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Review Article

Comparative Review of Keratoconus Patients Who Rub Their Eyes with Those Who Don't: Disease Severity, Progression and Vision Related Quality of Life

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ABSTRACT

Keratoconus is a bilateral, asymmetric disease of the cornea. It's characterised by progressive thinning and steepening of the cornea, which results in irregular astigmatism and visual impairment. Globally, the prevalence of keratoconus is estimated at approximately 1.38 in every 1000 individuals. It most commonly manifests in the second decade of life and tends to stabilise by the fourth decade. Many genetic and environmental risk factors are associated with the development and progression of keratoconus. These include congenital diseases such as Leber's congenital amaurosis, Down syndrome, Ehlers-Danlos syndrome, as well as atopy, UV light exposure, eye rubbing, sleep position and contact lenses. Amongst these, eye rubbing has been intensively studied.

Keywords: Keratoconus; Ehlers-Danlos syndrome; Disease; VRQOL; Eye rubbing

INTRODUCTION

A pivotal study by Bawazeer, et al. identified eye rubbing as the most significant risk factor for keratoconus [1]. Gomes, et al. posited that other risk factors such as eczema, allergy and atopy may be linked to keratoconus primarily due to their propensity to induce ocular itch and subsequent eye rubbing rather than being independent risk factors [2]. Notably, in cases of asymmetric keratoconus, the more severely affected eye has shown a significant correlation with hand dominance and eye rubbing. Mazharian, et al. emphasised that in these patients, the eye subjected to rubbing is associated with greater asymmetry in corneal curvature and refractive error [3]. Consequently, even if both eyes in a patient are affected by keratoconus, the eye subjected to rubbing may exhibit more advanced disease. While there is an abundance of literature examining the role of eye rubbing in keratoconus, there remains a cap in those comparing the severity of keratoconus between those who rub their eyes and those who don't and in understanding the differences in their demographic data. This distinction is crucial, as keratoconus patients who rub their eyes may exhibit an earlier age of diagnosis, more advanced state of disease upon presentation, and higher incidence of previously identified risk factors such as eczema and ocular allergy. More severe disease or accelerated progression may also lead to a diminished Vision Related Quality of Life (VRQOL). Previous studies examining VRQOL in keratoconus patients found the overall quality of life is closely related to the vision in the better eye. Given that patients with asymmetric disease are projected to develop bilateral disease within 5 years, those who rub their eyes may also experience a lower VRQOL. This article therefore aims to review the literature comparing the demographic, clinical and VRQOL data between keratoconus patients who do and do not rub their eyes.

LITERATURE REVIEW

Eye rubbing and disease severity

A multitude of meta-analyses have established the connection between eye rubbing and keratoconus. However, literature exploring demographic and clinical differences between keratoconus patients based on their eye rubbing habits, particularly in terms of disease severity remains sparse. An early indication of the impact of eye rubbing on asymmetric disease arose from paediatric case reports featuring ocular allergies. In these reports, keratoconus development was frequently attributed to intense and regular eye rubbing. Notably the more affected eye was often ipsilateral with the dominant hand, suggesting that severe disease may be tied to excessive eye rubbing using the stronger, dominant hand.

This observation was supported by McMonnies and Boneham [4]. In their study of 53 keratoconus patients, those who

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reported the most severe eye rubbing exhibited more severe disease on the side corresponding to their dominant hand. Interestingly, this dominant hand correlation was not observed in patients who practiced more gentle eye rubbing. This may account for discrepancies in the literature regarding the connection between eye rubbing and keratoconus severity. In a study by Mou, et al. 91.3% of 391 keratoconus patients reported eye rubbing, but only 48.8% did so frequently [5]. When the frequency of eye rubbing was compared with the severity of keratoconus in patients over 21, regularly eye rubbing was significantly associated with more pronounced astigmatism and steeper K_{max} (maximum keratometry) at diagnosis. Other studies, such as those by Naderan, et al. and Moran, et al. echoed these findings [6,7]. However, these are not universally observed across the literature. For instance, a study by Yang, et al. involving 307 keratoconus patients in Central China, found that while 68.40% of the participants reported eye rubbing, no significant correlation between eye rubbing and disease severity was observed [8]. A similar outcome was seen in an Australian study of keratoconus patients, who also failed to find a significant association. The inconsistency in these results may be explained by the assertion made by McMonnies and Boneham; it's possible that only the most severe, frequent eye rubbing has a significant bearing on keratoconus progression. Supporting this theory, Moran, et al. only found a correlation between eye rubbing and keratoconus when the rubbing was performed with knuckles. They utilised a questionnaire that inquired about the duration, dominant side and method of rubbing, such as using fingertips, base of thumbs, knuckles. The specific type of rubbing may be crucial to understanding this relationship. Therefore, studies that merely posed a binary choice rubbing or no rubbing (as apparent from their methodology) as in Yang, et al. and Sahebjada, et al. largely failed to demonstrate significant outcomes in their analyses [9].

DISCUSSION

Eye rubbing and progression

The eye rubbing habits of keratoconus patients may hold significant clinical implications. Understanding these habits is crucial, as patients who frequently rub their eyes may experience faster disease progression and require earlier interventions compared to those who do not engage in eye rubbing. Mazharian, et al. conducted a longitudinal study, monitoring the progression of 77 keratoconus patients over 3 years. Although individuals with inflammatory corneal conditions, and those with compulsive eye rubbing tendencies (as observed in conditions like autism, Tourette's syndrome or Down syndrome) were excluded from the study, every single one of the 4.58% of patients who showed disease progression admitted to persistent eye rubbing.

This pattern was mirrored in another study focusing on the rate of keratoconus progression post initial collagen Cross-Linking (CXL). Antoun, et al. found that 3.17% of the study's participants displayed disease progression over a 9-48 month period [10]. Notably, every one of these progressing patients reported a history of allergic conjunctivitis, coupled with eye rubbing. This correlation between disease progression and eye rubbing was further reinforced by Saglik, et al. His findings indicated that every patient who showed a progression of more than 1 dioptre increase in K_{max} compared to their baseline following CXL reported a history of eye rubbing [11].

Eye rubbing and correlation with atopy

Although studies have examined the relationship between keratoconus severity and eye rubbing habits, comprehensive demographic analysis between these two groups remains lacking. One demographic factor of particular interest is atopy. Meta-analyses have indicated a significant association between atopic conditions; including allergies asthma and eczema and keratoconus. However, it's posited that these conditions may be indirectly related to keratoconus by increasing ocular itch, leading to more frequent eye rubbing.

To ascertain the relationship between atopic conditions and keratoconus, its crucial to examine the prevalence of atopy amongst keratoconus patients who rub their eyes compared to those who don't. Mou, et al. reported that while there was no significant association between conditions like eczema, urticaria, asthma and allergic rhinitis with keratoconus severity, correlation analysis showed atopic patients were found to be more prone to frequent eye rubbing. In a similar vein, both Antoun, et al. and Saglik, et al. observed that post CXL, keratoconus patients showing progression had histories of allergic conjunctivitis at rates of 100% and 75% respectively.

A plausible explanation for the observed discrepancy could be due to varying definitions of atopy or methodological differences. Specifically, while univariate analyses might identify significant associations, multivariate analyses that adjust for confounding factors may not regard eczema, allergy or asthma as significant. Therefore, once confounders are adjusted for, these analyses support the hypothesis that atopic conditions by inducing ocular itch contribute to keratoconus primarily through increased eye rubbing.

Mechanism of disease

While the exact mechanism relating eye rubbing to keratoconus progression remains to be fully elucidated, there's growing evidence suggesting eye rubbing instigates a chronic inflammatory response in the eye. This is exemplified by the observed elevated levels of inflammatory cytokines in the eyes of keratoconus patients. For instance, Balasubramanian, et al. discovered that a mere 60 seconds of eye rubbing in tears from normal eyes resulted in increased levels of IL-6, TNF-α and MMP-13 [12]. Lema and Duran made a similar finding in keratoconus patients, finding elevated levels of IL-6, TNF-α and MMP-9 in tears [13]. Interestingly, these inflammatory mediator levels correlated directly with the severity of the disease.

Beyond the inflammatory response, the act of eye rubbing may also exert mechanical trauma leading to fluctuations in Intraocular Pressure (IOP). McMonnies demonstrated a significant IOP increase of up to 60 mmHg after firm digital force for the eyes [14]. This has led to the theory that IOP fluctuations from eye rubbing leads to diminished keratocyte density, increased release

of inflammatory cytokines and direct mechanical injury to the cornea's collagen fibrils. This structural distorsion of collagen fibrils diminishes the cornea's biomechanical resistance. When combined with inflammation driven tissue degradation and remodelling by MMPs, it culminates in the hallmark epithelial and stromal thinning of keratoconus. In light of this, it becomes evident that while eye rubbing stands as a risk factor for keratoconus, distinguishing between patients who do and do not rub their eyes may be crucial. The former seems to harbor an elevated risk of disease progression, which may warrant earlier medical intervention.

Vision Related Quality of Life (VRQOL)

The impact of eye rubbing on VRQOL in keratoconus patients may hold significance. If eye rubbing does indeed exacerbate the disease, it may result in diminished quality of life. Numerous studies have examined VRQOL in keratoconus using various assessment tools and have shown VRQOL may be as poor as those with macular degeneration. Yet, none have compared the VRQOL in keratoconus patients who rub their eyes, with those who don't. However, the influence of ocular asymmetry on VRQOL in keratoconus has been explored. In this study by Jones-Jordan, et al. 961 keratoconus patients completed the National Eye Institute Visual Function Questionnaire (NEI-VFQ) [15]. This tool was developed to assess the impact of low vision, chronic eye diseases on VRQOL. This study found that while greater ocular asymmetry and diminished visual acuity were linked to poorer VRQOL, the only statistically significant correlation was between visual acuity in the better eye and overall quality of life. This correlation has also be reaffirmed by various analyses of VRQOL in keratoconus patients also utilising the NEI-VFQ, disease specific Keratoconus Outcomes Research Questionnaire (KORQ) and Impact on Vision Impairment questionnaire (IVI).

The progression of disease and changes in VRQOL has also been investigated. Steinberg, et al. highlighted that keratoconus patients with stable disease exhibited VRQOL similar to early myopes [16]. However, there was a discernible decline in VRQOL amongst those with progressive keratoconus, defined as an increase in K_{max} and/or refractive astigmatism of >1D within 1 year. Interestingly, this deterioration in VRQOL did not correspond to marked alterations in corneal morphology and visual function. Instead, it seemed to be related to be related with the burden of being diagnosed with a progressive disease, which is consistent with the poorer composite and subscale 'mental health' scores of the NEI-VFQ.

Furthermore, the impact of keratoconus treatments, particularly post collagen cross-linking on VRQOL has been investigated. Ferrini, et al. examined the VRQOL preoperatively and postoperatively following CXL at intervals of 1, 3 and 6 months in 38 participants [17]. This was examined using the KORQ which can be subdivided into activity limitation and symptom scores. Eye rubbing habits were also recorded according to a Visual Analogue Scale (VAS) at each time point. Prior to CXL, greater disease severity in all parameters (best corrected visual acuity, K_{max}, flattest, steepest keratometry and higher order aberration) correlated with more significant activity limitation. Following CXL this dynamic shifted, whereby VRQOL aligned more closely with the visual acuity of the fellow eye. Collectively, the data suggests a trend whereby progressive disease leads to a deterioration in VRQOL which stabilises post treatment. For the most part, this quality of life mirrors the visual function in the healthier eye.

CONCLUSION

Eye rubbing in keratoconus presents a pivotal factor in understanding disease progression and severity. Recognising and understanding the severity of this behaviour offers clinicians the opportunity to anticipate disease trajectory and potentially modify treatment strategies. Early identification allowed for patient education on the risks associated with eye rubbing, potentially prompting behavioural change. Furthermore, frequent clinical monitoring may be essential for these patients, especially post CXL, to ensure timely intervention. As the relationship between eye rubbing and keratoconus becomes clearer through research, integrating these findings into clinical practice will be crucial to optimise patient outcomes.

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