Predictors of Discordance between Symptoms and Signs in Dry Eye Disease

Vehof, Jelle; Smitt-Kamminga, Nicole Sillevis; Nibourg, Simone A.; Hammond, Christopher J.

Published in:
Ophthalmology

DOI:
10.1016/j.ophtha.2016.11.008

Publication date:
2017

AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Predictors of Discordance between Symptoms and Signs in Dry Eye Disease

Jelle Vehof, MD, PhD,[1,2,3,4] *Nicole Sillevis Smitt-Kamminga, MD,*[2] *Simone A. Nibourg, BSc,*[2] *Christopher J. Hammond, MD, FRCOphth*[1,4]

Purpose: To investigate predictors of discordance between symptoms and signs in dry eye disease (DED).

Design: Cross-sectional association study.

Participants: A total of 648 patients with dry eye from the Groningen LOngitudinal Sicca StudY (GLOSSY), a tertiary dry eye clinic patient cohort from the Netherlands.

Methods: Patient symptoms were assessed using the Ocular Surface Disease Index (OSDI) questionnaire. Dry eye signs were assessed by tear osmolarity, Schirmer test, tear breakup time, corneal and conjunctival staining, and meibomian gland dysfunction, all in both eyes, and a composite dry eye signs severity score was calculated from these 6 tests for each patient. Linear regression analysis was used to test the association of discordance between symptoms and signs with a wide range of independent variables (demographic and environmental variables, systemic diseases, ocular traits, and medications).

Main Outcome Measures: Predictors of discordance between symptoms and signs in DED, defined by the difference between the rank score of the OSDI and the rank score of the dry eye signs severity score.

Results: Of the 648 subjects in this cohort, 536 (82.7%) were female and the mean age was 55.8 years (standard deviation, 15.6 years). Significant predictors of greater symptoms than signs were the presence of a chronic pain syndrome, atopic diseases, a known allergy, the use of antihistamines (all $P < 0.001$), depression ($P = 0.003$), osteoarthritis ($P = 0.008$), and the use of antidepressants ($P = 0.02$). Predictors of lesser symptoms than signs were increased age ($P < 0.001$) and the presence of Sjögren's disease ($P < 0.001$) (primary Sjögren's disease, $P < 0.001$) more than secondary Sjögren's disease ($P = 0.08$), and graft-versus-host disease ($P = 0.04$). Furthermore, greater symptoms compared with signs were highly associated with lower self-perceived health ($P < 0.001$).

Conclusions: This large clinical study has shown that discordance between symptoms and signs in DED is an indicator of self-perceived health. The study found important predictors of greater symptoms to signs but also predictors of lesser symptoms to signs. Awareness of these predictors is helpful in assessing patients with dry eye in clinical practice. *Ophthalmology 2017;124:280-286 © 2016 by the American Academy of Ophthalmology*

Dry eye disease (DED) is a highly prevalent disorder[1,2] and has a serious impact on the daily life of patients.[3–5] Dry eye disease can cause damage of the ocular surface or lead to symptoms of pain, irritation, and visual disturbance.[6] There is no gold standard for diagnosing DED, and mostly a combination of DED symptoms and signs on the ocular surface is used to diagnose DED in clinical practice.[7] It is well described that dry eye symptoms are poorly correlated with dry eye signs.[8] This has been shown in both population-based cohorts[9–11] and patient cohorts.[12–15] The discordance between symptoms and signs hampers studies of DED and the management of patients with DED.[7,15,16] However, relatively little is known about factors that are associated with discordance between symptoms and signs. A few case-control studies reported discordance in signs and symptoms in specific patient populations (e.g., patients with Sjögren's disease),[12,17] but there are no specifically designed cohort studies investigating predictors of discordance. Therefore, we performed a cohort study investigating numerous possible predictors of discordance between dry eye symptoms and dry eye signs commonly assessed in clinical practice, using a large tertiary DED clinic patient cohort.

Methods

Study Sample

The Groningen LOngitudinal Sicca StudY (GLOSSY) cohort is a clinic-based cohort of patients with DED from the tertiary dry eye clinic at the University Medical Center Groningen in the Netherlands. General and ophthalmic medical history, dry eye symptoms, dry eye test results using standardized methods, and dry eye therapies have been recorded longitudinally since September 2014, resulting in a clinical cohort with data on approximately 2000 patient visits per year. For this study, the cross-sectional data from the first visit of all patients after the start of our cohort were used. The University Medical Center Groningen is a national referral center for Sjögren's disease and has a multidisciplinary approach to Sjögren's disease, with regular assessments by rheumatologists, ophthalmologists, and oral surgeons. Consequently, approximately half of the patients visiting the tertiary dry eye clinic are patients with Sjögren's disease. All patients in the GLOSSY cohort have dry eye diagnosed by an ophthalmologist or are under the care of the multidisciplinary Sjögren's disease service. The study was approved by the institutional review board of the University Medical Center Groningen. The research followed the tenets of the Declaration of Helsinki.

