Long term course of tear gland function in patients with keratoconjunctivitis sicca and Sjögren's syndrome

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Abstract

***Aims*—To assess the course of tear gland function of patients with keratoconjunctivitis sicca (KCS) associated with primary (KCS-PSS) or secondary Sjögren's syndrome (KCS-SSS), and of patients with KCS not related to Sjögren's syndrome (KCS-NS).**

***Methods*—In 106 patients with dry eye an ophthalmic diagnosis of KCS was made. Subsequent evaluations revealed a diagnosis of KCS-PSS in 31, KCS-SSS in 19, and KCS-NS in 56 patients. Follow up assessments have been performed 10–12 years after initial diagnosis.**

***Results*—At baseline and at follow up tear gland function tests were worse in patients with KCS-PSS compared with the other forms of KCS. At follow up in the KCS-SSS patient group the tear gland function variables returned to marginal normal limits. In contrast with expectation, a marked improvement of the tear gland function variables in the KCS-NS patient group was noted.**

***Conclusions*—In KCS-PSS patients tear gland function is characterised by a steady state situation. In KCS-SSS patients the normalisation of tear gland function variables most probably reflects a remission of the underlying disease. In view of the overall improvement in KCS-NS patients the term age related KCS should be avoided.**

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Keratoconjunctivitis sicca (KCS) is an eye disease caused by a secretion disorder of the main and accessory lacrimal glands that takes its name from the most conspicuous signs, a decrease in tear volume. KCS not related to Sjögren's syndrome (KCS-NS) is considered to be a consequence of an age related involution of the glands, a hazardous diagnosis without histopathological confirmation. Less frequently, autoimmune induced lymphoid infiltration of the tear gland may lead to loss of function.[1–7]

It is assumed that KCS-NS deteriorates more slowly and less profoundly than the dry eye states associated with primary (KCS-PSS) and secondary Sjögren's syndrome (KCS-SSS), but hard data on the evolution of these distinct disease entities are not available. This makes it difficult to assess prognosis and to assist in patient counselling.

Ocular complications occasionally occur in KCS associated with Sjögren's syndrome. Early differential diagnosis between KCS associated with Sjögren's syndrome and KCS-NS is therefore important. Because of the possible development of extraglandular manifestations and an increased risk for lymphoproliferative disease, PSS patients need clinical evaluation on a regular base, whereas SSS patients need careful supervision because of their associated connective tissue disorder.[8–14]

In the present study we assessed the course of tear gland function and the medical status in patients with KCS-PSS, KCS-SSS, and KCS-NS in a 10 year interval.

Methods

In the department of ophthalmology a clinical diagnosis KCS was made in 106 patients, based on the Schirmer test results, lysozyme tear fluid concentration, and the rose bengal scores. All patients were seen at the departments of internal medicine and rheumatology at study entrance and after a 10 year follow up period to determine a possible association with PSS or SSS according to the classification criteria for Sjögren's syndrome as proposed by Daniels and Talal.[15 16]

Tear function tests were done at study entrance and at follow up. At follow up tear fluid lactoferrin concentration and the tear film break up time were added to the tear function tests. All tests were performed according to standard procedures.[1 4–7 17 18] Seventy one patients qualified for the follow up examination.

To determine the statistical significance of differences *between* patient groups at study entrance and at follow up, the χ^2 test and generalised Kruskal–Wallis test or Mann–Whitney test, were used for dichotomous and continuous variables, respectively. Statistical significance of differences *within* patient groups between study entrance and 10 year follow up was determined with the McNemar test and Wilcoxon signed ranks test for dichotomous and continuous variables, respectively.

