Acta Neurol Belg (2015) 115:329–333
DOI 10.1007/s13760-014-0359-y

ORIGINAL ARTICLE

The relationship between dry eye and migraine

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Received: 16 July 2014 / Accepted: 8 September 2014 / Published online: 18 September 2014
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Abstract Presently, migraine and dry eye are both thought to have an inflammatory pathogenesis. We aimed to investigate dry eye findings and any relationship with headache characteristics in migraine patients with and without aura. In total, 58 migraineurs and 41 age- and gender-matched controls were enrolled in this prospective clinical study. The migraine diagnosis was made according to the International Classification of Headache Disorders II diagnostic criteria. All patients underwent a complete ophthalmologic examination including tear meniscus measurements, meibography, tear breakup time, Schirmer test and the Ocular Surface Disease Index questionnaire. The presence of dry eye was higher in migraineurs as compared to the control group, but this did not reach statistical significance ($p = 0.282$). Among the headache characteristics, the presence of aura was significantly higher, and disease and attack durations were significantly longer in migraineurs with dry eye than in those without dry eye ($p = 0.009$, $p = 0.010$, and $p = 0.003$, respectively). In multiple logistic regression model, attack duration was found to be independently associated with the presence of dry eye in migraine patients (OR; 95 % CI; $p = 0.029$). The results show that dry eye may present in migraine patients with greater presence of auras and longer disease and attack durations.

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Keywords Dry eye · İnflammation · Migraine · Migraine attack · Migraine with aura

Introduction

Migraine is a chronic disorder with complex pathophysiology involving neuronal and vascular mechanisms [1]. Several studies support the role of inflammation in the pathogenesis of migraine in which the attacks are associated with neurovascular inflammation of the cerebral and extracerebral vessels [2]. Increased inflammatory cytokines and interleukins have been reported during interictal periods and acute attacks of migraine [3–5].

Inflammation is also proposed to be a central feature of ocular surface diseases [6–8]. Dry eye is a condition that results in dryness of the conjunctiva and cornea due to decreased tear function of tear glands (hyposecretive) or rapid evaporation of tears (hyperevaporative) [8, 9]. Hyposecretive dry eye includes Sjogren's syndrome and non-Sjogren's etiologies, mainly due to lacrimal dysfunction. Meanwhile, hyperevaporative dry eye causes tear film instability, accompanied by tear film hyperosmolarity which may be predominantly involved in inflammatory mechanisms [7, 10]. According to current knowledge, tear film hyperosmolarity induces a cascade of inflammatory events from the epithelial cell with potential damage to the ocular surface [6–8, 10]. Hyperevaporative dry eye may be intrinsic as a result of meibomian lipid deficiency, poor lid dynamics and low blink rate, and/or extrinsic because of vitamin A deficiency, allergic eye disease, contact lenses and the effects of drug use including toxic topical agents such as benzalkonium chloride and topical anesthesia [8].

In the literature, an association between headaches, particularly migraine, and inflammatory connective tissue

diseases has been described previously [11–14]. However, there is only one study available examining the link between migraine and dry eye [15], both of which are thought to have an inflammatory pathogenesis, at least in one aspect [2, 16]. In the published study by Koktekir et al. [15], an increased frequency of dry eye was found in migraineurs suggesting that migraine headaches are related to dry eye. In the present study, we investigated dry eye findings and any relationship with headache characteristics in migraine patients with and without aura.

Methods

Study population

In total, 58 migraineurs and 41 age- and gender-matched controls, from 18 to 50 years old, were enrolled in this cross-sectional prospective study, conducted in the Yozgat region of Turkey, in the winter of 2013. Patients with malignancies, chronic renal, hepatic or cardiovascular disease, diabetes, thyroid disease, psychiatric illness, inflammatory or autoimmune diseases such as Sjogren's syndrome, any kind of ocular disease including allergic eye disease and/or lacrimal dysfunction, a history of ocular trauma or surgery and use of certain medications, including antihistamines, decongestants, isotretinoin, artificial eye-drops, topical agents, oral contraceptives or anti-inflammatory drugs were excluded. Additionally, those who were pregnant, morbidly obese, current smokers or current consumers of alcohol and who wear contact lenses were excluded.