http://dx.doi.org/10.1016/j.ophtha.2016.11.008
ISSN 0161-6420/16

Assessment of Risk Factors

Subjects completed a baseline questionnaire including questions about risk factors for DED. The assignment of comorbidities (systemic diseases, ocular diseases) was based on self-report by asking the following question: "Have you ever been treated for or diagnosed by a physician as having…?" A similar question was asked about certain medications that are known to be risk factors for DED. Furthermore, patients were asked how many hours they spend on average per day using a computer screen (including tablets), whether they wear glasses for distance vision, and whether they use contact lenses on a daily basis. In addition to the risk factors, patients were asked to score their health on an ordinal scale, with possible answers: bad, reasonable, good, very good, and excellent.

Assessment of Dry Eye Symptoms

All patients completed the Ocular Surface Disease Index (OSDI) at the beginning of their visit. The OSDI, developed by the Outcomes Research Group at Allergan Inc. (Irvine, CA), is a 12-item questionnaire designed to provide a rapid assessment of the symptoms of ocular irritation consistent with DED and their impact on vision-related functioning.[18] Presence of symptoms during the past week is rated per item on a 5-point scale (0–4) from "none of the time" to "all of the time." The OSDI total score (ranging from 0–100) can be calculated with a formula using the sum score of all completed questions.

Assessment of Dry Eye Signs

Dry eye tests were performed in both eyes, in the following order: tear osmolarity, Schirmer test without anesthesia, staining of the cornea with fluorescein, tear breakup time (TBUT), staining of the nasal and temporal conjunctiva with lissamine green, and meibomian gland dysfunction. Tear osmolarity was measured from the inferior lateral meniscus with a laboratory-on-a-chip by the TearLab Osmolarity System (TearLab Corp, San Diego, CA) following standard protocols.[7] An unanesthetized Schirmer-1 value after 5 minutes (millimeters/5 min) using sterile strips was measured following standard protocols.[7] The cornea was stained with fluorescein using the Oxford Schema grading, ranging from grade 0 to 5, based on the number of punctate dots for the total exposed interpalpebral cornea. A single drop of unit dose saline was instilled on a fluorescein-impregnated strip. After the drop saturated the impregnated tip, the excess was shaken into a waste bin.[7] The cornea was stained with lissamine green in a similar way using the Oxford Schema grading, scoring both the interpalpebral temporal and the nasal zone and taking the sum of these scores per eye, ranging from 0 to 10.[7] Graders were carefully instructed not to count linear/artifactual staining that could have been caused by the Schirmer test strip. The TBUT was measured by instilling a drop of fluorescein and counting the seconds after a blink before the tear film was broken up, following standard protocols.[7] A median of 3 measurements per eye was taken. After 10 seconds, we stopped counting, so the TBUT ranges from 0 to 10. Meibomian gland dysfunction was assessed by averaging the quality score (0 clear; 1 cloudy; 2 granular; 3 toothpaste) and expressibility score (0 minimal; 1 light; 2 moderate; 3 heavy pressure needed) of the meibum.[19] Ophthalmologists who graded the dry eye were not aware of the study question.

Statistical Analysis

A composite severity score was calculated for each eye, as suggested by the dry eye workshop,[6] using methodology reported by Sullivan et al,[20] with minor modifications to reflect differing tests. Each of the 6 dry eye tests was transformed to a common unit severity score between 0 and 1, with 0 being no sign of DED at all and 1 being the severest signs of DED. This transformation was based on the data in Table 1. Test scores that lie between the quartile points were transformed using linear interpolation. The score from the eye with the higher value was used for the analyses of all DED tests.[14,21] A composite signs severity score was calculated by taking the mean of the severity scores of the 6 independent tests. Next, all patients were ranked on the basis of the OSDI score and ranked on the basis of the composite signs severity score (both ranging from 0 [minimal symptoms/signs] to 1 [maximal symptoms/signs]). The primary outcome variable of this study was the difference between the rank score of the OSDI and the rank score of the composite signs severity score. This difference is a score for discordance between symptoms and signs and theoretically ranges from −1 (minimal symptoms and maximal signs) to 1 (maximal symptoms and minimal signs).

Data were cross-sectionally analyzed with the SPSS statistical package (version 22.0; SPSS, Inc., Chicago, IL). The distribution of the primary outcome variable discordance between symptoms and signs was first checked for normality. Subsequently, linear regression analysis was used to test for the association with a wide range of independent variables (demographic and environmental variables, systemic diseases, ocular traits, and medications). A multivariable stepwise linear regression model using backward elimination including all predictors that were univariably associated ($P < 0.10$) was used to assess predictors that were independently associated with a discordance between signs and symptoms. $P < 0.05$ was considered statistically significant in all analyses.