Results

STUDY ENTRANCE

Of the 106 patients at entry 73% were females. There were statistically significantly more females in the PSS patient group compared with the other two patient groups—93% versus

Table 1 Baseline characteristics of KCS-PSS, KCS-SSS, and KCS-NS patient groups

	KCS-PSS (n=31)	KCS-SSS (n=19)	KCS-NS (n=56)	p Value
Female (%)	29 (93)	11 (58) [a]	37 (66) [b]	**
Age (SD)	55.8 (13.2)	58.2 (13.2)	50.7 (16.0)	
Duration (SD)	5.4 (5.1)	3.0 (2.6)	3.4 (3.6)	
Dryness of eyes (%)	28 (90)	15 (79)	51 (91)	
Sandy feelings in eyes	25 (81)	10 (53) [a]	47 (84)*	
Inflammatory reaction in eyes	12 (39)	2 (10)	16 (29)	
Tear lysozyme concentration (µg/ml) (SD)	511 (308)	1066 (770)[a]	1061 (727)[b]	***
Schirmer-I test (mm/5 min) (SD)	4.5 (3.3)	6.6 (5.0)	9.9 (8.7)[b]	**
Rose bengal test (SD)	4.6 (1.7)	3.0 (1.7)[a]	3.4 (2.0)[b]	**

KCS-PSS = keratoconjunctivitis sicca in association with primary Sjögren's syndrome; KCS-SSS = keratoconjunctivitis sicca in association with secondary Sjögren's syndrome; KCS-NS = keratoconjunctivitis sicca not related to Sjögren's syndrome.
Statistical significance of differences *between* all three patient groups: * = $0.01 < p < 0.05$; ** = $0.001 < p < 0.01$; *** = $p < 0.001$.
Statistical significance of differences *between* KCS-PSS and KCS-SSS patient groups: a = $p < 0.05$. Statistical significance of differences *between* with KCS-PSS and KCS-NS patient groups: b = $p < 0.05$.
Abnormal values: tear lysozyme concentration <1400 µg/ml; Schirmer-I test ⩽ 5 mm/5 min; rose bengal test ⩾3.

Table 2 Dropout at follow up

	KCS-PSS	KCS-SSS	KCS-NS
Patients at entry:	31	19	56
Death	8	6	10
Unwilling to cooperate	1	1	5
Lost to follow up	1	0	3
Total	10	7	18
Patients at follow up:	21	12	38
With rheumatoid arthritis		6	
With dermatomyositis		2	
With systemic sclerosis		3	
With systemic lupus erythematosus		1	

KCS-PSS = keratoconjunctivitis sicca in association with primary Sjögren's syndrome; KCS-SSS = keratoconjunctivitis sicca in association with secondary Sjögren's syndrome; KCS-NS = keratoconjunctivitis sicca not related to Sjögren's syndrome.

58% for KCS-SSS and 66% for KCS-NS (Table 1). The average age was 53.5 years and the mean duration of the dry eye status judged from the beginning of ocular discomfort was 3.9 years. No statistically significant differences in mean age and mean duration of disease were noticed between the three patient groups. Based on the criteria of Daniels and Talal,[16] 31 patients had KCS associated with PSS, 19 had KCS-SSS, and 56 patients had KCS-NS. Extensive ophthalmic examination revealed no cause of KCS in the KCS-NS patient group. Of the 19 KCS-SSS patients 11 had rheumatoid arthritis, four had systemic sclerosis, two had dermatomyositis, and two had systemic lupus erythematosus.

Table 3 Characteristics of KCS-PSS, KCS-SSS, and KCS-NS patient groups at follow up

	KCS-PSS (n=21)	KCS -SSS (n=12)	KCS-NS (n=38)	p Value
Female (%)	19 (90)	8 (67) [a]	29 (76) [b]	**
Age (SD)	65.8 (15.5)	66.2 (13.2)	58.9 (14.8)	
Duration (SD)	17.7 (6.4)	14.4 (1.8)	15.4 (4.4)	
Dryness of eyes (%)	19 (90)	9 (75)	30 (79)	
Sandy feelings in eyes	15 (71)	4 (33)	26 (68)	
Inflammatory reaction in eyes	2 (9)	0 (0)	1 (3)	
Tear lysozyme concentration (µg/ml) (SD)	815 (570)	1971 (1029) [a]	2163 (1252) [b]	***
Tear lactoferrin concentration	5.5 (2.2)	12.5 (4.7) [a]	12.0 (5.5) [b]	***
Schirmer-I test (mm/5 min)	6.2 (2.2)	13.6 (8.0) [a]	14.0 (9.4) [b]	**
BUT	3.8 (4.4)	7.0 (4.5)	7.1 (3.8) [b]	*
Rose bengal test	4.7 (2.0)	3.3 (1.3)	2.1 (1.6) [b]	***

