Original Article

# Alterations in the tear film and ocular surface in pediatric migraine patients

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**Purpose:** To evaluate the ocular surface (OS) parameters in the pediatric migraine patients (PMPs). **Methods:** This prospective case–control study consisted of 51 PMPs (PMP group) and 55 healthy pediatric patients (HPP group). In all participants, tear function was evaluated subjectively using the Ocular Surface Disease Index (OSDI) questionnaire, objectively using Schirmer tear test (STT) and tear film disintegration time (TBUT), and with clinical and laboratory examinations (conjunctival impression cytology). The PMP group was subdivided into two groups according to their aura. **Results:** The mean age and gender distribution of the study groups were almost the same ($P > 0.05$ for both of them). In the PMP group, both the STT value and the TBUT value were significantly lower than those determined in the HPP group ($P = 0.021$ and $P = 0.018$, respectively). In the PMP group, the OSDI scores were higher than those in the HPP group ($P = 0.032$). In the PMP group, the goblet cell density values were lower than those in the HPP group ($P = 0.01$). With regard to the aura, the TBUT and STT values were nonsignificantly lower in the PMP aura-positive group than in the PMP aura-negative group ($P > 0.05$ for both of them). The OSDI assessment was similar in both the groups. With regard to the goblet cell count, it was observed to be less in the PMP aura-positive group than in the PMP aura-negative group ($P = 0.01$). **Conclusion:** Influence of OS in children with migraine was also demonstrated using the samples taken from the conjunctiva. These changes were also demonstrated by objective tests such as STT and TBUT. Both clinical objective evaluations and pathologic changes were more prominent in the migraine with aura group.

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Although a throbbing headache is mainly observed in migraine, it is a neurologic disease in which nausea, vomiting, mood changes, and a hypersensitivity toward environmental factors are observed.[1] The most common types of headaches in children are usually migraine and tension headaches.[2] As for migraine, the prevalence, reported as 3% during the preschool period, increases over time and reaches 8%–23% after secondary school.[3-5] In the 8-year-old patient population, migraine prevalence is nearly equal among females and males, and in older age groups, males have it lesser than females.[6]

In migraine, there are headaches first, sensitivity to light and sound, dizziness, and increased pain while performing physical activity and increased aura.[7,8] In these patients, bright scotoma and blurred vision are the most predominantly seen visual symptoms, especially with aura, and this is followed by somatosensory symptoms such as slow speech, dyspraxia, and hand numbness.[9] Fatigue, emotional changes, and stiffness in the neck are the commonly seen premonitory symptoms in pediatric migraine.[10] At the same time, postdrome symptoms such as thirst, extreme drowsiness, disturbances in vision, cravings, paresthesia, and pain in the eyes are seen in 80%–85% of patients in this population.[11] Migraine is a chronic disease that includes both neuronal and vascular mechanisms, the pathophysiology of which has not been fully elucidated.[12] Another point of view is that there is a basis for neurovascular inflammation in brain vessels.[12,13] High levels of both interleukin and inflammatory cytokines were detected, especially during interictal periods and acute migraine attacks.[14] Deteriorated tear homeostasis on the ocular surface (OS) may be the cause of dry eye (DrE), which is characterized by symptoms of irritation. Increased evaporation of the tears and ocular as well as systemic pathophysiologic mechanisms are responsible for hyperosmolarity.[15] The reason why some researchers have opined that a connection exists between migraine and tear function is that migraine has a complex pathophysiology that includes neuronal and vascular mechanisms. There are no studies on this in the pediatric population in the literature.

## Methods

### Ethics approval

The current work is a prospective case–control study conducted together in the Department of Pediatric Neurology and Ophthalmology of a tertiary university hospital. All

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applications made within the scope of this research content adhered to the Declaration of Helsinki. The study protocol was given approval by the institutional committee, which is part of the local ethics committee for the clinic at which the study was performed. All study participants, in addition to their parents, gave the necessary informed consent in a written form before being accepted for enrollment into the study.

### Inclusion and exclusion criteria and examinations

Pediatric migraine patients (PMPs) with and without aura who were referred from the pediatric neurology clinic and who had applied to the eye clinic consecutively comprised the PMP group, and healthy pediatric patients (HPPs) who had consecutively applied to the eye clinic comprised the HPP group as controls. Of the 106 subjects, 106 eyes, including 51 eyes of 51 PMPs and 55 eyes of 55 age-/sex-matched HPPs, were included as the study population.