Results

The first consecutive 648 patients with DED from the GLOSSY cohort were included. The majority was female (n = 536, 82.7%), and the mean age was 55.8 years (standard deviation, 15.6 years). Most patients (n = 494, 76.2%) used 1 or more lubricants at the time of visit.

Median scores of the dry eye tests are presented in Table 2, including their mean contributions to the signs severity score. Schirmer test and TBUT contributed most to the signs severity score. The correlation between symptoms score and signs severity score was 0.14 ($P < 0.001$, Spearman), which is line with findings by Sullivan et al.[14] The discordance score between symptoms and signs was normally distributed ($P = 0.20$, Kolmogorov–Smirnov test). The score had (by definition) a mean of 0, with a standard deviation of 0.38, and ranged from −0.95 to 0.93, indicating that discordance is also common in this patient sample.

Table 1. Conversion of Dry Eye Test Measurements into a Common Unit System

DED Test	Severity Grade				
	0	*0.25*	*0.5*	*0.75*	*1.0*
Osmolarity (mOsm/L)	275	308	324	364	400
TBUT (sec)	10	7	5	3	0
Schirmer test (mm/5 min)	35	7	5	2	0
Staining cornea (Oxford, 0–5)	0	1	2	3	5
Staining nasal and temporal conjunctiva (Oxford, 0–10)	0	2	4	6	10
Meibomian gland dysfunction score (0–3)	0	0.75	1.5	2.25	3

DED = dry eye disease; TBUT = tear breakup time.

Table 2. Descriptive Statistics of Dry Eye Test Outcomes (n = 648)

DED Test	Median	Min	Max	Mean Severity Grade
Osmolarity (mOsm/L)	314	275	390	0.32
TBUT (sec)	4	0	10	0.56
Schirmer test (mm/5 min)	2	0	35	0.66
Staining cornea (Oxford, 0–5)	1	0	5	0.38
Staining nasal and temporal conjunctiva (Oxford, 0–10)	2	0	10	0.32
Meibomian gland dysfunction score (0–4)	1	0	3	0.31
OSDI symptoms score	33.3	0	100	n/a

DED = dry eye disease; Max = maximum; Min = minimum; n/a = not applicable; OSDI = Ocular Surface Disease Index; TBUT = tear breakup time.

Table 3 shows the results of the univariable association analysis between predictors and discordance between symptoms and signs. Significant predictors of greater symptoms than signs were irritable bowel syndrome, chronic pelvic pain, fibromyalgia, allergy, eczema, asthma, hay fever, use of antihistamines (all $P < 0.001$), depression ($P = 0.003$), osteoarthritis ($P = 0.008$), and use of antidepressants ($P = 0.02$). The highest effect sizes were found in patients with any of the chronic pain syndromes (CPSs), scoring approximately 30% higher on symptoms rank compared with signs rank. Patients with atopic disorders or an allergy scored approximately 20% higher on symptoms rank compared with signs rank.

Significant predictors of a lower symptom score than signs score were age and Sjögren's disease (both $P < 0.001$) and graft-versus-host disease (GVHD) ($P = 0.04$). Primary Sjögren's disease particularly was associated with lesser symptoms than signs (−16.7%; $P < 0.001$) compared with secondary Sjögren's disease (−7.0%; $P = 0.08$). Patients with GVHD scored on average 16% lower on symptom score than on signs score.

The multivariable model including all variables that were univariably associated ($P < 0.10$) revealed that age, the presence of a CPS, Sjögren's disease (all $P < 0.001$), the presence of atopic disease ($P = 0.02$), diabetes ($P = 0.03$), and GVHD ($P = 0.04$) were independently associated predictors for discordance between symptoms and signs. This model explained 15.4% (r^2) of the variance of discordance between symptoms and signs.

Self-perceived health was significantly associated with discordance between symptoms and signs ($P < 0.001$), with greater symptoms than signs in patients with low self-perceived health and vice versa (Fig 1).

Discussion

To our knowledge, this study is the largest clinical study to date investigating signs and symptoms in patients with DED and the first to specifically investigate predictors of discordance between symptoms and signs. This population, with a relatively large group of patients with Sjögren's syndrome (44%) and women (83%), has revealed not only several predictors of greater symptoms than signs but also predictors of fewer symptoms than signs. In addition, it has shown that patients with lower self-perceived overall health report greater symptoms than signs would suggest, indicating the importance of this phenomenon.

