More Than Meets the Eye: The Relationship Between Dry Eye Disease and Multisystem Exocrinopathy

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Introduction

Sjögren's Syndrome is a chronic, autoimmune exocrinopathy that promotes T-cell mediated destruction and atrophy of the salivary and lacrimal glands, resulting in severe xerostomia and xerophthalmia.[1,2] Sjögren's Syndrome primarily affects women with onset in the 4th-5th decade of life. With an estimated prevalence of 1.4% in the United States, Sjögren's Syndrome is one of the most common autoimmune diseases. Diagnosis of Sjögren's Syndrome is hindered by the absence of definitive biomarkers and the varied clinical presentation of the disease, thus many suffer for years before diagnosis.

Over 16 million American adults suffer from non-Sjögren's dry eye disease.[3] Similar to Sjögren's Syndrome, current treatment strategies are not sufficient to reduce or eliminate the chronic symptoms associated with dry eye. In severe cases, this can lead to painful and sometimes blinding complications, increasing both the economic and emotional burden of this disease. Moreover, diagnosing the severity of dry eye disease and monitoring response to therapy is complicated by the subjective nature and reproducibility of clinical testing methodology.

Purpose

The objective of this study is to establish whether patients with non-Sjögren's dry eye disease also exhibit symptoms of a multisystem exocrinopathy. The identification of subsets of patients with non-Sjögren's dry eye disease accompanied by specific systemic manifestations may lead towards more accurate diagnoses and targeted therapies for this challenging patient population.

Methods

- This was a retrospective chart review of the first 199 consecutive dry eye patients who were seen between January 2015 and April 2017 in the Department of Ophthalmology at the Aston Ambulatory Care Center.
- For inclusion in this study, patients were required to have a diagnosis of dry eye disease in their medical chart. For data analysis, patients were grouped into one of three groups: non-specified dry eye, dry eye associated with rheumatoid arthritis, and Sjögren's Syndrome. A medical diagnosis of rheumatoid arthritis or Sjögren's Syndrome was required for inclusion in these categories.
- Comprehensive data was collected for patient demographics, recent ocular symptoms and ophthalmic findings, serology for Ro/La, ANA, and RF, oral and topical medications, and known diagnoses.
- Using a validated exocrine dysfunction questionnaire, data was collected on reported patient symptoms for all body systems.[4]
- Exclusion criteria included a past history of trigeminal nerve damage, neurotrophic keratopathy, or radiation of the head and neck.
- A univariate analysis was performed to test for differences between dry eye subtypes.

Results

Table 1: Patient demographics

Demographic	Dry Eye Non-specified (n=126)	Rheumatoid Arthritis (n=51)	Sjögren's Syndrome# (n=22)	P value
Age				
Mean ± Std*	66.4 ± 15.8	69.1 ± 11.6	65.3 ± 17.7	0.481
Range (min – max)	(24 – 97)	(43 – 91)	(28 – 90)	
Gender				
Male	38 (30.2%)	10 (19.6%)	1 (4.5%)	<0.001**
Female	88 (69.8%)	41 (80.4%)	21 (95.5%)	
Race				
Caucasian	97 (77.0%)	37 (72.5%)	18 (81.8%)	0.001**
African American	9 (7.1%)	9 (17.6%)	4 (18.2%)	
Asian	6 (4.8%)	2 (3.9%)	0	
Other	14 (11.1%)	3 (5.9%)	0	
Smoking history				
Yes	36 (28.6%)	18 (35.3%)	8 (36.4%)	0.525
No	90 (71.4%)	33 (64.7%)	14 (63.6%)	
Height (inches)				
Mean ± Std*	5.5 ± 0.3 ft	5.4 ± 0.3 ft	5.2 ± 0.2 ft	0.048***
95% CI	(5.4, 5.5)	(5.3, 5.5)	(5.1, 5.3)	
Weight (pounds)				
Mean ± Std*	167.0 ± 41.6 lbs	167.1 ± 43.8 lbs	147.0 ± 31.6 lbs	0.906
95% CI	(158.6, 175.3)	(154.2, 179.9)	(130.8, 163.3)	
Body mass index				
Mean ± Std*	27.5 ± 6.3	27.6 ± 6.6	25.7 ± 5.1	0.508
95% CI	(26.2, 28.8)	(25.7, 29.5)	(22.9, 28.5)	

#36.4% were primary Sjögren's Syndrome, 62.6% were secondary Sjögren's Syndrome.
*Std: standard deviation; **Chi-square test; ***One-Way ANOVA