KCS-PSS = keratoconjunctivitis sicca in association with primary Sjögren's syndrome; KCS-SSS = keratoconjunctivitis sicca in association with secondary Sjögren's syndrome; KCS-NS = keratoconjunctivitis sicca not related to Sjögren's syndrome.
BUT = break up time of tear film.
Statistical significance of differences *between* all three patient groups: * = $0.01 < p < 0.05$; ** = $0.001 < p < 0.01$; *** = $p < 0.001$.
Statistical significance of differences *between* KCS-PSS and KCS-SSS patient groups: a = $p < 0.01$. Statistical significance of differences *between* KCS-PSS and KCS-NS patient groups: b = $p < 0.01$.
Abnormal values: tear lysozyme concentration <1400 µg/ml; tear lactoferrin concentration <9.8 mm diameter of precipitation (= <950 µg/ml); Schirmer-I test ⩽ 5 mm/5 min; BUT = break up time of tear film < 10 seconds; rose bengal test ⩾3.

Signs and symptoms

No statistically significant differences between the three groups were found with regard to the symptoms and signs with the exception of suffering from a sandy feeling in the eyes. This symptom was reported in more than 80% of KCS-PSS and KCS-NS patients, but in only 53% of the KCS-SSS patients. At the time of the last examination none of the patients had major corneal, scleral, or choroidal complications.

Tear function tests

The lysozyme tear fluid concentrations in all three patient groups were well below the limit of 1400 µg/ml (Table1). Lowest values were found in the KCS-PSS patient group, and no significant differences were noted between the KCS-SSS and the KCS-NS patient groups (Table1). In the KCS-PSS patient group the Schirmer test values were low when compared with the other groups, whereas in this patient group highest values of the rose bengal test were noted (Table 1).

STUDY FOLLOW UP

After a 10 year period 71 patients were evaluable for follow up (Table 2). Owing to a variety of reasons 35 patients had dropped out: 24 patients had died, seven patients were unwilling to participate in the study, and four patients were lost for follow up as a result of moving to another location.[13] At baseline no differences in ophthalmic variables were found between patients not evaluable for follow up and patients who were, with exception of suffering from a sandy feeling in the eyes. In patients who dropped out this symptom was present in 62%, whereas 84% of the patients who also were evaluable at follow up reported this complaint ($p < 0.05$) (data not shown). Of the remaining 71 patients 21 had KCS-PSS, 12 patients had KCS-SSS, and 38 patients had KCS-NS. Data of these patients are shown in Table 3. At the time of examination none of these patients had major ocular complications.

Signs and symptoms

At follow up no statistically significant differences in signs and symptoms between the three patient groups were noted (Table 3).

Tear function tests

In the 10 year period the KCS-PSS patient group remained essentially the same. The KCS-SSS group showed a tendency to improvement (Table 4). The patients in the KCS-NS group showed a significant and sizeable improvement in both symptoms and signs.

At follow up, again the KCS-PSS patient group showed the poorest tear function, the mean values of all variables, including tear fluid lactoferrin concentration, being within the

Table 4 Differences within patient groups between study entrance (t=1) and follow up (t=2)

	KCS-PSS			*KCS-SSS*			*KCS-NS*		
	t= 1	*t= 2*	*p Value*	*t= 1*	*t= 2*	*p Value*	*t= 1*	*t= 2*	*p Value*
n	21	21		12	12		38	38	
Dryness of eyes n (%)	19 (90)	19 (90)		9 (75)	9 (75)		33 (87)	30 (79)	
Sandy feeling in eyes	19 (90)	15 (71)		7 (58)	4 (33)		34 (89)	26 (68)	*
Inflammatory reaction in eyes	9 (43)	2 (9)	*	2 (17)	0 (0)		13 (34)	1 (3)	***
Tear lysozyme concentration	538 (352)	815 (570)	*	206 (903)	1971 (1029)	**	1163 (793)	2163 (1252)	***
Schirmer-I test	4.3 (3.4)	6.2 (5.9)		8.1 (5.8)	13.6 (8.0)	*	10.0 (8.2)	14.0 (9.4)	**
Rose bengal test	4.5 (1.9)	4.7 (2.0)		2.2 (1.4)	3.3 (1.3)	*	3.3 (2.0)	2.1 (1.6)	**