Of all the investigated risk factors of DED, this study reveals CPSs as the strongest predictor of a discordance between symptoms and signs, with the highest effect sizes in irritable bowel syndrome, fibromyalgia, and chronic pelvic pain. This is not a surprise because we have shown in a subset of this cohort and in a population-based cohort in the United Kingdom that patients with CPSs score on average higher symptom scores, whereas signs are similar or even less compared with patients without CPSs.[17] This finding has been confirmed by Galor et al[22] in a cohort in the United States. In a population-based cohort in the United Kingdom, we have also found CPSs to be the most significant risk factor of having DED symptoms and a DED diagnosis.[2] This finding adds to the growing evidence that part of the dry eye population may show signs of dysfunctional somatosensory pathways, indicating neuropathic ocular pain.[23–26] Depression also was highly associated with greater symptoms than signs, but this association did not remain significant in the multivariate model, possibly because of the high co-occurrence of depression and CPS.[27] Nevertheless, depression might be a helpful indicator in clinical practice of discordance between symptoms and signs. Likewise, osteoarthritis was highly associated with greater DED symptoms than signs. Although we are not aware of any shared etiological factors, this finding might be explained by a patient with increased pain sensitivity being more likely to be diagnosed as having osteoarthritis, and this shared pain sensitivity underlies the association with greater DED symptoms. Indeed, Mesci et al[28] showed in patients with knee osteoarthritis that those with neuropathic pain had lower knee pain threshold values than those without neuropathic pain, whereas femoral condylar cartilage thickness was similar between the 2 groups. Our group has shown that high pain sensitivity and low pain tolerance are associated with symptoms of DED.[29]

Allergy and atopic disorders also were highly associated with greater DED symptoms than signs. Atopic patients are predisposed to develop hypersensitivity reactions to certain allergens mediated by an excessive immunoglobulin-E reaction and often have allergic conjunctivitis. Both allergic conjunctivitis and DED are inflammatory disorders of the ocular surface and are common in the general population.[30] It has been shown that most patients with itchy eyes consistent with allergic conjunctivitis also have dry eye.[31] The 2 conditions have similar characteristics, including signs and symptoms, making differential diagnosis difficult.[32] So, a misdiagnosis of DED in patients with an allergic conjunctivitis could be an explanation for the greater dry eye symptoms than signs in patients with atopy or allergy. Another hypothesis explaining our results is that patients with atopy or allergy have a sensitized ocular surface because of inflammatory processes influencing corneal nerves, which can lead to symptoms of dry eye even when the homeostasis of the ocular surface is minimally compromised. Whatever the explanation of our finding, our results suggest it is important to assess allergy signs on the ocular surface (e.g., papillae and hypertrophy on the tarsal conjunctiva,

Table 3. Univariable Linear Regression Analysis of Predictors of a Difference between Symptoms and Signs in Patients with Dry Eye Disease (n = 648)

Predictor	Patients (no. [%]) or Value (mean ± SD)	Mean Symptom Rank*	Mean Sign Rank*	β†	*P* Value
Age (yrs)	55.8 ±15.6	n/a	n/a	−0.003	<0.001
Female	536 (82.7)	0.52	0.51	0.032	0.42
Any CPS	116 (17.9)	0.66	0.42	0.285	<0.001
Irritable bowel syndrome	54 (8.3)	0.62	0.41	0.229	<0.001
Fibromyalgia	66 (10.2)	0.67	0.41	0.288	<0.001
Pelvic pain	11 (1.7)	0.73	0.45	0.281	0.01
Chronic fatigue syndrome	29 (4.5)	0.68	0.60	0.080	0.27
Depression	44 (6.8)	0.62	0.46	0.175	0.003
Migraine	59 (9.1)	0.52	0.54	−0.013	0.80
Sjögren's disease	288 (44.4)	0.48	0.58	−0.131	<0.001
Primary Sjögren's disease	184 (28.4)	0.45	0.57	−0.167	<0.001
Secondary Sjögren's disease	104 (16.0)	0.55	0.60	−0.070	0.08
Rheumatoid arthritis	124 (19.1)	0.57	0.59	−0.021	0.58
Scleroderma	11 (1.7)	0.39	0.54	−0.145	0.21
Mixed connective tissue disease	12 (1.9)	0.56	0.55	0.012	0.91
SLE	33 (5.1)	0.42	0.39	0.025	0.71
Sarcoidosis	8 (1.2)	0.58	0.55	0.036	0.79
GVHD	23 (3.5)	0.58	0.73	−0.162	0.04
Rosacea	42 (6.5)	0.54	0.46	0.081	0.18
Hypertension	157 (24.2)	0.51	0.50	0.008	0.82
Hypercholesterolemia	75 (11.6)	0.53	0.46	0.087	0.06
Thyroid disease	89 (13.7)	0.50	0.50	0.008	0.85
Diabetes	35 (5.4)	0.63	0.52	0.115	0.08
Osteoarthritis	114 (17.6)	0.61	0.52	0.103	0.008
Postmenopause	344 (53.1)	0.53	0.54	−0.045	0.20
Any atopic disease	169 (26.1)	0.57	0.41	0.211	<0.001
Hay fever	85 (13.1)	0.56	0.38	0.211	<0.001
Eczema	85 (13.1)	0.58	0.41	0.196	<0.001
Asthma	72 (11.1)	0.61	0.40	0.246	<0.001
Any allergy	102 (15.7)	0.61	0.48	0.159	<0.001
Use of distance glasses	459 (70.8)	0.52	0.51	0.008	0.74
Use of contact lenses	20 (3.1)	0.40	0.43	−0.026	0.76
Hours spent behind computer per day	3.0 ±2.5	n/a	n/a	0.005	0.45
Use of any lubricants	494 (76.2)	0.54	0.54	−0.025	0.47
Any previous surgery on eyes	132 (20.4)	0.54	0.55	−0.010	0.78
Use of antihistamines	57 (8.8)	0.60	0.43	0.187	<0.001
Use of antidepressants	51 (7.9)	0.57	0.45	0.127	0.02
Use of antidiuretics	78 (12.0)	0.51	0.48	0.036	0.43
Use of beta-blockers	119 (18.4)	0.54	0.49	0.051	0.19

