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Evaluation of Patients with Dry Eye for Presence of Underlying Sjögren's Syndrome

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Abstract

Purpose—To evaluate the rate of Sjögren's syndrome (SS) in a cohort of patients with dry eye syndrome.

Methods—Medical records of patients with a primary diagnosis of dry eye syndrome (ICD code 375.15 or 370.33) were reviewed retrospectively. Patients who had 2 or more visits to a single dry eye center, during a 2-year period (1/2004 to 1/2006) were considered.

Results—Two hundred and twenty patients with dry eye syndrome were identified. A total of 57 (25.9%) patients had an underlying rheumatic condition; 25 patients (11.4%) had rheumatoid arthritis (RA) and 24 (10.9%) had primary Sjögren's syndrome (PSS). Majority of the patients with RA (96%) carried the diagnosis at the time of presentation. Of all patients with primary SS, only 33.3% (8/24) carried diagnosis at the time of presentation. Fifty percent (12/24) were diagnosed as a result of the initial evaluation. Among those only 66.6% (8/12) tested SSA or SSB positive. One third (4/12) tested only ANA positive at a titer of <1/320, and required minor salivary gland biopsy for definitive diagnosis. Additional 16.7% (4/24), who were initially serologically negative, eventually underwent minor salivary gland biopsy and became diagnosed with SS.

Conclusions—Primary SS appears to be underdiagnosed in dry eye patients and should be the focus of diagnostic evaluations. A minor salivary gland biopsy might be required for a definitive diagnosis in a significant proportion of the patients with SS.

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INTRODUCTION

Dry eye syndrome is often an unrecognized, unattended condition affecting a significant proportion of the population. Epidemiologic studies in the United States have found that dry eye affects as many as 17% of women and 11.1% of men (1).

Dry eye syndrome is a multifactorial disease. A variety of risk factors for dry eye have been identified including advanced age, female sex, menopausal hormone therapy, low androgen levels, and medication use (2). There is a well-known association of several systemic diseases with dry eye syndrome such as Sjögren's syndrome (SS), rheumatoid arthritis, scleroderma, polymyositis, lymphoma, amyloidosis, hemochromatosis, sarcoidosis, and systemic lupus erythematosus (3).

An etiopathogenetic classification of dry eye syndrome was recently revisited by an international workshop, which recognizes two sub-groups: aqueous-deficient and evaporative (4). Aqueous tear deficient dry eye syndrome has two major subclasses; Sjögren's syndrome (SS) dry eye and non-SS dry eye syndrome. Two forms of SS were recognized, in harmony of the classification criteria by European-American collaboration (5). Primary SS consists of the occurrence of aqueous deficient dry eye syndrome in combination with symptoms of dry mouth, in the presence of autoantibodies, evidence of reduced salivary secretion and with a positive focus score on minor salivary gland biopsy. Secondary SS consists of the features of primary SS together with the features of an overt autoimmune connective tissues disease, most common of which is rheumatoid arthritis.

Although the rate of dry eye in various diseases has been reported (6-13), the frequency of SS among patients with dry eye is unknown. Furthermore, none of the previous reports has evaluated the relative onset of the SS and occurrence of dry eye condition in patients seen at ophthalmology clinics. Therefore, we sought to investigate the presence of underlying SS, the relative timing of the diagnosis, and the results of the initial diagnostic evaluation in a consecutive series of patient with dry eye *syndrome* from a large Ocular Surface Diseases and Dry Eye Clinic practice at a single institution.

PATIENTS AND METHODS

Patients

All patients who presented to the Ocular Surface Diseases and Dry Eye Clinic during a 2-year period (January 2004 and January 2006) with a primary diagnosis of tear film insufficiency (ICD code 375.15) or keratoconjunctivitis sicca (ICD code 370.33), which are the only diagnostic codes used, were considered. The diagnosis of 710.2 was only used, as secondary diagnosis, in the presence of confirmed SS. All patients were complaining of foreign body sensation, burning, stinging, itching, dryness, soreness, heaviness of the lids, photophobia, or ocular fatigue. Aqueous tear deficiency was defined as a Schirmer test value with topical anesthesia of less than 7 mm at 5 minutes or less than 10 mm at 5 minutes with concomitant conjunctival staining (14). The Schirmer test was performed in a uniform fashion by a single physician (EKA). Single drop of fluorescein with benoxinate hydrochloride solution (0.25%/0.4%) (Fluress, Akorn Inc., Buffalo Grove, IL, USA) was placed into the lower forniceal conjunctiva in each eye. The fornices were then dried using sterile cotton tip applicators. Standardized Schirmer tear test strips (Alcon Laboratories, Inc., Fort Worth, TX, USA) were then used to measure the amount of aqueous tearing. Tear film break-up time as well as ocular surface staining studies with lissamine green as well as fluorescein were also performed. The ocular surface stains (first lissamine green staining of the conjunctiva followed by fluorescein staining of the cornea) were performed prior to Schirmer's test or intraocular pressure measurement in an effort to prevent inadvertent staining of the conjunctiva and/or cornea from