KCS-PSS = keratoconjunctivitis sicca in association with primary Sjögren's syndrome; KCS-SSS = keratoconjunctivitis sicca in association with secondary Sjögren's syndrome; KCS-NS = keratoconjunctivitis sicca not related to Sjögren's syndrome.
* = 0.01 < p < 0.05; ** = 0.001 < p < 0.01; *** = p < 0.001.
Statistical significance of differences *between* KCS-PSS and KCS-SSS patient groups:
a = p < 0.01. Statistical significance of differences *between* KCS-PSS and KCS-NS patient groups: b = p < 0.01.
Abnormal values: tear lysozyme concentration <1400 µg/ml; Schirmer-I test ⩽ 5 mm/5 min; rose bengal test ⩾3.

pathological range. At follow up in the KCS-SSS and the KCS-NS patient groups, mean Schirmer-I test values and mean lysozyme and lactoferrin concentrations were within the normal range, but the tear film break up time values were poor.

Discussion

After an obvious initial period a remarkable steady state situation in ocular findings as well as general situation in the KCS-PSS patient group was observed.[13]

Within the KCS-SSS group the tear gland function variables reached the normal range at follow up. As secondary Sjögren's syndrome represents a heterogeneous group of patients, remission of the underlying disease may have similar consequences for the ocular findings.

In contrast with our expectation of a steady state situation in the KCS-NS patient group a marked improvement of the tear function variables was noted. At follow up tear gland function variables reached the normal range, and some symptoms disappeared. The most common and, in fact, unavoidable situation leading to a dry eye state is assumed to be advanced age: the age related dry eye. In itself age related alterations of the lacrimal gland do not necessarily cause a dry eye unless the tear function was marginal to begin with. In a few documented cases of these so called age related dry eyes histopathological atrophy of the secretory elements and the lymph follicles of the eye and an increase of fibrous tissue as well as plasmacytic infiltration have been reported.[19] In sublabial salivary gland biopsy specimens similar findings have been seen.[20] In a small series, abnormal lacrimal gland histology including lymphocytic infiltration and an increase in fibrous tissue was observed not only in Sjögren's syndrome patients, but also in KCS-NS patients.[21] In contrast, in bulbar conjunctiva biopsy specimens from a normal elderly population morphological changes including irregularities in thickness of the epithelium were observed exclusively in patients over 80 years old.[22] In Sjögren's syndrome patients as well as KCS-NS patients bulbar conjunctiva biopsy specimens revealed stratification of the conjunctival epithelium with separation of the superficial cell layers, directly proportional to the clinical severity of the disease.[23] After nasolacrimal duct occlusion in two of these KCS-NS patients a reduction in epithelial cell stratification was noticed.[23]

At advancing age in healthy individuals a gradual decrease in tear secretion as measured by the Schirmer-I test has been demonstrated in both males and females. Also, a decrease in tear fluid lysozyme concentration has been shown.[24] In view of the findings of a significant overall improvement of tear gland function in the present study we favour avoiding the term 'age related KCS'. But the explanation of this phenomenon is difficult. One could speculate on a possible role of previous subclinical dacryoadenitis. Also intermittent focal adenitis of the lacrimal glands cannot be excluded.[21–23] However, because in healthy salivary gland tissue focal lymphocytic adenitis has been described,[25] a temporary decrease in tear secretion due to intermittent lacrimal adenitis is at least a doubtful theory.

In conclusion, within the population of dry eye patients, referred to a university hospital ophthalmic outpatients' department specialising in the dry eye syndrome, a considerable number of patients appears to suffer from Sjögren's syndrome. Tear gland function in PSS patients is characterised by a steady state situation. In KCS-SSS patients a normalisation of tear gland function variables at follow up was noted. In view of an overall improvement of tear gland function in KCS-NS patients seen over the years we suggest avoiding the term 'age related KCS'.

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