CPS = chronic pain syndrome; GVHD = graft-versus-host disease; n/a = not available; SD = standard deviation; SLE = systemic lupus erythematosus.
*If the mean rank is >0.50, it means that this group of patients has on average a higher rank score than other patients, and vice versa.
†A positive β means an increase in symptoms rank score compared with signs rank score. For example, patients with dry eye disease with a diagnosis of irritable bowel syndrome have a 22.9% higher rank symptoms score than what you would expect based on the signs severity score ($P < 0.001$).

and conjunctival hyperemia and edema) in patients with unexplained dry eye symptoms, because this might play a role in the increased symptoms.

Diseases that were associated with lesser symptoms to signs were Sjögren's disease and GVHD. The finding in patients with Sjögren's disease is in accordance with Mizuno et al,[12] who showed in 158 patients with DED (38% with Sjögren's disease) that those with Sjögren's disease had worse signs than those without Sjögren's disease, whereas subjective symptoms were similar.[12] In fact, this is replicated in our study with a signs rank score of 0.58 and a symptoms rank score of 0.48 in those with Sjögren's disease (Table 3). This discordance was most pronounced in patients with primary Sjögren's disease. The results of this study stress the importance of dry eye tests to carefully assess signs in patients with Sjögren's disease and GVHD and not to rely on symptoms only.

Of note, increasing age also was associated with fewer symptoms than signs. Studies related to the impact of age on general pain sensitivity have ranged from increased to decreased sensitivity to no change.[33] However, Spierer et al[34] showed in 129 subjects that mechanical and pain thresholds are correlated with age, implying decreased corneal sensitivity with age. They also showed that these thresholds are correlated with dry eye symptoms and ocular pain. Our study adds further evidence that the ocular surface desensitizes with age and leads to fewer DED symptoms.

In this study, we did not find any evidence for a sex difference for discordance between symptoms and signs in DED.

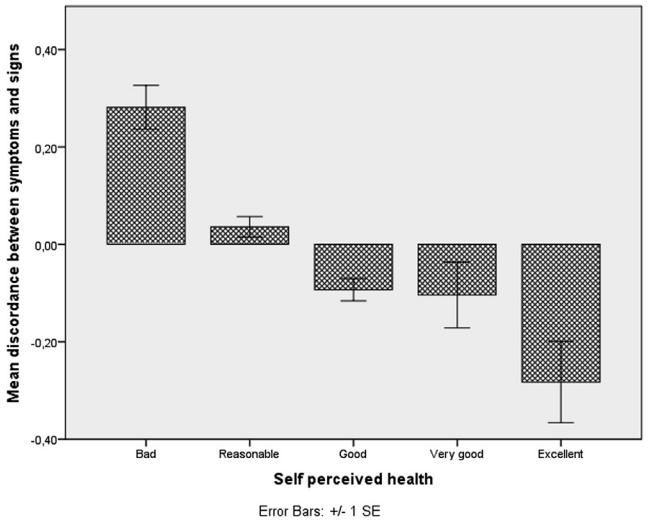


Figure 1. Relation between self-perceived health and discordance between dry eye symptoms and signs. A positive discordance means more symptoms than signs. Lower self-perceived health is significantly associated with greater symptoms than signs ($P < 0.001$). SE = standard error.

Several studies have reported that women experience more symptoms in DED compared with men.[35] We also found greater symptoms in women than men (mean rank symptoms score 0.52 vs. 0.43; $P = 0.004$), but this was accompanied by greater signs in women compared with men (mean signs rank score 0.51 vs. 0.46; $P = 0.07$). So, the greater experience of dry eye symptoms in women is possibly the result of increased signs and not the result of increased sensitivity in women. A recent review looking at sex differences in pain sensitivity concluded that "women often show lower pain thresholds and experience greater temporal summation of pain to brief, repeated, or dynamic stimuli than men. However, women also show greater adaptation to sustained longer stimuli and habituation to repeated long stimuli."[36] Thus, in a chronic disease like DED, greater adaptation and habituation in women may even out their lower pain thresholds.

