Original Article

Morphological changes in the meibomian gland in children with tic disorders

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Background: Since blinking accelerates meibomian gland (MG) expression, abnormal blinking in children with tic disorders may be associated with the morphological changes of the MGs. Our study aimed to quantitively evaluate the morphology of the MG in these children.

Methods: In this prospective case-control study, we examined 68 eyes of 68 children with tic disorders, 47 eyes of 47 children with dry eye, and 45 eyes of 45 healthy children at the Hangzhou Branch of the Eye Hospital of Wenzhou Medical University from October 2020 to March 2021. We used an Oculus Keratograph 5M (K5M) to capture the MG images, noninvasive breakup time (NIBUT), and tear meniscus height (TMH). An automated method was used to analyze MG length, width, area, gland diameter deformation index (DI), and gland signal index (SI). Parameters across the three groups were assessed using Kruskal-Wallis test followed by Mann-Whitney test with Bonferroni correction for multiple comparisons.

Results: The eyes in the tic disorders group exhibited lower MG length and area values compared with those of the other groups (all P values <0.001) and lower MG width values compared with those of children in the dry eye group (P=0.009). The tic disorder and dry eye groups both had a larger percentage of eyes with a U-shaped MG duct when compared with the control group (P<0.001 and P=0.017). The dry eye group had the lowest TMH and NIBUT values (both P values <0.001). The NIBUT values in the tic disorder group were lower than those in the control group (P<0.001). No significant correlations were detected between clinical tests and MG morphology in any of the groups.

Conclusions: Blinking disorders have a significant impact on MG morphology. In children with tic disorders, more attention should be devoted to monitoring the MG over time.

Keywords: Meibomian gland dysfunction (MGD); MG morphology; tic disorders; children; blinking

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Introduction

Tic disorders are common neuropsychiatric disorders in children and often exhibit recurring outbreaks. One meta-analysis reported the worldwide prevalence rates of transient and chronic tic disorders to be 2.99% and 1.61%, respectively (1), while, the prevalence rates of transient and chronic tic disorders in the Chinese population have been reported to be 1.7% and 1.2%, respectively (2).

Initial signs of tic disorders in children include increased blinking rate and eye-blinking tics, which are typically combined with dry eye (3,4). Meibomian glands (MGs) are sebaceous glands on the eyelids, and their function is to secrete meibum to the ocular surface. Blinking is a rapid eyelid movement that helps generate a smooth tear film and accelerates MG expression (5). The meibum secreted by the MGs constitutes the lipid layer of the tear film and plays a vital role in maintaining tear film stability (6,7). In children younger than 12 years old, meibum is more fluid due to a lower cholesteryl to wax ester ratio (8). MG dysfunction (MGD) is considered to be the main cause of evaporative dry eye, which appears as an abnormal quantity and quality of meibum (6). Blinking abnormalities influence meibum secretion and, in the long-term, cause MGD (3,4,9). Jie *et al.* (3) reported decreased tear breakup time, increased ocular surface disease index (OSDI), and an increased risk of MGD in adults with abnormal blinking. Meanwhile, incomplete blinking, prolonged eyelid closed time, and short blink intervals were also reported to be characteristics of blinking in adults with dry eye disease (DED) (10). Similarly, abnormal blinking in children may be linked to morphological changes in MG and eventually lead to MGD.

In recent years, morphological alterations in MG in individuals with MGD have received considerable attention (11-14). In most previous studies, MG atrophy was assessed as the main indicator of MG morphology. However, few studies have assessed the specific characteristics of MG structure. On the basis of meibographs taken by a "portable non-contact infra-red meibograph" (15), Pult *et al.* (16) found that the MG thickness and bent angle of the upper lid were related to shorter noninvasive breakup time (NIBUT). Liang *et al.* (11) detected a decrease in MG length and width in patients with MGD using optical coherence tomography meibography. It has been further reported that the early stages of MGD can be successfully indicated by morphological alteration of the MG, which can include shortening, dilation, distortion, and atrophy (12,13). In a previous study, we identified five unique MG shapes (vertical, tortuous, overriding, hooked, and U-shaped) in asymptomatic children, suggesting that the assessment of MG morphology might be a useful diagnostic tool for MGD assessment (17).