the probe of the tonometer or the Schirmer's test strips. Intraocular pressure measurements followed by dilated fundus examination were performed last. Evaporative dry eye syndrome was defined as a tear film break-up time of less than 10 seconds. Patients with normal Schirmer's test results as well as tear film break-up time were excluded. Also, patients with abnormal Schirmer tests and/or break-up time in the presence of other ocular surface diseases (who had the above mentioned ICD codes as a secondary diagnosis) were excluded.

An associated rheumatic disease was systematically searched for at the initial visit (see below). All patients on whom laboratory tests or referral to a specialty clinic were requested to return for a follow-up visit to discuss the results of the tests, treatment plan and prognosis. Patients who had less than 2 visits were excluded since no follow-up data was available.

Diagnosis of Rheumatic Diseases

All patients were seen by a single physician (EKA) and evaluated in a uniform fashion. Evaluation of patients included a complete medical history and a review of systems, with attention paid to symptoms of rheumatic diseases, at presentation. A laboratory evaluation, including anti-SS-A/Ro, anti-SS-B/La, ANA, rheumatoid factor (RF), anti-Sm, anti-Scl-70 and anti-centromere antibodies, was performed in all suspected patients based on a positive review of systems questionnaire filled out by the patient at the initial visit. Additional testing included chest X-ray, thyroid function tests, echography of the extraocular muscles and orbits and conjunctival biopsy, based on review of systems and clinical findings.

All tested patients were also evaluated by a single rheumatologist (DM) for the presence of a rheumatic disease. The diagnosis of rheumatoid arthritis was based on the revised criteria for the classification of rheumatoid arthritis by the American Rheumatism Association (15). The Sjögren's syndrome was diagnosed based on the criteria proposed by the American-European Consensus Group (5). The consensus criteria for the classification of Sjögren's syndrome include both subjective and objective findings, with at least 4 of the 6 criteria required to be present for the diagnosis to be confirmed. The 6 criteria include subjective and objective ocular dryness, subjective and objective oral dryness, the presence of anti-SS-A/Ro and/or anti-SS-B/La antibodies, and an abnormal minor salivary gland lip biopsy. The medical records of all patients who carried a diagnosis of a rheumatic disease at the time of presentation were re-reviewed to ensure they met the appropriate diagnostic criteria.

At every return visit, an interval medical history was obtained and laboratory evaluations and/or referral to other specialty clinics were ordered as necessary.

Data Collection

Data collection was facilitated by an electronic database of the diagnoses of all patients seen at the Ocular Surface Diseases and Dry Eye Clinic. Medical records were reviewed for the presence of an underlying SS and the timing of the diagnosis relative to the onset of the dry eye syndrome. Patients with a diagnosis of SS upon presentation were classified as having a previously diagnosed disease. The second category included those patients in whom the diagnosis was made as a consequence of the initial evaluation at the time of presentation to the Ocular Surface Diseases and Dry Eye Clinic. The third category included those patients with no systemic disease present previously or diagnosed as a consequence of the initial evaluation, but in whom the symptoms and signs of a systemic disease emerged during follow-up, leading to the subsequent diagnosis of a SS. Data were abstracted from the medical records onto standardized data collection forms and entered into a new Microsoft Excel database for analysis.

The study was reviewed and approved by the Institutional Review Board in accordance with the Declaration of Helsinki, and was HIPPA compliant.

Statistics

Frequencies of variables were tabulated for the entire study population and for those patients with SS using the Intercooled Stata 9.0 statistical software program (College Station, TX). The timing of the diagnosis of SS was tabulated and compared across categories using the chi-square test or the Fisher's exact test when counts within a category were less than five. Nominal P-values were used for all comparisons with a P-value of less than 0.05 considered statistically significant. The incidence of developing a SS in patients presenting without a systemic disease after the initial evaluation was derived from Kaplan-Meier curves (16,17).

RESULTS

Five hundred and thirty nine consecutive patients were examined at The Ocular Surface Diseases and Dry Eye Clinic over a period of 2 years. Two hundred and twenty of those qualified to be included in the study. Patients with abnormal tear functions in the presence of other primary diagnoses such as Stevens Johnson Syndrome, mucous membrane pemphigoid, lichen planus, superior limbic keratoconjunctivitis, atopic keratoconjunctivitis, etc. were excluded. The demographics of the patients are summarized in Table 1. The majority of the patients (75.9%) were female with a median age of 59 years (range 10 to 91 years). One hundred and eleven (50.4%) patients were post-menopausal women.

A great majority of the patients (n= 191, 86.9%) had a combined aqueous and evaporative type of dry eye. This rate is higher than what has been reported in the literature and could be due to the fact that evaporative dry eye diagnosis was mostly based on the lower than normal tear film break-up time which actually can be seen in any case of any unstable tear film such as mucous deficiency or severe aqueous deficiency as well. All patients had conjunctival lissamine green staining. Corneal fluorescein staining was noted in two thirds of the patients (74.5%).

A total of 57 (25.9%) patients had an associated rheumatic disease; the most common being rheumatoid arthritis (25 patients, 11.9%) and primary SS (24 patients, 10.9%). Other diseases that were associated included sarcoidosis (4 patients), psoriasis (1), ulcerative colitis (1), CREST syndrome (1), and ankylosing spondylitis (1).

Table 2 demonstrates the relative timing of diagnosis of the SS relative to the diagnosis of dry eye syndrome. An overwhelming majority of the patients with rheumatoid arthritis (96%) carried a diagnosis of rheumatoid arthritis at the time of presentation. Of all the patients with primary Sjögren's syndrome 33.3% carried a diagnosis at the time of presentation, 50% were diagnosed as a result of the initial evaluation, and 16.7% were diagnosed during follow-up. Among patients with no evident rheumatic disease initially, the rate of occurrence of Sjögren's syndrome during the follow-up was 4% per person-year (Figure 1).

Table 3 demonstrates the risk factors for the diagnosis of SS. There was a significant correlation between the ANA, SSA and SSB antibodies. However the severity of disease parameters (as measured by Schirmer test results, tear film break-up time, and **corneal fluorescein staining**), age, or gender did not correlate with a diagnosis of SS.

Among the 16 patients who did not carry a diagnosis of primary SS on presentation and who were diagnosed as a result of diagnostic evaluations at the Ocular Surface Diseases and Dry Eye Clinic, only 8 (50%) patients were SSA and /or **SSB** positive. Another 8 patients (50%) required a minor salivary gland biopsy for definitive diagnosis. Four of those patients were ANA positive, albeit at a titer of <1/320. Additional 4 patients were diagnosed during follow-

up. These were the patients that initially tested negative for all antibodies. However, they continued to have systemic symptoms such as fatigue and joint pains. They eventually underwent minor salivary gland biopsy with findings consistent with SS.

DISCUSSION

Ocular irritation caused by dry eye syndrome is one of the most common problems encountered by eye care practitioners. An estimated 10 million people in the United States have *clinically significant* dry eye syndrome which might possibly underestimate if individuals with temporary and/or less severe symptoms are considered. A variety of medical conditions are well known to be associated with dry eye. However, currently no published data exist, to our knowledge, that demonstrate the frequency of these conditions. Our series demonstrated a significant association of dry eye syndrome with systemic medical conditions, the most common of which were rheumatoid arthritis, Sjögren's syndrome, and thyroid disease. Importantly, among patients with Sjögren's syndrome, the disease was previously undiagnosed in a significant proportion and diagnosed more often as a consequence of the initial evaluation.

Sjögren's syndrome is a common autoimmune disorder that affects approximately 1% of the population (18). It is a multisystem condition manifesting with broad organ-specific and systemic manifestations, the most prevalent being diminished lacrimal and salivary gland function. In addition, the symptoms do not always present concurrently. This diversity of symptomatic expression adds to the difficulty in initial diagnosis, making it widely underrecognized in clinical practice. One-third of patients with Sjögren's syndrome suffer from systemic manifestations including arthritis, fever, fatigue, and mucosal dryness. Those with major salivary involvement show a particularly increased risk of developing low-grade non-Hodgkin lymphomas (19).

Early diagnosis of Sjögren's syndrome is clinically relevant for several reasons. Identification of patients expressing SS-A/Ro antibodies is important as these patients are most likely to develop extraglandular manifestations, including cryoglobulinemia, vasculitis, anemia, leukopenia and thrombocytopenia (20). These patients should be monitored more closely. Patients with more severe sicca symptoms and those who develop extraglandular (systemic) disease may need to be treated more aggressively with systemic medications such as hydroxychloroquine rather than the local measures used in those with milder sicca symptoms alone (21). Although there are no reports on the effects of oral hydroxychloroquine on dry eye findings, it is believed to improve the salivary gland function (22) and may prevent progression to neoplastic transformation by modulating lymphoproliferation (23).