Diabetes also was associated with increased symptoms to signs ($P = 0.03$ in the multivariable model). Diabetes is associated with peripheral neuropathy, and patients have been shown to have reduced sub-basal corneal nerve density and reduced corneal sensitivity.[37–39] In addition, patients with diabetes have reduced tear film stability and secretion.[39] Thus, one might predict more signs and fewer symptoms in this patient group, the opposite of what we found. A possible explanation for our result could be that patients with diabetes have more vision problems (because of associated retinopathy and cataract), and the visual symptoms in the OSDI might be contributing to a higher OSDI than the ocular signs suggest. However, further subanalysis in this group revealed that symptoms were greater across the whole range of symptoms, including symptoms of pain and discomfort, and not limited to vision-related symptoms. Further work is needed to explain increased DED symptoms to signs in patients with diabetes.

Greater symptoms than signs were highly associated with lower self-perceived health. This underlines the importance and clinical value of discordance between symptoms and signs, because it is a serious indicator of poor health-related quality of life for patients, which has an impact on mental health, employment, support service needs, and many other aspects of life.[40] We can only speculate about the cause of this association, but one possible explanation could be that patients with greater symptoms than signs have on average a more negative attitude toward health states, including symptoms.

Study Limitations

First, the findings of a study are specific to the cohort that was investigated, in this case a tertiary dry eye clinic with a relatively large group of female patients and patients with Sjögren's disease, with a relatively low Schirmer score (median value of 2 mm) (Table 2). We do not know how generalizable the results are to other DED patient cohorts. In addition, predictors specific to men might have been missed because of the relatively small population of men. Also, the sequence of the tests and specific techniques used in our cohort, such as the instillation and amount of dye used, could influence the generalizability of the study.[7] For example, the Schirmer test could have caused damage to the ocular surface, which could have increased the staining scores in some patients, although graders were instructed to exclude linear/artifactual staining in the inferior ocular surface from staining scores. We believe that performing a Schirmer test before grading staining scores also has advantages, with a more reliable outcome of tear flow in patients independent of irritation by fluorescein or slit-lamp investigation. Second, the predictors that we investigated were assessed by self-report questionnaires that are prone to recall bias. Third, this study was limited to the most common clinical tests in practice, because we aimed to make the results as useful and generalizable as possible for general clinical practice. Inclusion of more dry eye tests, such as tear meniscus height and tear film thickness measurements with Fourier-domain optical coherence tomography, could make our signs severity score more complete and reliable.[41,42] The main strengths of this study are the large size of the cohort investigated, one of the largest dry eye patient cohorts ever reported, and the systematic assessment of the most commonly used dry eye tests by a limited number of specialists, all in 1 center using standardized protocols.

In conclusion, discordance between symptoms and signs is common in DED and negatively associated with self-perceived health. A medical history including CPS, depression, atopic disorders, allergy, and diabetes, and ocular examination for allergy signs is important in assessing patients with DED, especially when symptoms outweigh signs. However, in patients with Sjögren's disease and GVHD, it is important to fully assess dry eye signs and not to rely on the (lack of) symptoms.

Acknowledgments. The authors thank the Gratama Stichting for funding part of the tear osmolarity tests performed in this study and Luuk Mooibroek for his extensive work in maintaining the database of the GLOSSY cohort.