Patient medical histories, physical and neurological examinations were performed by the same neurologist. The migraine diagnosis was made according to the International Classification of Headache Disorders II diagnostic criteria [17]. Of the patients, 23 had migraine with aura, while the remainder had migraine without aura. The control subjects were healthy individuals with no headache of any kind. Migraine patients were evaluated according to headache characteristics, including severity, frequency and duration of the migraine attack, and duration of the disease. Based on a visual analog scale, the headache was defined as mild (score 1–3), moderate (4–6), severe (score 7–8) or very severe (score 9–10) [18]. Migraine headache attack frequency was noted in terms of the number of attacks per month [19]. The duration of the headache attack was defined in hours, whereas disease duration was in years. All patients were studied during a headache-free period and they were not on any medication. Routine laboratory analyses were performed for each subject using standard methods in our laboratory.

All patients and control subjects underwent a complete ophthalmologic examination by the same ophthalmologist. Anterior segment optical coherence tomography (Optovue Inc., Fremont, CA, USA)-derived tear meniscus height, tear meniscus depth and tear meniscus area were measured. Meibography, by using Sirius corneal topography machine (Costruzione Strumenti Oftalmici, Florence, Italy), tear breakup time with fluorescein stain (TBUT) and the Schirmer test under topical anesthesia using proparacaine hydrochloride (Alcaine 0.5 %, Alcon) were also assessed. At least 10 min of break was given between the tests. For the evaluation of symptoms, all of the patients completed the Ocular Surface Disease Index (OSDI) questionnaire. Schirmer test value <10 mm/5 min, TBUT shorter than 10 s and OSDI value higher than 33 were considered to be abnormal [8, 20]. Participants having at least two of these three criteria were defined as having dry eye [20] and in those in whom the apparent etiology was absent were described as idiopathic. Those who could not tolerate and/or complete the performed tests and, for control subjects, those who had dry eye symptoms and/or history of use of artificial tears were excluded from the study pool.

The study protocol was approved by the Bozok University Local Research Ethics Committee. Written informed consent was obtained from all participants.

Statistical analysis

A Shapiro–Wilk's test, histograms and q–q plots were used to test the normality of the data and Levene's test was used to assess variance homogeneity. Independent-sample t tests and Mann–Whitney U tests were used to compare differences between continuous variables, and Chi-squared (χ^2) analyses were used to assess differences between categorical variables. Values are expressed as frequencies and percentages, means and standard deviations, or medians and interquartile ranges. Among the headache characteristics, univariate and multiple binary logistic regression analysis was performed to identify the predictors of dry eye in migraine patients. For each factor, odds ratios (OR) were calculated with 95 % confidence intervals (CI). Analyses were conducted using the SPSS software (ver. 15.0; SPSS Inc.; Chicago, IL; USA). Statistical significance was set at $p < 0.05$.

Results

The demographic and laboratory data of the migraine patients and controls are summarized in Table 1. No significant difference was found between the groups with respect to age or gender ($p > 0.05$). The two groups were also similar with respect to all laboratory results

Table 1 Demographic and laboratory data of migraine patients and controls

Variables	Control ($n = 41$)	Migraine ($n = 58$)	p
Age (years)	28.3 ± 7	29.4 ± 6.1	0.404
Gender (female/male)	38 (92.7)/3 (7.3)	55 (94.8)/3 (5.2)	0.660
FG (mg/dL)	87 (81–93)	89 (86.7–92.2)	0.188
Creatinine (mg/dL)	0.71 (0.68–0.75)	0.72 (0.66–0.79)	0.929
WBC (10^3/mm^3)	6.9 ± 1.5	7.2 ± 1.5	0.294
Hemoglobin (mg/dL)	12.9 (12.2–13.5)	12.6 (12–13.6)	0.504
Platelet (10^3/mm^3)	252.5 ± 49.6	266.2 ± 52.4	0.193
AST (IU/L)	15 (13–17.5)	17 (14–19)	0.195
ALT (IU/L)	13 (10–16)	14 (11–17)	0.153
TC (mg/dL)	157.5 ± 33.3	190.2 ± 35.1	<0.001
TG (mg/dL)	76 (58–102)	114.5 (73.2–146)	0.005
HDL-C (mg/dL)	45.2 ± 7.1	48.3 ± 8.4	0.054
LDL-C (mg/dL)	97.9 ± 26.5	117.1 ± 28.7	0.001
TSH (μIU/mL)	1.5 (1.1–2)	1.7 (1.2–2.2)	0.224
Dry eye (absent/present)	20 (48.8)/21 (51.2)	22 (37.9)/36 (62.1)	0.282

