swelling, is noteworthy and may provide further insights on disease pathogenesis. It is important to note that the lack of dryness symptoms does not necessarily correlate with the absence of inflammatory infiltrates in the minor salivary glands. In fact, no statistically significant difference was observed in the focus score between the two groups or compared to patients with both oral and ocular dryness. Apart from the overall degree of inflammation at the level of minor salivary glands which does not seem to differ, the composition of the infiltrate and especially the regulatory component may be different. The expansion of regulatory elements could potentially contribute to less injury of the salivary epithelium and less chronic antigenic stimulation leading to lower frequency of parotid swelling and future risk of MALT lymphoma. In this line, it is also important to emphasise in terms of pathogenesis that in the ocular surfaces the effect of microbiome is missing as opposed to the oral cavity which is massively colonised by other microbial species. The microbiome as a fundamental difference between ocular and oral mucosae may interfere with both the perception of dryness and the dynamics of the inflammatory response at the local level (16). The majority of MALT lymphomas are originated in the salivary glands while adnexa lymphomas are very rare, pointing out the overall net effect of local microenvironment on lymphoma development (17). Interestingly, 15% of SjD patients with ocular dryness only, may still develop parotid enlargement despite the lack of subjective oral dryness. This finding further confirms the hypothesis that inflammation might be present and evolving at a subclinical level and that minor salivary gland biopsy is a useful tool to unravel the underlying process despite the absence of dryness symptom. Such changes in the inflammatory infiltrate, the microbiome and in other yet unknown parameters such as specific polymorphisms may also explain the lack of subjective oral dryness in the inflamed minor salivary glands.

In the case of isolated oral dryness, it is notable that despite the absence of subjective eye dryness, approximately half of the patients still exhibited objective findings of ocular dryness, as determined by positive Schirmer's and/or ocular staining score tests. This suggests that the severity of ocular dryness symptoms does not necessarily correlate with the extent of tissue damage, and vice versa. It also implies that performing Schirmer's test and ocular staining score in oral dryness only patients with a high suspicion of SjD may be diagnostically useful, implying early diagnosis of eye disease and thus a potential for prompt intervention, potentially preventing irreversible damage to the eyes. This finding may also highlight the limitations of questionnaires in detecting milder cases of ocular dryness. Several questionnaires, including the NEI-VFQ25 (National Eye Institute Visual Function Questionnaire-25), the SANDE (Symptom Assessment in Dry Eye), and the widely used Ocular Surface Disease Index (OSDI), have been developed to assess ocular dryness (18). However, no available data regarding other ocular dryness questionnaires were available in the present study. Furthermore, the reduced prevalence

Table III. Comparison of clinical and laboratory features between patients experiencing isolated dry eyes and isolated dry mouth.

Demographics	Dry eyes n=72	Dry mouth n=74	*p*-value
Median age at disease diagnosis, (range)	46, (21-68)	53.5, (16-79)	**0.005**
Median disease duration from SjD diagnosis to last follow up, (range)	3, (0-23)	3, (0-21)	0.33
Glandular and non-specific manifestations			
Salivary gland enlargement	15,4% (11/71)	29,7% (22/74)	0.06
Raynaud's phenomenon	26,1% (17/65)	23.4% (15/64)	0.87
Arthralgias	51,3% (37/72)	39.1% (29/74)	0.18
Arthritis	11,6% (7/60)	8.6% (6/69)	0.79
Extraepithelial manifestations			
Glomerulonephritis	1.8% (1/53)	0% (0/61)	0.46
Interstitial lung disease	0% (0/68)	5.6% (4/71)	0.11
Autoimmune hepatitis	0% (0/56)	0% (0/59)	1
Peripheral nervous disease	1.6% (1/61)	4.8% (3/62)	0.61
Palpable purpura	12.5% (9/72)	4.0% (3/74)	0.07
Persistent lymphadenopathy	20.6% (11/61)	17.7% (11/62)	0.84
Periepithelial manifestations			
Tubulointerstitial nephritis	0% (0/69)	5.4% (4/74)	0.12
Small airway disease	9.6% (6/62)	4.8% (3/62)	0.49
Primary biliary cholangitis	0% (0/72)	0% (0/74)	1
Autoimmune thyroiditis	30.0% (12/40)	37.8% (14/37)	0.62
Focus score	1.86	1.87	1
Serology			
Rheumatoid factor	50.7% (33/65)	54.5% (36/66)	0.79
Anti-Ro	86.9% (56/72)	82.1% (60/73)	0.64
Anti-La	31.9% (23/72)	40.2% (29/72)	0.38
LOW C4	40.3% (25/62)	30.5% (18/59)	0.34
Monoclonality	7.8% (5/64)	8.3% (5/60)	0.82
Cryoglobulinaemia	8.1% (3/37)	2.7% (1/36)	0.61
ANA antibodies	94.1% (80/85)	93.0% (67/72)	0.98
Lymphoma	0% (0/72)	9.4% (7/74)	**0.01**

of articular manifestations in patients with isolated oral dryness is not easily explained but could represent either a lower pain threshold for reporting any symptom-based complaints or could be a coincidental association.

The comparison between the two study groups revealed that patients with isolated eye dryness are younger at the time of SjD diagnosis. This may be due to the fact that eye dryness tends to be more bothersome, prompting earlier medical evaluation and diagnosis. However, disease duration in our study was relatively short and not sufficient to reach the age at which patients typically develop isolated oral dryness. Extending the follow-up period for these patients would be particularly interesting to observe whether their dryness symptoms progress or expand over time. Additionally, the existence of these two clusters of patients with isolated dryness symptoms suggests that, although the ocular and oral epithelia are typically considered a single entity in SjD, this assumption may be misleading. Despite the fact that oral and ocular mucosae share common epithelial structures and self-antigens, other reasons mentioned previously may finally interfere with the subjective perception of dryness and the extent of inflammation leading to different clinical courses between eye and mouth disease in some individuals. Ideally, although clinically difficult, comparative biopsy analysis from the oral and ocular surfaces in the same patients might shed new insights into the underlying pathogenetic mechanisms of each affected tissue.

This study is subject to several limitations, including its inherent retrospective design, the absence of some ophthalmologic dryness assessments (such as ocular surface staining and extended dryness questionnaires), the limited number of recruited patients presenting with isolated oral or ocular dryness symptoms and a relatively short follow-up period. The potential biases associated with the use of questionnaires, despite their validation to assess symptom disturbances, combined with the lack of longitudinal data, represent further limitations that should be acknowledged. Finally, data analyses based on the clarification of anti-Ro/SSA positivity into anti-Ro52 and anti-Ro60 autoantibodies could not be performed due to lack of relative data. Such distinction could potentially provide further associations linked to isolated dryness.

In conclusion, SjD may manifest with isolated sicca symptoms in either the eyes or mouth, each representing a distinct clinical phenotype with distinct disease potential. Patients with isolated eye dryness appear to exhibit a milder clinical presentation, without high risk of lymphoma as opposed to patients with oral dryness only. Such rare clinical phenotypes underline the dynamic state of the disease and the important regulatory role of the affected tissue. Large multicentric studies with extended follow-up periods will offer the opportunity to recruit such patients and perform in depth studies to reveal the unknown local regulatory circuits which drive disease progression in every involved tissue.

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