References

1. Dry Eye Workshop. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*. 2007;5:93-107.
2. Vehof J, Kozareva D, Hysi PG, Hammond CJ. Prevalence and risk factors of dry eye disease in a British female cohort. *Br J Ophthalmol*. 2014;98:1712-1717.
3. Pflugfelder SC. Prevalence, burden, and pharmacoeconomics of dry eye disease. *Am J Manag Care*. 2008;14(3 Suppl):S102-S106.
4. Miljanovic B, Dana R, Sullivan DA, Schaumberg DA. Impact of dry eye syndrome on vision-related quality of life. *Am J Ophthalmol*. 2007;143:409-415.
5. Schiffman RM, Walt JG, Jacobsen G, et al. Utility assessment among patients with dry eye disease. *Ophthalmology*. 2003;110:1412-1419.
6. Dry Eye Workshop. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*. 2007;5:75-92.
7. Dry Eye Workshop. Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf*. 2007;5:108-152.
8. Bartlett JD, Keith MS, Sudharshan L, Snedecor SJ. Associations between signs and symptoms of dry eye disease: a systematic review. *Clin Ophthalmol*. 2015;9:1719-1730.
9. Schein OD, Tielsch JM, Munoz B, et al. Relation between signs and symptoms of dry eye in the elderly. A population-based perspective. *Ophthalmology*. 1997;104:1395-1401.
10. Hay EM, Thomas E, Pal B, et al. Weak association between subjective symptoms or and objective testing for dry eyes and dry mouth: results from a population based study. *Ann Rheum Dis*. 1998;57:20-24.
11. Hua R, Yao K, Hu Y, Chen L. Discrepancy between subjectively reported symptoms and objectively measured clinical findings in dry eye: a population based analysis. *BMJ Open*. 2014;4:e005296.
12. Mizuno Y, Yamada M, Miyake Y; Dry Eye Survey Group of the National Hospital Organization of Japan. Association between clinical diagnostic tests and health-related quality of life surveys in patients with dry eye syndrome. *Jpn J Ophthalmol*. 2010;54:259-265.
13. Fuentes-Paez G, Herreras JM, Cordero Y, et al. [Lack of concordance between dry eye syndrome questionnaires and diagnostic tests]. *Arch Soc Esp Oftalmol*. 2011;86:3-7.
14. Sullivan BD, Crews LA, Messmer EM, et al. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications. *Acta Ophthalmol*. 2014;92:161-166.
15. Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. *Cornea*. 2004;23:762-770.
16. Lemp MA. Advances in understanding and managing dry eye disease. *Am J Ophthalmol*. 2008;146:350-356.
17. Vehof J, Sillevis Smitt-Kamminga N, Kozareva D, et al. Clinical characteristics of dry eye patients with chronic pain syndromes. *Am J Ophthalmol*. 2016;162:59-65 e2.
18. Schiffman RM, Christianson MD, Jacobsen G, et al. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol*. 2000;118:615-621.
19. Tomlinson A, Bron AJ, Korb DR, et al. The international workshop on meibomian gland dysfunction: report of the diagnosis subcommittee. *Invest Ophthalmol Vis Sci*. 2011;52:2006-2049.
20. Sullivan BD, Whitmer D, Nichols KK, et al. An objective approach to dry eye disease severity. *Invest Ophthalmol Vis Sci*. 2010;51:6125-6130.
21. Lemp MA, Bron AJ, Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. *Am J Ophthalmol*. 2011;151:792-798 e1.
22. Galor A, Covington D, Levitt AE, et al. Neuropathic ocular pain due to dry eye is associated with multiple comorbid chronic pain syndromes. *J Pain*. 2016;17:310-318.
23. Vehof J, Zavos HM, Lachance G, et al. Shared genetic factors underlie chronic pain syndromes. *Pain*. 2014;155:1562-1568.
24. Galor A, Levitt RC, Felix ER, et al. Neuropathic ocular pain: an important yet underevaluated feature of dry eye. *Eye (Lond)*. 2015;29:301-312.
25. Galor A, Felix ER, Feuer W, et al. Dry eye symptoms align more closely to non-ocular conditions than to tear film parameters. *Br J Ophthalmol*. 2015;99:1126-1129.
26. Galor A, Zlotcavitch L, Walter SD, et al. Dry eye symptom severity and persistence are associated with symptoms of neuropathic pain. *Br J Ophthalmol*. 2015;99:665-668.
27. Kato K, Sullivan PF, Evengard B, Pedersen NL. A population-based twin study of functional somatic syndromes. *Psychol Med*. 2009;39:497-505.
28. Mesci N, Mesci E, Kulcu DG. Association of neuropathic pain with ultrasonographic measurements of femoral cartilage thickness and clinical parameters in patients with knee osteoarthritis. *J Phys Ther Sci*. 2016;28:2190-2195.
29. Vehof J, Kozareva D, Hysi PG, et al. Relationship between dry eye symptoms and pain sensitivity. *JAMA Ophthalmol*. 2013;131:1304-1308.
30. Kubicka-Trzaska A, Romanowska-Dixon B. [Dry eye syndrome and allergic conjunctivitis—epidemics of XXI century—diagnostic problems and management]. *Przegl Lek*. 2009;66:967-971.
31. Hom MM, Nguyen AL, Bielory L. Allergic conjunctivitis and dry eye syndrome. *Ann Allergy Asthma Immunol*. 2012;108:163-166.
32. Mathers WD, Lane JA, Sutphin JE, Zimmerman MB. Model for ocular tear film function. *Cornea*. 1996;15:110-119.
33. Yezierski RP. The effects of age on pain sensitivity: preclinical studies. *Pain Med*. 2012;13(Suppl 2):S27-S36.
34. Spierer O, Felix ER, McClellan AL, et al. Corneal mechanical thresholds negatively associate with dry eye and ocular pain symptoms. *Invest Ophthalmol Vis Sci*. 2016;57:617-625.
35. Rapoport Y, Singer JM, Ling JD, et al. A comprehensive review of sex disparities in symptoms, pathophysiology, and epidemiology of dry eye syndrome. *Semin Ophthalmol*. 2016;31:325-336.
36. Hashmi JA, Davis KD. Deconstructing sex differences in pain sensitivity. *Pain*. 2014;155:10-13.
37. Nielsen NV. Corneal sensitivity and vibratory perception in diabetes mellitus. *Acta Ophthalmol (Copenh)*. 1978;56:406-411.
38. Cousen P, Cackett P, Bennett H, et al. Tear production and corneal sensitivity in diabetes. *J Diabetes Complications*. 2007;21:371-373.
39. Misra SL, Braatvedt GD, Patel DV. Impact of diabetes mellitus on the ocular surface: a review. *Clin Exp Ophthalmol*. 2016;44:278-288.
40. Halford C, Wallman T, Welin L, et al. Effects of self-rated health on sick leave, disability pension, hospital admissions and mortality. A population-based longitudinal study of nearly 15,000 observations among Swedish women and men. *BMC Public Health*. 2012;12:1103.
41. Kanellopoulos AJ, Asimellis G. In pursuit of objective dry eye screening clinical techniques. *Eye Vis (Lond)*. 2016;3:1.
42. Pekel E, Pekel G. Clinical characteristics of dry eye patients with chronic pain syndromes. *Am J Ophthalmol*. 2016;166:203.