Migraine severity was determined by a disability questionnaire called the Pediatric Migraine Disability Assessment Score, or the pedMIDAS, which was administered to pediatric patients by a pediatric neurologist.[16] The demographic structure and clinical data of the patients were evaluated. Migraine type, disease duration, number and duration of attacks (every 3 months), and accompanying symptoms (nausea, vomiting, photophobia, phonophobia) were recorded. The migraine group consisted of newly diagnosed individuals and those who did not take any medication other than analgesics within 24 h.

The PMP group was divided further into two subgroups according to the presence of aura. Those with migraine with aura were designated as the PMP aura-positive group, while those with migraine without aura were designated as the PMP aura-negative group. The control group was formed of age- and gender-matched healthy children who came for annual routine check-ups (the HPP group).

Inclusion criteria set for the study participants were given approval by a pediatric neurologist (RI) and an ophthalmologist (EA). Participants who were aged younger than 6 or older than 18 and those with various systemic diseases, such as hypertension, autoimmune disease, thyroid disease, or heart disease, were excluded from the study. The criteria set for ocular exclusion comprised the following: a history of any kind of ocular surgery or a corneal pathology or trauma, visual acuity <20/20, choroidal disease or an optic disc disorder, refractive error of >±1 D, an axial length of >24 mm, and an intraocular pressure (IOP) of >21 mmHg.

In the routine ophthalmologic examination of the patients who participated in the study, first, visual acuity (Snellen) measurement was performed; then, IOP was measured using pneumatometer, and an anterior segment as well as a fundus examination was done via slit-lamp biomicroscopy, respectively.

### Ocular Surface Disease Index score

The Ocular Surface Disease Index (OSDI) questionnaire, with a standardized content of 12 items specified by the Allergan Inc. Outcome Research Group (Irvine, CA, USA), was used to assess both rapidly and reliably the symptoms of irritation on OS in participants. The pediatric patients accepted for participation in this study were instructed to complete the OSDI form before any ophthalmologic examination was performed. Pediatric participants evaluated and filled out the questionnaire without any time limit and without any help from the relevant ophthalmologist. An experienced ophthalmologist (Dr. EA) explained the questions from the questionnaire to all pediatric participants. They were asked to grade the scores as 0–1–2–3–4 points: 0 for "never" and 4 points for "always" as answers. After completing the questionnaire, calculation of the OSDI score was done using the following formula: [(the sum of the scores/the total number of questions that were answered) ×25].[17]

### Tear film break-up time

Thirty minutes after the ophthalmologic evaluation, Schirmer tear test (STT) and tear film break-up time (TBUT) tests were performed with anesthesia. In the TBUT test, fluorescent staining of the cornea of the patients (ERC Medical Products, Ankara, Türkiye) was performed and then, they were instructed to blink three times consecutively. After using a fluorescent dye solution on OS, their tear film was evaluated with slit-lamp microscopy. The time was measured from the moment the two eyelids were opened after the third blink until a dry spot first became visible in the cornea. The average of three measurements taken consecutively was considered TBUT. Patients with a TBUT of less than 10 s were evaluated for dry eye disease (DED).

### Schirmer tear test

A strip of Whatman #41 filter paper (ERC Medical Products), standardized for use in STT, was placed in the area close to the lateral canthus. It remained there for 5 min until wetting of the filter paper, and after the time expired, the amount of wetness on the filter paper was measured in millimeters. This value was recorded as the result of STT.

### Conjunctival impression cytology

First, 5 mg (5%) of proparacaine HCl (Alcaine; Alcon Laboratories, S.A. Alcon-Covreur N.V. Puurs, Bornem, Belgium) drops was applied to the patients for anesthetic purposes. Then, a previously cut 4 × 5 mm piece of cellulose nitrate filter (Whatman; GE Healthcare, Chicago, IL, USA) was placed approximately 4–5 mm from the cornea of the bulbar superotemporal conjunctiva.

The filter was pressed lightly, and then, after about 5 s, it was removed from the conjunctiva using a pair of forceps. Afterward, the samples were placed in small tubes that contained a solution of 95% ethanol and were stained manually using periodic acid Schiff (PAS) stain. In the last step, the conjunctival impression in the cytological specimens stained with PAS was blindly examined by a pathologist (Dr. BAT) under a light microscope. Pathologist microscopic examination was performed with the Nelson scoring system, which is based on epithelial cell morphology and the goblet cell count and is graded from 0 to 3 according to Nelson's classification[18] [Fig. 1].