Values are expressed as n (%), mean ± SD or median (25th–75th percentiles)

FG fasting glucose, *WBC* white blood cells, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TSH* thyroid-stimulating hormone

($p > 0.05$), except for higher lipid profile in migraineurs than in controls ($p < 0.05$) with no statistical difference in those with or without dry eye. The presence of dry eye was higher in migraineurs as compared to the control group, but this did not reach statistical significance ($p = 0.282$; Table 1). Among the headache characteristics, the presence of aura was significantly higher, as well as disease and attack durations were significantly longer in migraineurs with dry eye than in those without dry eye ($p = 0.009$, $p = 0.010$, and $p = 0.003$, respectively; Table 2). In multiple logistic regression model, attack duration was found to be independently associated with the presence of dry eye in migraine patients (OR; 95 % CI; $p = 0.029$; Table 3).

Discussion

Two main findings emerged from the present study. First, a greater presence of dry eye was found in migraineurs than in controls, with no statistical difference. Second, greater presence of auras and longer disease and attack durations were found in migraineurs with dry eye than in those without.

Table 2 Comparison of headache characteristics among migraine patients with and without dry eye ($n = 58$)

Variables	With dry eye ($n = 36$)	Without dry eye ($n = 22$)	p
Aura (absent/present)	17 (47.2)/19 (52.8)	18 (81.8)/4 (18.2)	0.009
Disease duration	10.00 (6.00–14.00)	6.00 (3.00–9.25)	0.010
Attack severity	7.00 (6.00–8.00)	8.00 (6.00–8.00)	0.248
Attack frequency	4.00 (3.25–7.00)	4.00 (2.00–7.25)	0.509
Attack duration	72.00 (48.00–72.00)	24.00 (24.00–72.00)	0.003

Values are expressed as n (%) or median (25th–75th percentiles)

Table 3 Univariate and multiple logistic regression analysis to predict dry eye in migraine patients

Variables	Univariate		Multiple	
	OR (95 % CI)	p	OR (95 % CI)	p
Aura (absent/present)	5.03 (1.42–17.83)	0.012	–	–
Disease duration	1.10 (0.99–1.22)	0.060	–	–
Attack severity	0.78 (0.52–1.17)	0.238	–	–
Attack frequency	1.07 (0.85–1.35)	0.552	–	–
Attack duration	1.04 (1.01–1.07)	0.003	1.04 (1.004–1.07)	0.029

OR (95 % CI) odds ratio and 95 % confidence intervals

In recent years, migraine headaches have been reported to be associated with some inflammatory connective tissue diseases [11–14]. This association might be attributed to the endothelial cell dysfunction triggered by an inflammatory status in the vascular bed rather than having an underlying nature of chronic disease [14]. In this respect, we have speculated that the inflammatory status in migraine could work together with a similar inflammation in other body parts, such as the eyes, so as to have a relation with dry eye. According to current knowledge, migraine and dry eye are thought to be inflammatory states, at least in one aspect [2, 16]. Migraine is defined as a neurogenic inflammation involving the process by which inflammatory mediators, including neuropeptides, are released from afferent nerve terminals and trigger inflammation with plasma extravasation and hypersensitivity at the trigeminal ganglion neurons [21, 22]. Also, there is strong support for a similar role of neurogenic

inflammation in ocular surface diseases [16]. The ocular surface, which is constituted by cornea, conjunctiva, lacrimal glands and tear film, involves the most densely innervated tissue of the human body, particularly the cornea, and therefore represents a preferential target of a neurogenic inflammation [16]. Dry eye, especially with a hyperevaporative underlying pathology, causes tear film instability, accompanied by tear film hyperosmolarity which induces a cascade of inflammatory events from the epithelial cell with potential damage to the ocular surface [6–8, 10]. The hyperosmolarity-induced nociceptive nerve terminals reaching the conjunctival epithelium may further lead to peripheral sensitization and stimulation, which consequently result in neurogenic inflammatory responses by the release of neuromediators in inflamed tissues [16, 23].

In the literature, Koktekir et al. [15] first reported a significantly increased frequency of dry eye in a small group of migraineurs compared to the controls, suggesting a relation between these two conditions. For dry eye testing, they performed four diagnostic tests, including TBUT, Schirmer test, lissamine green staining and an OSDI score in 33 migraine patients and found significant differences in dry eye scores between the two groups. In addition to those tests, we performed supportive tests, such as tear meniscus measurements and meibography in a larger study group. Tear meniscus measurement is a noninvasive method in association with tear deficiency [8]. In the recent report by Altan-Yaycioglu et al. [24], tear meniscus dimensions were found to be positively correlated with Schirmer values and was suggested as being reliable for establishing a diagnosis of dry eye. Also, meibomian gland dysfunction, which results either from an altered composition of meibum or outflow obstruction of the gland, is the major cause of lipid anomaly and consequently of the evaporative dry eye [25]. Regarding this, meibography has been recommended to predict dry eye in several studies [26, 27]. In this study, we found a greater presence of dry eye in migraineurs than in controls, albeit not reaching statistical significance. We also made a secondary analysis regarding the correlation between dry eye and headache characteristics. We found greater presence of auras in migraine patients with dry eye than in those without. Current data suggest that aura seems to be a higher risk factor overall for ischemic vascular disorders [28, 29]. The reason for this can be explained through the idea that spreading oligemia during aura may lead to subclinical ischemia, resulting in the secretion of proinflammatory molecules in the vascular wall which is linked to vasculopathy [30]. In this sense, we may hypothesize that migraine patients with dry eye have a higher experience of aura, possibly indicating the increased risk of vasculopathy through the inflammatory cytokines during aura, which essentially needs basic science studies on this missing data. Additionally, we found longer disease and attack durations that mean a greater morbidity in migraineurs with dry eye than in those without. Based on this result, we may speculate that some migraine attacks may be prolonged by the presence of dry eye, maybe via the prolonged inflammatory pathways. Accordingly, an important question arises for confirming the hypothesis: whether the treatment of dry eye can shorten the attacking disability or not in migraineurs; all of this requires further research. On other hand, we found higher lipid profile in migraineurs than in controls with no statistical difference in those with or without dry eye. With respect to the importance of the lipid layer in tear film, systemic dyslipidemia may theoretically affect local lipid biosynthesis, such as the meibomian lipid composition [31]. Some epidemiologic data have already reported such an association between high serum cholesterol levels and dry eye [25, 31]. However, in the current study, these levels did not differ between the groups with and without dry eye among the migraine patients, which may be linked to the sample size.

Our study has some limitations. First, it is necessary to validate these findings with a larger cohort to reach a more definitive conclusion. Second, we performed the tests only in the attack-free period, whereas repeated measurements ictally and interictally may provide a more accurate picture of the underlying mechanisms. Third, we did not evaluate the effects of treatment for dry eye on attack disability in migraineurs.

Conclusions

The results of this study show that dry eye may present in migraine patients with greater presence of auras and longer disease and attack durations. Based on the present findings, we might hypothesize that migraine has a relation with dry eye and is more than just coincidence. However, we could not specify whether these two conditions represent a spectrum of one entity or rather are causative factors of each other. Future large-scale longitudinal studies that overcome the current study's limitations are needed to confirm our findings, as well as to clarify the actual underlying mechanisms of this relationship.

Conflict of interest None.

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