Previous research in this area has only focused on blinking abnormalities in adults and assessed MG atrophy, but an evaluation of the morphological changes is lacking. This study thus aimed to examine the morphological changes of MG in children with tic disorders and to compare these changes with those in children with dry eye. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-390/rc).

Methods

Participants

This prospective case-control study enrolled Chinese children younger than 14 years of age at the Hangzhou Branch of the Eye Hospital of Wenzhou Medical University from October 2020 to March 2021. Ethics approval was obtained from the Ethics Committee of the Eye Hospital, Wenzhou Medical University (No. 2021-124-K-106-01). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and informed consent was obtained from all patients' parents or legal guardians.

Participants were assigned to three groups: tic disorder, dry eye, and control (*Figure 1*). Children with complaints of abnormal blinking and diagnosed as having tic disorders by neurologists [according to the *Diagnostic and statistical manual of mental disorders (5th ed.) (DSM-5)* (18)] were included in the tic disorder group. We only included children who had exhibited tic disorders between 1 month and 5 years and excluded those with Tourette syndrome. Children who had been diagnosed with DED by an experienced specialist with complaint of dry eye (including foreign body sensation, pain, photophobia, and blurred vision) and NIBUT <10 s according to the Dry Eye WorkShop II criteria (19) were included in the dry eye group. Children without either tic disorders or dry eye were enrolled in the control group. Children with a history of ocular surgery, contact lens wearing, trauma, ocular diseases such as conjunctival and corneal inflammation, intraocular diseases, or topical or systemic medications that could affect the ocular surface were excluded from the study. Only the right eye of each child was examined in this study.

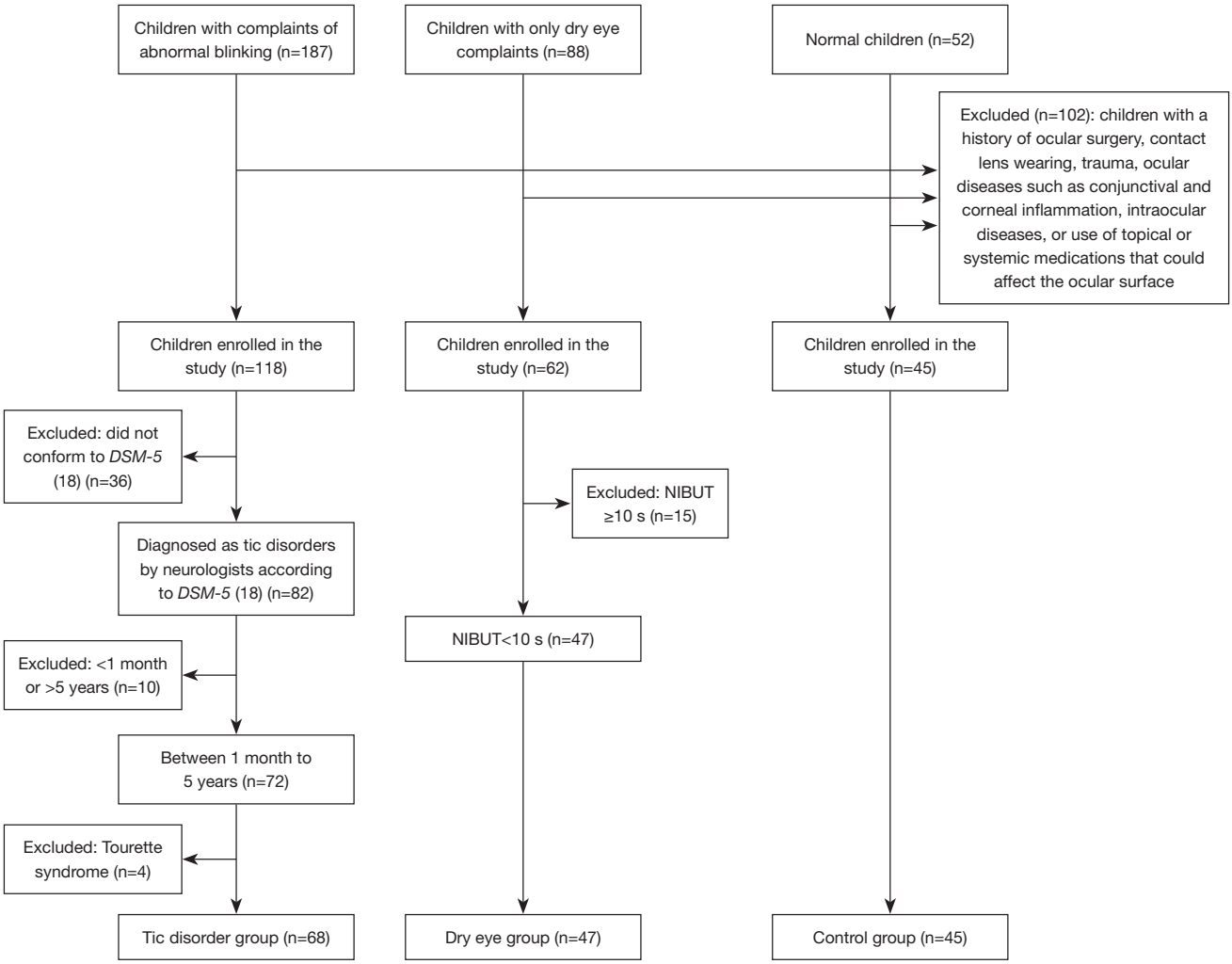


Figure 1 Flow diagram for participant selection (18). *DSM-5*, *Diagnostic and statistical manual of mental disorders (5th ed.)*; NIBUT, noninvasive breakup time.

Meibography and clinical tests

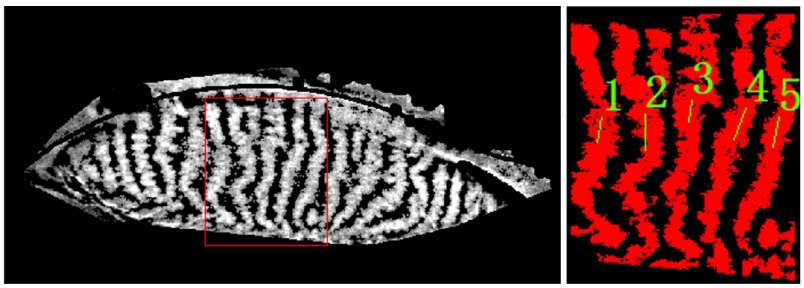
The Keratograph 5M (K5M, Oculus, Wetzlar, Germany) was employed to visualize the MG structure (20). A single specialist evaluated the MG image to determine whether there were any unique MG shapes according to the following scheme described in the literature (17): vertical, the MG duct is straight; tortuous, a single glandular duct is bent into a defined angle (45°); overriding, a single glandular duct crosses 1 or more adjacent ducts; hooked, the proximal part of duct has a slight, hook-like bend; and U-shaped, the ends of two glandular ducts connect in a "U" shape. The number of eyes that had at least one vertical MG, one tortuous MG, one overriding MG, one hooked MG, and at least one U-shaped MG shape in the whole upper lid was counted individually.

The tear meniscus height (TMH) and the average NIBUT were also measured using the K5M. Each measurement was repeated three times, and the average of the three attempts was recorded.

All examinations were conducted in a single examination room by a single investigator. The temperature ranged from 20 to 25 ℃, with humidity levels ranging from 40% to 60%.

Morphological parameters

Based on the image obtained with K5M, Meibomian Gland Bio-Image Analyzer V3 software (21) was used to provide



Gland number	Width (mm)	Length (mm)	Area (mm^2)	DI	SI
1	0.49	3.83	1.50	7.21	6.65
2	0.44	4.35	1.55	9.24	6.11
3	0.46	4.53	1.68	9.25	6.06
4	0.37	4.40	1.42	5.29	6.09
5	0.36	4.15	1.30	5.18	5.90
Average	0.42	4.25	1.49	7.23	6.16

Figure 2 The central five MGs in the upper lids of eyes from the tic disorder group, dry eye group, and control group were analyzed using Meibomian Gland Bio-Image Analyzer V3 software. DI, deformation index; SI, signal index; MG, meibomian gland.

multiple parameters of the MG morphology. This new automated algorithm was developed to offer quantitative indices including length (the distance between the endpoints of the gland central line), width (the average width across a single gland), area (the area of detected signals from five central glands), gland diameter deformation index (DI), and gland signal index (SI) to analyze MG morphology (*Figure 2*). The DI is an index used to quantify the variation of gland width, and SI is an index used to present the image gray value. Because the MGs on the nasal and temporal sides are mostly irregular and have poor imaging quality, we only evaluated the central five MGs in the upper lids, and the number of vertical glands among the central five MGs were recorded.

Statistical analysis

The sample size was calculated with PASS 15 software (NCSS, Kaysville, UT, USA). MG area was used in the calculation. In a single factor analysis of variance (ANOVA) study, sample sizes of 45, 37, and 35 are obtained from the three groups, whose means were compared. The total sample of 117 participants provided an 88% power in detecting a difference of at least 0.58 with a Tukey-Kramer (pairwise) multiple comparison test at a 0.05 significance level. The common standard deviation (SD) within a group was assumed to be 0.50. The dropout rate was 20%, so sample sizes of 57, 47, and 44 were obtained from the three groups, whose means were then compared.

The normal distribution of the data was verified using the Shapiro-Wilk test. The differences in clinical tests and morphological parameters across the three groups were assessed using one-way ANOVA, which was followed by Bonferroni post-hoc tests or the Kruskal-Wallis test. Mann-Whitney tests with Bonferroni correction were then applied for multiple comparisons according to data normality. The chi-squared test was used to analyze variations in sex and MG distortions. Spearman rank correlation coefficient was used to assess the correlations between TMH, NIBUT, and MG morphology. Statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA) for Windows. The criterion for statistical significance was set at $P<0.05$.

Results

Demographics

Table 1 shows the demographic characteristics of the three groups. The 160 eyes that met the criteria were separated into three groups: tic disorders (68 eyes), dry eye (47 eyes), and control (45 eyes). There was no significant difference in sex or age distribution across the groups.

MG distortion shapes

Figure 3 depicts the five different MG duct shapes

Table 1 Comparison of demographics among the three groups

Demographics	Tic disorder (n=68)	Dry eye (n=47)	Control (n=45)	P value			
				Overall	P_{tic} *vs.* P_{dry}	P_{tic} *vs.* P_{nor}	P_{dry} *vs.* P_{nor}
Age (years)	8.00 (6.00–9.00)	9.00 (8.00–10.00)	9.00 (6.50–10.00)	0.13	–	–	–
Sex (F/M)	23/45	25/22	22/23	0.09	–	–	–
TMH (mm)	0.16 (0.15–0.20)	0.15 (0.13–0.17)	0.18 (0.15–0.23)	<0.001*	0.003*	>0.99	<0.001*
NIBUT (s)	5.48 (3.89–7.76)	3.76 (3.00–5.16)	12.44 (8.68–18.03)	<0.001*	0.002*	<0.001*	<0.001*
MG length (mm)	4.46 (3.80–5.07)	5.28 (4.80–5.95)	5.37 (4.45–5.92)	<0.001*	<0.001*	<0.001*	>0.99
MG width (mm)	0.45 (0.40–0.59)	0.55 (0.44–0.75)	0.50 (0.43–0.65)	0.008*	0.009*	0.14	>0.99
MG area (mm^2)	1.63 (1.35–2.20)	2.47 (1.75–3.53)	2.23 (1.85–2.75)	<0.001*	<0.001	<0.001*	>0.99
DI	9.41 (7.01–13.30)	10.60 (8.63–14.63)	9.57 (7.61–12.19)	0.06	–	–	–
SI	5.84 (5.03–6.80)	6.15 (5.20–6.86)	5.76 (5.02–6.86)	0.75	–	–	–
Vertical glands	1.00 (0.00–3.00)	1.00 (0.00–2.00)	2.00 (1.00–4.00)	0.006*	>0.99	0.01*	0.02*

Data are presented as the n or median (IQR). *, P<0.05. F, female; M, male; TMH, tear meniscus height; NIBUT, noninvasive breakup time; MG, meibomian gland; DI, deformation index; SI, signal index; IQR, interquartile range.

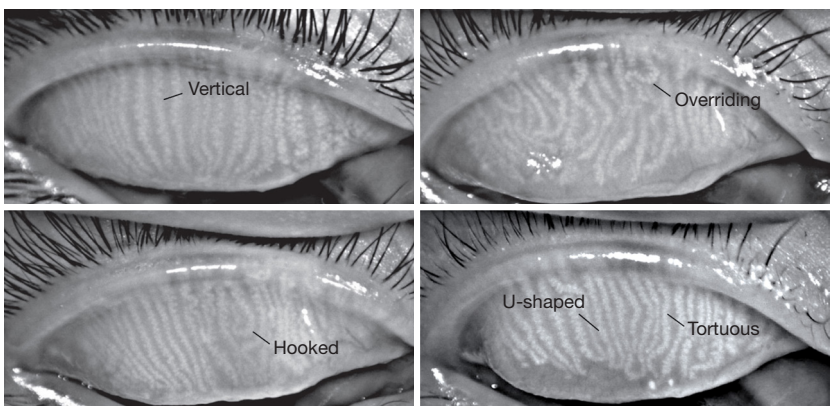


Figure 3 Five distinct morphological shapes of the MG ducts (vertical, tortuous, overriding, hooked, and U-shaped). MG, meibomian gland.

we found (vertical, tortuous, overriding, hooked, and U-shaped). All eyes in the control and dry eye groups had vertical MG ducts. However, 7 (10.3%) eyes in the tic disorder group had no vertical MG ducts. The chi-squared test was applied to compare the number of eyes with vertical MG ducts among three groups (P=0.007). The ensuing pairwise comparison among the three groups did not reveal any differences in the eyes with vertical MG ducts (P>0.05). Furthermore, U-shaped MG ducts were found in 30 (44.1%) eyes in the tic disorder group and 12 (25.5%) eyes in the dry eye group. The tic disorder and dry eye groups both had a larger percentage of eyes with a U-shaped MG duct when compared with the control group (P<0.001 and P=0.017). In all three groups, the prevalence of tortuous, overriding, and hooked MG ducts in the eyes was comparable (P=0.12, P=0.53, and P=0.08, respectively; *Figure 4*). In a comparison of the central five MG shapes, the tic disorder and dry eye groups both had fewer vertical glands than did the control group (P=0.01 and P=0.02, respectively; *Table 1*).

Morphological parameters of MG

The eyes in the tic disorder group showed lower MG length and area values compared with those of the other groups (all P values <0.001; *Table 1*). In a comparison of MG width,

the tic disorder group had a smaller value than did the dry eye group (P=0.009). DI and SI did not differ significantly across the groups (P=0.06 and P=0.75; *Figure 5*).

Comparison of TMH and NIBUT

When comparing TMH and NIBUT across the three groups, we observed significant differences (both P values <0.001; *Table 1*). The TMH value in eyes of the dry eye group was lower than that in the eyes of tic disorder and the control group (P=0.003 and P<0.001, respectively). The TMH values were similar in eyes of the tic disorder and the control group (P>0.99). Eyes with dry eye had the lowest NIBUT value, followed by eyes with tic disorders, both of which showed lower values than did eyes in the control group (both P values <0.001).

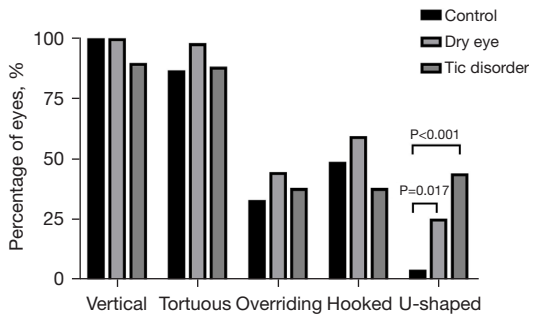


Figure 4 Comparison of the percentage of eyes including five MG duct shapes across the three groups. MG, meibomian gland.

Correlation between morphological and functional characteristics in the MG

We have considered all groups together to evaluate the correlations. The Spearman rank correlation coefficients and P values are shown in *Table 2*. However, no correlations were found between clinical tests and MG morphology in

Table 2 Overall correlation coefficients of clinical tests and MG morphology

Parameters	TMH (mm)		NIBUT (s)	
	r	P	r	P
MG length (mm)	−0.10	0.23	0.03	0.67
MG width (mm)	−0.01	0.93	−0.05	0.53
MG area (mm^2)	−0.05	0.55	0.001	0.99
DI	−0.06	0.42	−0.12	0.14
SI	−0.08	0.34	−0.06	0.47

MG, meibomian gland; TMH, tear meniscus height; NIBUT, noninvasive breakup time; DI, deformation index; SI, signal index.

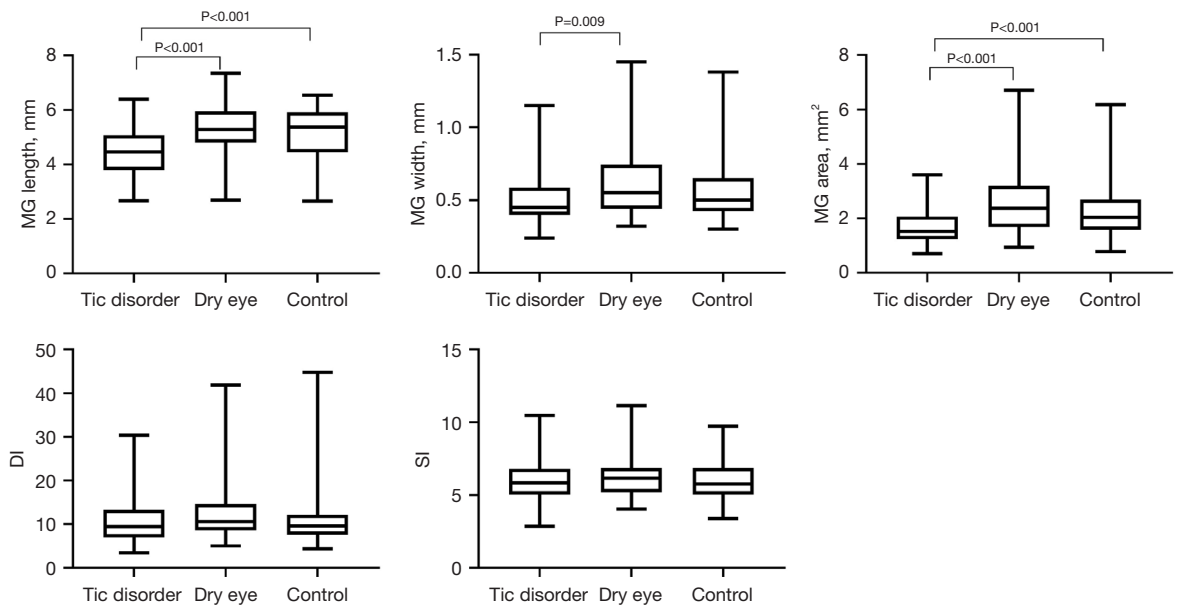


Figure 5 Comparison of morphological parameters of MGs among the three groups. MG, meibomian gland; DI, deformation index; SI, signal index.

any group (all P values >0.05).

Discussion

MGD is a major cause of evaporative DED, which starts with morphological abnormalities in the MG gland and progresses to reduced meibum secretion and dry eye symptoms (11-13). Blinking is necessary to maintain the lipid layer and MG expression (5). Blinking disorders, such as increased blinking rate and eye-blinking tics, are the first indicators of tic disorders (4). Children with tic disorders may also have DED and are frequently misdiagnosed. In the present study, the morphological characteristics of MGs were examined in children with tic disorders, children with dry eye, and a healthy control group.

Blinking is accomplished by the contraction of the orbicularis oculi muscles, which also provides MGs with the force required to extrude the meibum (22,23). In eyes with blinking disorders, frequent and strong contraction of the orbicularis oculi muscles induces excessive meibum secretion in a short period (23). Before the meibum is restored, the lipids on the surface of the tear film diminish, resulting in dry eye symptoms. Excessive meibum secretion affects the morphology of the MG over time. Lin *et al.* (24) reported reduced MG secretion, MG acinar area, and orifice diameter, as well as increased irregularity of the acinar and inhomogeneity of interstices in patients with blepharospasm, which was caused by involuntary spasmodic contractions of the orbicularis oculi muscles. The findings demonstrated an association between MG morphology and excessive contraction of the orbicularis oculi (24). These researchers only concentrated on changes in MG structure in adults; however, no previous studies have focused on changes in MG structure in children with blinking problems. Therefore, we conducted this study to examine this issue and to identify any substantial morphological changes in MGs, if any.

We identified five distinct MG shapes in each group, even in a single eye, which is consistent with our previous study (17). The tic disorder and dry eye groups both showed fewer vertical glands among the five MGs we assessed. The U-shaped MG ducts were found in more eyes in the tic disorder group and dry eye group. According to these results, children with tic disorders are more likely to have MG morphological alterations due to abnormal blinking.

Many previous studies used a 4-grade or 5-grade meiboscale to describe MG morphology, with the meibograde being classified according to gland dropout (13,14,25), percentage of partial glands (26), or number of glands (26,27). Several studies have attempted to quantify the morphology of the glandular duct. In one prior study, the difference area relative to a "standard gland" was used as a measure of structural variation of the MG (28). Lin *et al.* (29) utilized an index called "MG tortuosity" to describe MG morphology changes in patients with MGD. To analyze MG morphology, we previously defined the MG distortion index according to the angle and area (17). To obtain more reliable and repeatable results, we used an algorithm (21) to objectively assess MG morphology in the current study. This algorithm provides multiple parameters to evaluate the structure of the five central MGs, including length, width, area, DI, and SI. The tic disorder group had a shorter MG duct and smaller MG area compared with the other two groups, as well as a smaller MG width compared with the dry eye group. Surprisingly, the MGs in the dry eye group exhibited similar MG structural features to those of healthy children. This might have occurred due to not all eyes in the dry eye group exhibiting significant MGD, and some might have had aqueous tear deficiency. Therefore, we hypothesize that compared with children with dry eye, children with tic disorders may be more prone to MG morphological abnormalities. Previous studies (12,13,28) reported that MG morphological changes are early indications of MG function and ocular surface parameters. To guarantee timely treatment, more emphasis should be placed on monitoring changes in MG morphology in children with tic disorders.

According to Rahman *et al.* (30), frequent blinking is linked to poor tear film stability. As the blinking rate increases, there tends to be more incomplete blinking, which results in a decrease in tear breakup time and MGD (3). To assess the tear film, we examined TMH and NIBUT. Since the K5M calculated the NIBUT from a blink until the average time of tear breakup or if another blink occurred, the NIBUT might have been undervalued in tic disorder group and dry eye group; however, the eyes in the tic disorders group had a greater NIBUT value than did those in the dry eye group and a lower value than did those in the control group. The TMH value in the dry eye group was the lowest, whereas the TMH values in the other two groups were identical. Although the tic disorder group exhibited more MG morphological changes, the dry eye group had poorer dry eye test results. This finding may be attributable to the fact that the eyes we observed in the tic disorder group were in the early stages of dry eye. Thus, we suspect that the TMH and NIBUT values in children

with tic disorders might further decrease secondary to the morphological changes.

MG morphological changes exhibited no correlations with TMH or NIBUT. Similarly, Lin *et al.* (29) found no difference in TMH between patients with MGD and healthy controls. Ngo *et al.* (31) also found no correlations between MG dropout and NIBUT in female adults. Theoretically, the TMH and NIBUT values would be expected to be associated with MG morphological parameters (16,28). This discrepancy might have been caused by compensatory MG secretion and is an issue that warrants further investigation.

Several limitations of this study should be considered. First, because we did not evaluate blinking characteristics, we were unable to assess the correlation between blinking and MG morphology. Second, we did not conduct the OSDI questionnaire or other dry eye questionnaires because questionnaires can be difficult for children to understand. Third, we did not distinguish between aqueous-deficient DED and evaporative DED in this study. In addition, this study only evaluated the MG morphology in the upper lids according to the algorithm design. Due to the imaging quality and the limitation of the algorithm, not all MGs were evaluated, which might have introduced bias. As many children in tic disorder group also met the criteria of dry eye, it was hard to avoid bias by completely distinguishing these two diseases. To identify morphological changes in MG over time, more detailed follow-up studies with more parameters are required in the future.

Conclusions

Overall, blinking disorders had a significant impact on MG morphology in children, resulting in reduced MG length, decreased gland duct area, and a higher likelihood of a U-shaped MG duct. More attention should be devoted to monitoring MGs in children with tic disorders in order to prevent the development of MGD.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-22-390/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-390/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Eye Hospital, Wenzhou Medical University (No. 2021-124-K-106-01). Informed consent was obtained from all patients' parents or legal guardians.

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