Table 2: Medical History

Diagnosis	Dry Eye Non-specified (n=126)	Rheumatoid Arthritis (n=51)	Sjögren's Syndrome (n=22)	P value
Asthma	12 (9.5%)	10 (19.6%)	5 (22.7%)	0.041
Cancer (any)	42 (33.3%)	22 (43.1%)	8 (36.4%)	0.324
Glaucoma	26 (20.6%)	5 (9.8%)	4 (18.2%)	0.033*
Hepatitis	2 (1.6%)	4 (7.8%)	0 (0.0%)	0.005*
Hypertension	58 (46.0%)	24 (47.1%)	9 (40.1%)	0.559
Interstitial Lung Disease (ILD)	2 (1.6%)	2 (3.9%)	5 (22.7%)	<0.001*
Lymphoma	1 (0.8%)	1 (2.0%)	0 (0.0%)	0.364
Meibomian Gland Disease (MGD)	35 (27.8%)	19 (37.3%)	8 (36.4%)	0.300
Post-menopausal	63 (50.0%)	34 (66.7%)	16 (72.7%)	0.002*
Type 2 Diabetes Mellitus	16 (12.7%)	13 (25.5%)	3 (13.6%)	0.027*

*Chi-square test.
There were no cases of HIV or sarcoidosis in any of the three groups.

Table 3: Ocular symptoms at most recent clinical visit

Ocular symptoms	Dry Eye Non-specified (n=126)	Rheumatoid Arthritis (n=51)	Sjögren's Syndrome (n=22)	P value
Discharge	18 (14.3%)	5 (9.8%)	4 (18.2%)	0.265
Itching	24 (19.0%)	6 (11.8%)	6 (27.3%)	0.027*
Blurry vision	70 (55.6%)	28 (54.9%)	17 (77.3%)	0.001*
Epiphora	11 (8.7%)	4 (7.8%)	3 (13.6%)	0.328
Foreign body sensation	33 (26.2%)	16 (31.4%)	7 (31.8%)	0.609

*Chi-square test.

Table 4: Treatment for dry eye

Treatment	Dry Eye Non-specified (n=126)	Rheumatoid Arthritis (n=51)	Sjögren's Syndrome (n=22)	P value
Artificial tears	106 (84.1%)	44 (86.3%)	20 (90.9%)	0.317
Systane	43 (34.1%)	21 (41.2%)	10 (45.5%)	0.221
Restasis	28 (22.2%)	18 (35.3%)	18 (81.8%)	<0.001*
Xiidra	1 (0.8%)	0	0	0.367
Punctal plugs	13 (10.3%)	8 (15.7%)	9 (40.9%)	<0.001*
Cevimeline (Evoxac)	0 (0.0%)	1 (2.0%)	5 (22.7%)	<0.001*
Pilocarpine (Salagen)	6 (4.8%)	4 (7.8%)	5 (22.7%)	<0.001*
Autologous serum	7 (5.6%)	0	5 (22.7%)	<0.001*
Tarsorrhaphy	3 (2.4%)	1 (2.0%)	0	0.363

*Chi-square test

Table 5: Manifestations of exocrinopathy by systems

System	Dry Eye Non-specified (n=126)	Rheumatoid Arthritis (n=51)	Sjögren's Syndrome (n=22)	P value
Cardiovascular	24 (19.0%)	13 (25.5%)	3 (13.6%)	1.000
Dermatological				
Dry skin	8 (6.3%)	11 (21.6%)	3 (13.6%)	0.005
Rash	26 (20.6%)	16 (31.4%)	7 (31.8%)	0.160
Ears				
Hearing loss	24 (19.0%)	17 (33.3%)	9 (40.0%)	0.003*
Earache	10 (8.7%)	9 (17.6%)	3 (13.6%)	0.178
Endocrine				
Thyroid disorder	8 (6.3%)	10 (19.6%)	3 (13.6%)	0.014*
Digestive				
Dry mouth	7 (5.6%)	6 (11.8%)	22 (100.0%)	<0.001*
Chewing difficulty	1 (0.8%)	0 (0.0%)	0 (0.0%)	0.367
Swallowing difficulty	6 (4.8%)	6 (11.8%)	6 (27.3%)	<0.001*
Taste change	6 (4.8%)	3 (5.9%)	3 (9.1%)	0.498
GI reflux	26 (20.6%)	24 (47.1%)	5 (22.7%)	<0.001*
GI ulcer	3 (2.4%)	4 (7.8%)	1 (4.5%)	0.150
Indigestion	2 (1.6%)	10 (19.6%)	5 (22.7%)	<0.001*
Diarrhea	10 (7.9%)	12 (23.5%)	6 (27.3%)	0.001*
Constipation	10 (7.9%)	17 (33.3%)	8 (36.4%)	<0.001*
Gallbladder	8 (6.3%)	12 (23.5%)	3 (13.6%)	0.002*
Liver	5 (4.0%)	3 (5.9%)	1 (4.5%)	0.810
Pancreas	1 (0.8%)	4 (7.8%)	0 (0.0%)	0.001*
Genitourinary				
Urgency/incontinence/ frequency	24 (19.0%)	25 (49.0%)	10 (45.5%)	<0.001*
Recurrent Candidiasis	5 (4.0%)	1 (2.0%)	2 (9.1%)	0.065
Urinary tract infection	9 (7.1%)	12 (23.5%)	6 (27.3%)	<0.001*
Musculoskeletal				
Joint pain	25 (19.8%)	23 (45.1%)	7 (31.8%)	<0.001*
Back pain	27 (21.4%)	24 (47.1%)	6 (27.3%)	<0.001*
Neurological	34 (27.0%)	28 (54.9%)	10 (45.5%)	<0.001*
Respiratory				
Dry nose	1 (0.8%)	3 (5.9%)	0 (0.0%)	0.011*
Sinusitis	16 (13.5%)	12 (23.5%)	5 (22.7%)	0.154
Nosebleeds	2 (1.6%)	2 (3.9%)	1 (4.5%)	0.517
Nasal congestion	19 (15.1%)	21 (41.2%)	5 (22.7%)	<0.001*
Allergies	44 (34.9%)	31 (60.8%)	11 (50.0%)	0.001*
Change in smell	5 (4.0%)	2 (4.0%)	0 (0.0%)	0.128
Recurrent bronchitis	8 (6.3%)	0 (0.0%)	7 (33.3%)	<0.001*
Shortness of breath	16 (12.5%)	0 (0.0%)	7 (33.3%)	<0.001*
Renal	19 (15.1%)	23 (45.1%)	7 (31.8%)	<0.001*

*Chi-square test.

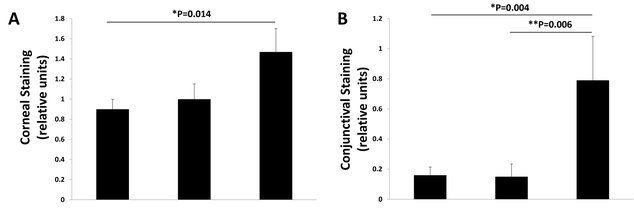

Figure 1: Corneal and conjunctival staining at last ophthalmic exam. (A) Corneal staining using sodium fluorescein or lissamine green was assigned a score of 0-3 for each eye and averaged to achieve a mean staining score per patient. The grading scale was defined according to the following criteria notated in the medical chart. Grade 0: no staining; 1: trace or few punctate epithelial erosions (PEEs); 2: 1+ PEEs; 3: 2+ or more PEEs. There was a significant increase in corneal staining in patients with SS compared to the NSDE group (P=0.045, One-way ANOVA, Bonferroni correction). (B) Conjunctival staining using lissamine green was also assigned a score of 0-3 based on notations in the medical chart for each eye and averaged for a mean staining score per patient. Grade 0: no staining; 1: trace or mild staining; 2: staining in one quadrant; 3: staining in multiple quadrants. There was a significant increase in conjunctival staining in patients with SS compared to the other groups (P=0.005, One-way ANOVA, Bonferroni correction). NSDE: non-specified dry eye, RA: rheumatoid arthritis, SS: Sjögren's Syndrome.

Summary

- 25.6% of the total dry eye (DE) cohort had RA; 11.1% had SS. Of the patients with SS, 36.4% had primary disease while 63.2% had secondary disease (Table 1).
- The majority of DE patients in all groups were female (Table 1).
- There were no significant differences in the percentage of patients with MGD across test groups (Table 2).
- There was an increased proportion of patients in the SS cohort that manifested respiratory problems including asthma, shortness of breath, recurrent bronchitis, and ILD (Tables 2 & 5).
- With the exception of reflux, the SS cohort had an increase in digestive symptoms compared to the other two groups.
- Patients with SS were more likely to complain of blurry vision (Table 3), have greater ocular surface damage (Fig. 1A & B), and were more aggressively treated for dry eye than patients in the other two cohorts (Table 4).
- The most common symptoms of exocrinopathy manifested by the NSDE group included reflux, sinusitis, nasal congestion, allergies, hearing loss, and skin rashes.
- In the NSDE group, 20% of patients were undergoing treatment for glaucoma. Toxicity from chronic use of topical preservatives may confound the assessment of dry eye in this subpopulation.

Conclusions

This is a preliminary, interim report of the first retrospective study to investigate the potential for a multisystem exocrinopathy in patients with non-SS DE disease. The findings of an increase in females with DE is consistent with published epidemiological studies as is the proportion of women to men with SS.[2,3] While these results suggest that additional exocrine symptoms may be associated with non-SS dry eye disease, a larger cohort is needed to further separate out distinct subpopulations in the NSDE group in order to perform a sufficiently powered multivariate analysis and validate these findings.

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