### Statistical analysis

IBM Statistical Package for the Social Sciences Statistical program for Windows version 24.0 (IBM Corporation, Armonk, NY, USA) was used to conduct all the statistical analyses. The participants' right eyes only were included for use in the statistical analyses. Histograms and probability plots, in addition to analytical methods that included the Kolmogorov–Smirnov test and the Shapiro–Wilk test were utilized when testing the normality of data. The results that were obtained

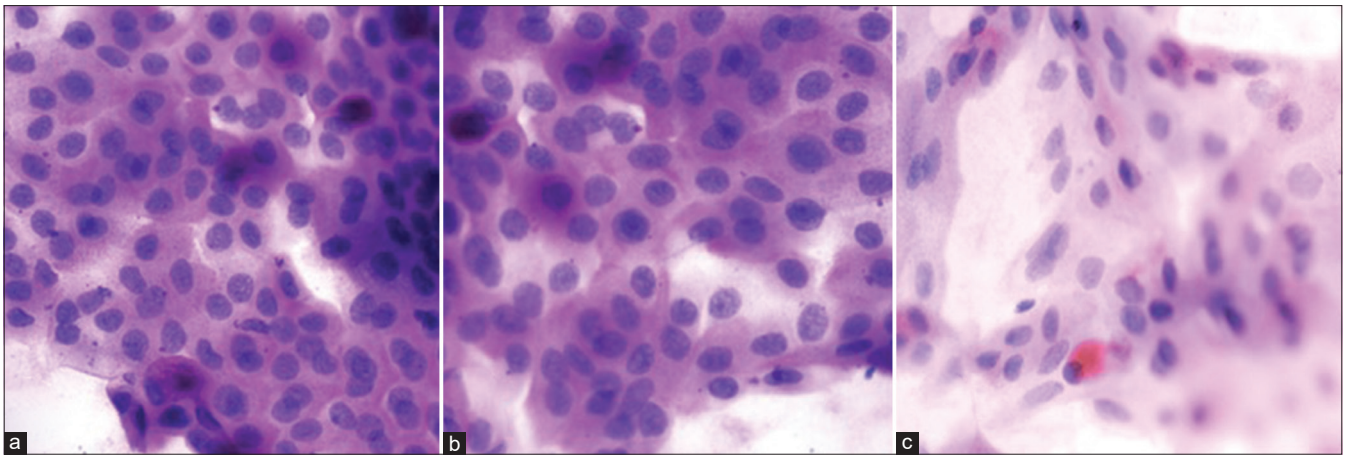


**Figure 1:** (a) Control group (higher goblet cell number), Grade 0. Conjunctival epithelium and goblet cells took on cellulose paper by impression cytology. (b) Pediatric migraine patients without aura, Grade 0. Conjunctival epithelium and goblet cells took on cellulose paper by impression cytology. (c) Pediatric migraine patients with aura, Grade 1. Conjunctival surface epithelial cells with a nucleus: cytoplasm ratio of 1:2–3 with decreased number of goblet cells

from the descriptive analyses were presented as mean and standard deviation (SD). For pairwise comparison of the study groups, Student's *t*-test was used in the analysis of normally distributed variables, whereas the Mann–Whitney U-test was used for abnormally distributed variables. The Chi-square test was utilized for comparison of the categorical variables. $P$ <0.05 was considered to be statistically significant in all measurements.

## Results

The PMP group consisted of 51 participants, while the HPP group consisted of 55 participants. The mean age in the PMP group was 14.25 ± 2.35 (10–17) years, whereas that in the HPP group was 13.13 ± 2.86 (10–17) years. The male/female ratio (RM/F) in the PMP group was 21/30 and in the HPP group was 21/34. There was no significant difference in the demographic characteristics of the PMP and HPP groups ($P$ > 0.05 for both of them). When considering the sample size of the PMP group subgroups, it was 11 in the PMP aura-positive group and 40 in the PMP aura-negative group. The mean ages and RM/Fs were also not that different between the PMP group subgroups ($P$ > 0.05 for both of them).

While the mean TBUT and STT values in the PMP group were lower in comparison to those in the HPP group, with statistical significance ($P$ < 0.05 for all of them), the OSDI scores were nonsignificantly higher ($P$ = 0.123) [Table 1].

In the cytologic assessment of the conjunctiva, seven of the 58 samples in the PMP group were excluded. Of these, three had insufficient cells and four were insufficiently stained. Moreover, 51 sufficient samples were assessed and of these, 11 were grade 1 and 40 were grade 0. The mean goblet cell density (GCD) was 238.7 ± 152.5 cells/mm$^2$ in the PMP group. In the HPP group, four of the 59 samples were excluded due to insufficient material. Thus, 55 samples were evaluated: five as grade 1 and the rest as grade 0. The mean GCD was 399.2 ± 165.06 cells/mm$^2$. The GCD values in the PMP group were lower in comparison to those in the HPP group ($P$ < 0.001) [see Table 1]. A detailed analysis of the OS parameters of those in the PMP subgroups is presented in Table 2.

## Discussion

DED is a multifactorial OS disease that is also known to occur with other ocular symptoms, tear film homeostasis imbalance/loss, OS damage, as well as inflammation, in addition to neurosensory abnormalities which are involved in its etiology.[15] In ophthalmology, histopathologic studies for diagnostic purposes in OS-related diseases have been increasing in recent years. The findings of this current study might provide important information about the pathogenetic effects of migraine on OS in pediatric patients diagnosed with migraine.

Currently, in the literature, there is not a high volume of articles evaluating tear function in adult migraine patients.[15,19] The OSDI questionnaire, TBUT, STT, and conjunctival impression cytology (CIC) were evaluated in the current study by dividing pediatric patients with migraine into subtypes as migraine with and without aura to investigate whether or not OS changes developed in children diagnosed with migraine and then compare the results obtained with those of healthy children. With CIC, morphologic, cytologic, and immunocytologic changes associated with DrE can be analyzed by taking samples from the conjunctival surface.[20] With this method, it is possible to detect OS changes like squamous metaplasia or goblet cell loss during the early stages.[16,21] When the pathologic materials taken were grouped according to Nelson classification, grades 0 and 1 were normal and grades 2 and 3 were considered abnormal.[17]

Among the important aspects of our research was our investigation of cytologic changes in pediatric patients with migraine by CIC, which has been recommended by some researchers as the gold standard when testing for DED. The findings of this current study might provide important information about the pathophysiologic effects of migraine on tear functions in pediatric participants.[15]

Findings obtained in this current study showed that there were no participants who had abnormal cytology such as grade 2 and grade 3. A decrease that was statistically significant was seen in GCD in both the PMP subgroups compared to the HPP group. Some of the patients in the PMP group exhibited

**Table 1: Details of the clinical and laboratory assessments**

| | PMP group (*n*: 51) | HPP group (*n*: 55) | *P*[a] |
|---|---|---|---|
| Clinical findings | | | |
| Median Tf-BUT (s) | 11.8 (6–17) | 14.8 (9–20) | **0.006** |
| Median Schirmer-1 (mm) | 9.6 (5–17) | 11.4 (6–19) | **<0.001** |
| Median OSDI score | 12.2 (9–23) | 9.4 (4–18) | 0.123 |
| Impression cytology | | | |
| Grade (categorical [0/1/2/3])[b] | 40/11/0/0 | 50/5/0/0 | **<0.001**[c] |
| Median grade | 0.6 (0–3) | 0.3 (0–2) | **0.044** |
| Mean goblet cell count | 325.9±180.5 (90–600) | 410.3±190.5 (120–850) | **<0.001** |
| Median neutrophil count | 0.7 (0–19) | 0.3 (0–15) | 0.450 |
| Median lymphocyte count | 0.1 (0–2) | 0.1 (0–2) | 0.897 |

HPP=healthy pediatric patients, OSDI=Ocular Surface Disease Index, PMP=pediatric migraine patients, Tf-BUT=tear film break-up time. [a]Independent *t*-test. [b]Grades 0 and 1 are considered normal and grades 2 and 3 are considered as abnormal. [c]Chi-square test. Bold values indicate statistically significant values.

**Table 2: Comparison of clinical and laboratory evaluations between the subgroups**

| | PMP aura-positive group (*n*: 11) | PMP aura-negative group (*n*: 40) | *P*[b] |
|---|---|---|---|
| Median Tf-BUT (s) | 11.6±3.1 | 12.1±4.2 | 0.450 |
| Median Schirmer 1 (mm) | 8.9±4.8 | 10.7±4.1 | 0.064 |
| Median OSDI score | 13.1±4.3 | 11.8±3.8 | 0.530 |
| Grade (categorical [0/1/2/3])[a] | 7/4/0/0 | 33/7/0/0 | **<0.001** |
| Median grade | 0.7±0.86 | 0.5±0.63 | 0.072 |
| Mean goblet cell count | 315.9±192.9 | 370. ± 144.9 | **0.02** |
| Median neutrophil count | 0.9±2.2 | 0.5±1.9 | 0.128 |
| Median lymphocyte count | 0.1±0.9 | 0.1±0.7 | 0.890 |

OSDI=Ocular Surface Disease Index, PMP aura-negative group=pediatric migraine without aura), PMP aura-positive group=pediatric migraine with aura, Tf-BUT=tear film break-up time. Results are denoted as the mean±standard deviation. [a]Grades 0 and 1 are considered as normal, and grades 2 and 3 are considered as abnormal. [b]Paired *t*-test. Bold values indicate statistically significant values

grade 1 cytology, which was characterized by the presence of epithelial cells that were slightly large and polygonal, a nucleus-to-cytoplasm ratio of 1/3, and a GCD which showed a slight decrease.

There may be several reasons why CIC on OS did not change as morphologic grades 2 and 3 in participants in the PMP group: 1) as the study population was made up of pediatric patients, morphologic changes on OS may not have occurred yet, since the disease duration was shorter; 2) it may be that the regeneration capacity of cells in the pediatric population is higher than in the adult population, and that the regeneration ability has prevented changes in the conjunctival morphology; 3) due to the nature of our study, it may be that we did not choose to include patients diagnosed with DED who were morphologically grades 2 and 3. Another important finding of this study was that the histopathologic abnormalities as well as the GCD exhibiting a decrease were strongly associated with migraine with aura. The low TBUT and STT values found in children with migraine were also supported by histopathologic findings in the conjunctival material taken.

In the literature, it has been shown that DED that is immune mediated and/or inflammatory can occur in adult patients with migraine.[19] The histopathologic abnormalities and decreased goblet count observed in CIC in this study can be considered as the causes of migraine causing inflammatory pathways, which may, in fact, play a role in changes seen in clinical manifestations related to tear function in children.

Mucin, water, and lipid are the main constituents making up the tear film. Pediatric patients with migraine are at risk of adverse effects on these components. The low STT results in our study may be related to lacrimal gland dysfunction (GD), which is the gland in control of secreting the watery parts of tear film. The cornea is densely packed with nerves, which transverse along the path of the ophthalmic section of the trigeminal nerve. Some animal studies have suggested that the decreased tear secretion may have a connection with the decreased trophic effect from the trigeminal sensory nerves that are located on the cornea and conjunctiva.[22] In another study, it was shown that the length as well as the density of the trigeminal nerve fiber decreased in patients diagnosed with migraine.[23] The low STT results in our study may be the effect of a reduction in the excitatory signals coming from OS and going to the lacrimal gland as a result of decreased corneal sensation.

The TBUT test shows any instability that is present in the tear film. This test is not just for the absence of the film's aqueous layer, but also for the deficiency of the mucin and/or lipid component of the film which is produced via the meibomian glands as well as the conjunctival goblet cells. Low TBUT test values may also be related to the decrease in goblet cells and the resulting decrease in mucin content. Another possible reason for the low TBUT values in these patients may be the effects of lipid metabolism detected in patients with migraine.[24] The lipid layer protects against premature film evaporation and ensures its continuity. Another possible mechanism for the low

TBUT values in these patients is thought to be associated with an accompanying lipid layer disorder and meibomian GD in pediatric patients with migraine.[24]

Meibomian GD should be taken into consideration as possibly being a mechanism for these changes in OS associated with PMPs and DED. However, the validity of this hypothesis should be tested with further investigations such as meibography, with further studies investigating the association with PMPs and DED at longer follow-up.

According to the consensus in both literature and ophthalmology practice, detection of TBUT results <10 s and STT results <5 mm is considered to be in favor of DED. According to the results obtained in the current study, although the measurements for STT and TBUT were not high in the children diagnosed with migraine, the median values obtained for these groups were not considered to be low enough to be seen as abnormal for either test or to diagnose DED.

However, it is of high importance to detect early changes in objective clinical examinations related to tear function, especially when taking into consideration the chronic course of DED starting from the point of diagnosis until the end of the patient's life.

Koktekir *et al*.,[25] with 33 adult migraine patients and 33 control patients, and Sarac *et al*.,[19] with 46 adult migraine patients and 50 control patients, found statistically significantly lower TBUT and STT values in adult patients with migraine. Similarly, Celikbilek and Adam[15] found lower TBUT and STT values in adult patients with migraine, although it was not statistically significant. In this context, the findings obtained in the current study, which consisted of pediatric participants, are quite consistent with the results reported in the literature. Another important outcome determined in our study was that worse STT and TBUT values were seen in the PMP aura-positive group. These results are in agreement with previous studies. Although all these studies were performed on adult participants, results of this study have indicated that one should expect to see similar effects in pediatric participants with migraine. The strength of this study is that it evaluates DrE parameters in pediatric participants diagnosed with migraine and is the first study on this subject.

When the OSDI scores are evaluated, there are two possible outcomes: first, values of 0–25 are normal and second, values >25 are considered to be in favor of DED. OSDI is a clinician's quantitative measure of the effects of DrE-related ocular irritation symptoms, consisting of subjective assessments of the patient to assess how severe the DrE is. Schiffman *et al*.[17] reported a specificity of 79% and a sensitivity of 60% for the OSDI questionnaire. The sample of the current research did not include DrE patients. Moreover, the OSDI scores recorded in both the groups were well within a normal range. In this study, the results of the OSDI scores and the objective test results, like TBUT and STT, which were determined to be worse in the participants diagnosed with migraine, were not combined. There could be several reasons for this situation. The first reason may be that the patients in the study group consisted of a pediatric population. A study conducted by Han *et al*.[26] showed that children diagnosed with DrE may not exhibit the same number of symptoms as adults diagnosed with similar DrE conditions. A possible explanation for this might possibly be that children may not have the same level of discomfort or pain, and therefore, they may describe the discomfort caused by OS disorder less.[26] Second, it may have something to do with the method in OSDI scoring having a subjective nature and the fact that the sample was not made up of actual DrE patients. Also, this is not that unusual because in previous studies, some researchers reported a discrepancy similar to this between the OSDI score and tests like TBUT and STT.[17]

Although the pathogenesis of migraine has not been clarified, it is thought to be a type of neurovascular headache.[19] Neural events have an effect on blood vessels by causing them to dilate, exacerbating pain and leading to greater activation of the nerves.[27] Trigeminovascular input coming from the meningeal vessels is the main pain pathway. However, the exact mechanism by which migraines are triggered and the sequence of events after being activated have not yet been fully understood. The cornea is made up of very densely packed trigeminal nerve endings that are believed to have involvement in the process of headaches with pain.[28] Kinard *et al*.[23] conducted an investigation of the structural differences occurring in corneal nerve plexuses in patients diagnosed with chronic migraine by *in vivo* corneal confocal microscopy. The density and length of nerve fibers were found to be lower in patients diagnosed with migraine than in healthy individuals in their study. These results are supportive of the hypothesis that the trigeminal system has a vital role in the way in which migraines develop.[19] These findings showed consistency with the results obtained for CIC, STT, and TBUT, which were determined to be more significant in the aura-positive migraine patients in our study. Future studies with a focus on treatments for objective DrE in patients diagnosed with migraine, and especially with aura-positive migraine patients, may be able to reveal clearer insight regarding this connection.

Compared to the literature, the patient population was pediatric, and the patients were grouped as aura-positive migraine patients and aura-negative migraine patients, which were the strengths of this research. This study expands our knowledge on this subject and makes two important contributions to the literature: 1) although there is no DrE in patients diagnosed with migraine, DrE may start in the pediatric period, especially in the aura-positive migraine patients, and 2) contrary to previous studies, it is important to remember that not only adult population, but also pediatric population with migraine may have DrEs. Based on this information, possible DrE findings should be considered, especially in pediatric patients with migraine resistant to conventional treatments.

The limitations of our study are as follows: meibography, *in vivo* confocal microscopy, and the absence of tear film osmolarity were not used. In addition, whether the diseases are acute or chronic does not have the same effect on tear function. Conducting a subgroup analysis with the aim of determining the duration of migraine in patients could provide important insight regarding the risk that is associated with OS damage. As far as we have been able to determine, this study represents the first research to have evaluated tear function parameters in pediatric patients with migraine and divided and evaluated pediatric patients based on whether they were aura positive or aura negative. Examination of tear function by subjective (OSDI questionnaire), objective (STT and TBUT),

clinical and laboratory investigations (CIC), and then reporting these results comprise the important strengths of this work.

In summary, changes occur in OS in children diagnosed with migraine. These changes are also demonstrated by the STT and TBUT measurements and histopathologic evaluation from the conjunctiva. Significant changes in the histopathologic as well as clinical findings are seen more prominently, especially in aura-positive migraine patients.

## Conclusion

In our study, histopathologic evaluations in pediatric migraine were supported by objective and subjective results.

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