As with all retrospective studies, our results must be interpreted cautiously. Our series is clinic-based and from a single practice: it is not a population-based study. As such, there is the potential for ascertainment bias. Other services at our institution also may see patients with dry eye syndrome; however, it is our impression that the number of patients not referred to us is small. Our institution is a tertiary care referral center, and as such, there is the potential for bias towards those patients with more severe disease. This is reflected by the fact that, all of our patients demonstrated conjunctival lissamine green staining with two thirds (74.5%) also having corneal fluorescein staining. Another point is that in our study, the median follow up was less than a year (7 months with a range of 0 to 54 months) which might have led to an underestimation of the rate of Sjögren's Syndrome in our population. Therefore, the frequency of SS may be different than that found in primary care clinics. Also, patients that were being treated at the time of the study might have had an improved Schirmer score and could have been inadvertently excluded.

In conclusion, our results demonstrate a high frequency of associated SS in a group of patients with dry eye syndrome. Most patients had a previously diagnosed disorder; however, the number of new diagnoses of primary SS was not insignificant. Importantly half of the patients (8/16) required a minor salivary gland biopsy for definitive diagnosis due to lack of positive antibody testing. We suggest that laboratory evaluation tailored to the patient's clinical presentation as well as a detailed review of systems should be performed in all dry eye patients. Among all, patients with primary SS are the most likely to be diagnosed in the ophthalmology clinic and should be the focus of diagnostic evaluation. A larger scale prospective study is needed to estimate the true rate of SS in dry eye population, as well as clinical predictors of it.

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Figure 1.

Kaplan-Meier curve of time to diagnosis of primary Sjögren's syndrome among patients with dry eye syndrome without a known rheumatologic disease at presentation (n = 16)

Table 1
Demographic and Clinical Characteristics of the Patients Presenting with a Dry Eye Syndrome

Characteristic	Result
No of Patients	220
Age (years)	
Median	59
Range	10-91
Interquartile Range	22-88
Gender (% female)	75.9
Race (% white)	84.6
Follow-up (months)	
Median	7
Range	0-54
Interquartile Range	0-45
Type of Dry Eye Syndrome (%)	
Aqueous Tear Deficiency	10.9
Evaporative Dry Eye	2.3
Combined Aqueous Tear Deficiency and Evaporative Dry Eye	86.8
Medical Conditions Associated with Dry Eye Syndrome (%)	
Any Rheumatic Disease	25.9
Primary Sjögren's syndrome	10.9
Rheumatoid Arthritis	11.4
Other*	3.6
Any Non-Rheumatic Conditions	77.3
Thyroid Disease	23.2
Menopause	50.4
Other†	2.7

* Includes sarcoidosis (4 patients), psoriasis (1), ulcerative colitis (1), CREST syndrome (1), and ankylosing spondylitis (1).

† Includes diabetes (4 patients), and graft-versus-host disease (2).

Table 2

Diagnosis of Sjogren's Syndrome Relative to Diagnosis of Dry Eye Syndrome

Systemic Disease	No of Patients	Present Before Presentation % (n)	Diagnosed as a Result of Initial Evaluation % (n)	Occurred During Follow-up % (n)
Rheumatic Conditions				
Primary Sjögren's Syndrome	24	33.3 (8)	50.0 (12)	16.7 (4)
Rheumatoid Arthritis	25	96.0 (24)	4.0 (1)	0
Other *	8	75.0 (6)	25.0 (2)	0 (0)

* Includes sarcoidosis (4 patients), psoriasis (1), ulcerative colitis (1), CREST syndrome (1), and ankylosing spondylitis (1).

Table 3

Risk Factors for the diagnosis of Sjögren's syndrome

Risk Factor	OR	95% CI	P-value
Age	1.01	0.99, 1.02	0.31
Gender (women vs men)	1.97	0.89, 4.35	0.09
Race (white vs non-white)	0.69	0.31, 1.51	0.35
Tear break-up time (<5 seconds vs 5-10 seconds)	1.09	0.93, 1.27	0.28
Schirmer test (<5 mm vs 5-10 mm)	1.17	0.96, 1.41	0.12
<i>Corneal fluorescein staining</i>	<i>1.14</i>	<i>0.77, 1.70</i>	<i>0.501</i>
Rheumatoid factor (positive vs negative)	2.61	1.37, 4.95	0.003
Antinuclear antibody (positive vs negative)	2.19	1.46, 3.30	<0.001
SSA (yes vs no)	2.79	1.60, 4.89	<0.001
SSB (yes vs no)	2.58	1.38, 4.82	0.003

CI = confidence interval; OR = odds ratio; SSA = Anti-Ro antibodies; SSB = Anti-La antibodies