Footnotes and Financial Disclosures

Originally received: October 3, 2016.
Final revision: November 3, 2016.
Accepted: November 8, 2016.
Available online: December 23, 2016. Manuscript no. 2016-482.

[1] Department of Twin Research & Genetic Epidemiology, King's College London, St. Thomas' Hospital, Waterloo, London, United Kingdom.

[2] Department of Ophthalmology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

[3] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands.

[4] Department of Ophthalmology, King's College London, St. Thomas' Hospital, Waterloo, London, United Kingdom.

Financial Disclosure(s):
The author(s) have made the following disclosure(s): C.J.H.: Grants – pending from Alcon.

Supported by a grant from the Gratama Stichting, University of Groningen. The funding organization had no role in the design or conduct of this research.

Author Contributions:

Conception and design: Vehof, Smitt-Kamminga, Hammond

Data collection: Vehof, Smitt-Kamminga, Nibourg

Analysis and interpretation: Vehof, Hammond

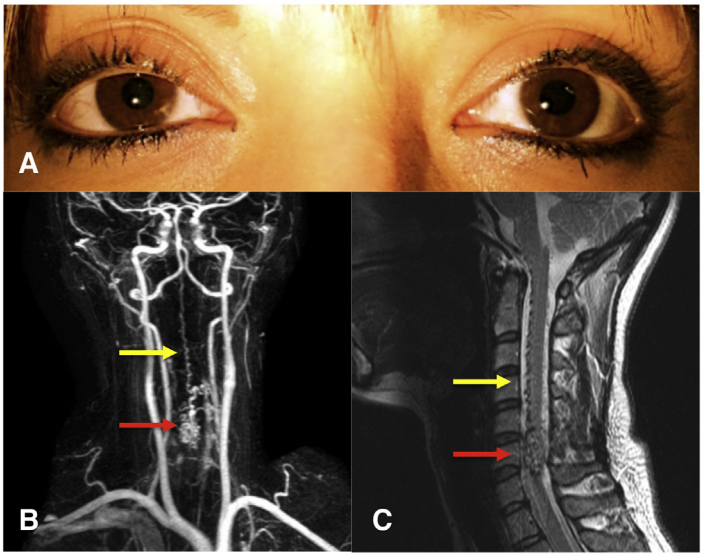
Obtained funding: Not applicable

Overall responsibility: Vehof, Smitt-Kamminga, Hammond, Nibourg

Abbreviations and Acronyms:
CPS = chronic pain syndrome; **DED** = dry eye disease; **GLOSSY** = Groningen LOngitudinal Sicca StudY; **GVHD** = graft-versus-host disease; **OSDI** = Ocular Surface Disease Index; **SLE** = systemic lupus erythematosus; **TBUT** = tear breakup time.

Correspondence:
Jelle Vehof, MD, PhD, Department of Twin Research and Genetic Epidemiology, King's College London, St. Thomas' Hospital Campus, 3rd Floor South Wing Block D, Westminster Bridge Road, London SE1 7EH, UK. E-mail: jelle.vehof@kcl.ac.uk.

Pictures & Perspectives



Cervical Arteriovenous Malformation Causing Horner's Syndrome

A 35-year-old woman presented with a 5-month history of right upper eyelid ptosis and anisocoria (Fig 1**A**) consistent with Horner's syndrome. Magnetic resonance (MR) angiography of the head and neck (Fig 1**B**) revealed an extensive arteriovenous malformation (AVM) of the cervical spine (*red arrow*), with marked dilation of the anterior cervical artery (*yellow arrow*). Dedicated MR imaging of the cervical spine better characterized the intramedullary portion of the AVM at the C5/C6 level (Fig 1**C**). Given the risk of spinal cord infarction from an embolization procedure, observation was recommended. Cervical cord lesions are an important cause of central Horner's syndrome.

Crandall Peeler, MD[1]
Sashank Prasad, MD[2]

[1]Departments of Ophthalmology and Neurology, Boston Medical Center, Boston University School of Medicine, Boston, Massachusetts; [2]Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts