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Research Paper

Allergic Conjunctivitis-induced Retinal Inflammation Promotes Myopia Progression

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ABSTRACT

Myopia is a highly prevalent eye disease. There is limited information suggesting a relationship between myopia and inflammation. We found children with allergic conjunctivitis (AC) had the highest adjusted odds ratio (1.75, 95% confidence interval [CI], 1.72–1.77) for myopia among the four allergic diseases. A cohort study was conducted and confirmed that children with AC had a higher incidence and subsequent risk of myopia (hazard ratio 2.35, 95%CI 2.29–2.40) compared to those without AC. Lower refractive error and longer axial length were observed in an AC animal model. Myopia progression was enhanced by tumor necrosis factor (TNF)-α or interleukin (IL)-6 administration, two cytokines secreted by mast cell degranulation. The TNF-α or IL-6 weakened the tight junction formed by corneal epithelial (CEP) cells and inflammatory cytokines across the layer of CEP cells, which increased the levels of TNF-α, IL-6, and IL-8 secreted by retinal pigment epithelial cells. The expression levels of TNF-α, IL-6, IL-8, monocyte chemoattractant protein-1, and nuclear factor kappa B were up-regulated in eyes with AC, whereas IL-10 and the inhibitor of kappa B were down-regulated. In conclusion, the experimental findings in mice corroborate the epidemiological data showing that allergic inflammation influences the development of myopia.

1. Introduction

Myopia is a major cause of visual loss and has a tremendous impact on the public health systems and economies. It is estimated that 2.5 billion people will be affected by myopia in the next decade (Wojciechowski, 2011). In Taiwan, the prevalence of myopia is 9.4% in 6-year-old children and >75% in 15-year-old adolescents. By the age of 18, the prevalence increases to 80–90%, and approximately 10–20% of these children are highly myopic (Lin et al., 2001). High myopia increases the risk of pathologic ocular changes such as premature cataract, glaucoma, retinal detachment, and myopic macular degeneration, all of which can cause irreversible visual loss (Saw et al., 2005; Leo and Young, 2011; Morgan et al., 2012).

Although the exact causes of myopia are unclear, multiple lines of evidence support that interactions between hereditary factors and environmental exposures play crucial roles in ocular growth and refractive development (Wojciechowski, 2011; Leo and Young, 2011; Morgan et al., 2012). Myopia primarily results from abnormal elongation of the vitreous chamber of the eye (Rada et al., 2006; Curtin, 1985). Results from clinical and experimental studies have clearly demonstrated that ocular elongation is associated with altered extracellular matrix (ECM) and remodeling of the connective tissue of the scleral shell (Rada et al., 2006; Harper and Summers, 2015). ECM composition and scleral remodeling are regulated by genes as well as environmental influences and individual behavioral factors (Rada et al., 2006; Harper and Summers, 2015; Hornbeak and Young, 2009). To date, the precise biological mechanisms

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by which environmental factors influence ocular refraction in humans are still unclear. Several reports have proposed a role for inflammation in myopia susceptibility (Kung et al., 2017; Herbort et al., 2011). Our recent population-based cohort study showed that patients with autoimmune diseases, such as type 1 diabetes mellitus; systemic lupus erytheomatosus, and uveitis, have higher risks of myopia compared to those without autoimmune diseases (Lin et al., 2016). Moreover, in an animal model of myopia, we found that inflammatory markers, such as c-Fos, nuclear factor kappa B (NFκB), interleukin (IL)-6, and tumor necrosis factor (TNF)-α were upregulated in myopic eyes and downregulated upon treatment with atropine and the immunosuppressive agent, cyclosporine A (CSA) (Lin et al., 2016). Therefore, both clinical and experimental results support that inflammation may contribute to myopia progression (Lin et al., 2016).

Allergic conjunctivitis (AC) is a group of inflammatory diseases affecting the ocular surface, caused by abnormal immune-hypersensitivity response to environmental allergens (Cordova et al., 2014). The immune mechanism of AC is characterized by immunoglobulin (Ig)-*E*-mediated mast cell degranulation and/or T-lymphocyte-mediated immune response. AC is characterized histologically by infiltration of the conjunctiva with inflammatory cells, including neutrophils, eosinophils, lymphocytes, and macrophages. Chronic AC may result in remodeling of the ocular surface tissues (Cordova et al., 2014). However, it is unknown whether the inflammatory process of AC may cause myopia progression. We hypothesized that allergic inflammation of the eye would mediate the development of myopia. Therefore, we first conducted a case-control study to investigate the prevalence of allergic diseases, including asthma, atopic dermatitis, allergic rhinitis, and AC, in children with and without myopia. Secondly, we conducted a cohort study to investigate the incidence and risk of myopia in children with AC compared to those without AC. Finally, we established an AC animal model to demonstrate the possible mechanisms underlying allergic inflammation as a risk factor of myopia.

2. Materials and Methods

2.1. Epidemiological Study Design

2.1.1. Study Population

The National Health Insurance (NHI) program was implemented in 1995 and has information about up to 99% of the 23.74 million people living in Taiwan. We compiled data files for children (aged <18 years) from the NHI program, which were established and maintained by the National Health Research Institutes (NHRI). In this study, we used the registry for half of all insured children (age < 18 years) in Taiwan from 1996 to 2012. The disease criteria were defined and classified according to the diagnostic codes of the International Classifications of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The refraction power was measured after cycloplegia to avoid accommodative spasm. All patient identifications had been scrambled to protect privacy in the data linkage. This study was approved by the China Medical University ethical review committee (CRREC-103-048(CR-2)).

2.1.2. Case Control Study

We first conducted a case-control study to compare the prevalence of allergic diseases is compared between children with and without myopia (Table 1). We identified a total of 197,237 patients aged 1–18 years with newly diagnosed myopia (ICD-9 code 367.1x) during 2008–2012 as the myopia group, and the diagnosed date of myopia was considered as the index date. For each patient with myopia, one insured children without history of myopia were matched by sex, age (within 1-year intervals), parents' occupational status, urbanization of residential area, and year of index date, as the non-myopia group (Table 1). We identified subjects who were diagnosed with asthma (ICD-9-CM 493.xx), atopic dermatitis (ICD-9-CM 691.8x), allergic rhinitis (ICD-9-CM 477.xx), and AC (ICD-9-CM 372.05, 372.10, and 372.14). We used Pearson's chi-square test and Student's *t*-test to compare demographic data and allergic diseases between the myopia and non-myopia groups. Multiple logistic regression models to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for the association between allergic diseases and myopia after adjusting for sex, age, urbanization of residential area, parents' occupational status and allergic disease. A p value lower than 0.05 was deemed statistically significant. The data were analyzed using the SAS statistical package (version 9.3).

2.1.3. Cohort Study

Secondly, we conducted a cohort study to examine the incidence rate and relative risk of myopia in the AC cohort compared to the non-AC cohort using a Cox proportional hazard regression. We identified patients aged 1–18 years with newly diagnosed allergic conjunctivitis (AC) in the year of 2000 as the AC group, and the diagnosed date of AC was considered as the index date. Then we randomly matched one child without AC to every patient with AC using frequency matching by sex, age (in 1-year intervals), parents' occupational status, urbanization of residential area, and year of index date, as the non-AC group.

Table 1
Demographic characteristics in children with or without myopia and odds ratios for myopia by the presence of specific allergic disease in multiple logistic regression models.

Variables	Non-myopia group N = 197,237		Myopia group N = 197,237			Adjusted OR[a] (95% CI)
	n	%	n	%	p-Value	
Sex					>0.99	
Girls	98,517	49.9	98,517	49.9		
Boys	98,720	50.1	98,720	50.1		
Age, years (SD)[b]	8.71	(2.54)	8.73	(2.51)	0.07	
Asthma					<0.001	
No	154,251	78.2	148,073	75.1		Ref
Yes	42,986	21.8	49,164	24.9		0.99 (0.98–1.01)
Atopic dermatitis					<0.001	
No	182,730	92.6	179,709	91.1		Ref
Yes	14,507	7.36	17,528	8.89		1.06 (1.04–1.09)***
Allergic rhinitis					<0.001	
No	127,333	64.6	110,529	56.0		Ref
Yes	69,904	35.4	86,708	44.0		1.32 (1.30–1.34)***
Allergic conjunctivitis					<0.001	
No	154,777	78.5	131,551	66.7		Ref
Yes	42,460	21.5	65,686	33.3		1.75 (1.72–1.77)***

Abbreviation: OR, odds ratio; CI, confidence interval; SD, standard deviation.
[a] Model adjusted for sex, age (continuous), urbanization, parents' occupational status and allergic disease.
[b] Student's *t*-test.
*** $p < 0.001$.

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