Photodiagnosis and Photodynamic Therapy 36 (2021) 102494

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Choroidal vascularity index and choroidal thickness changes in patients with allergic asthma

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ARTICLE INFO

Keywords:
Asthma
Choroidal thickness
Allergic
Vascularity index
Retinal nerve fiber layer
Optical Coherence Tomography

ABSTRACT

Background: This study aimed to investigate whether the choroidal vascularity index (CVI), choroidal thickness (ChT), and retinal nerve fiber thickness (RNFL) of patients with allergic asthma change compared to the healthy control group.

Methods: This cross-sectional, observational study comprised 59 eyes of 59 patients with allergic asthma (Group 1) and 50 eyes of 50 age and sex-matched healthy volunteers as a control group (Group 2). CVI was measured by binarization of images obtained from choroidal enhanced depth imaging (EDI) mode optic coherence tomography. CVI was defined as the ratio of the choroidal luminal area to the total circumscribed choroidal area. ChT was measured manually at 3 points, subfoveal and 1000 microns nasal and temporal to the fovea (SFCT, N1000, and T1000 respectively). RNFL measurements were subdivided as global, nasal, temporal, superonasal, superotemporal, inferonasal, and inferotemporal quadrants.

Results: Subfoveal CVI and ChT were significantly lower in asthma patients (p:0,043 and p: 0.034, respectively). N1000 and T1000 ChT and RNFL thicknesses were lower in asthma patients compared to the control group, though no significant difference was found between them ($p > 0.05$).

Conclusion: Our findings suggest that asthma patients have choroidal structural changes. In the literature, there are not enough studies regarding the effects of asthma on ocular parameters.

1. Introduction

Asthma is the most common chronic respiratory disease in the world. It is characterized by hypersensitivity to environmental stimuli, chronic inflammation in the lower respiratory tract, and subsequent narrowing of the airways. Genetic predisposition, environmental factors, and epigenetic mechanisms contribute to its pathophysiology [1].

The choroid comprises rich vascular structures providing nourishment to the outer retina and retinal pigment epithelium, and ensures the maintenance of healthy visual function [2]. With recent advances in choroidal imaging modalities, there has been an increase in research regarding choroidal tissue and the factors affecting it. It has been demonstrated that the stromal and vascular structure of the choroid is affected by a wide variety of systemic diseases [3]. On the other hand, the health status of the choroid can give us hints about the systemic health condition [4].

There is strong evidence that asthma is not a disease limited to the airways, but it has widespread effects on extrapulmonary tissues as well. [5] For instance, an association between asthma and vascular disorders has been shown. There is a significant increase in the risk of vascular diseases such as hypertension, atherosclerosis and ischemic events (coronary heart disease and stroke) in patients with asthma [5]. It is clearly known that choroidal vessels are directly affected by vascular disorders [2].

There are reports showing that systemic inflammatory processes also lead to alterations in choroidal thickness and the choroidal vascularity

Abbreviations: AMD, Age-related macular degeneration; CVI, Choroidal vascularity index; ChT, Choroidal thickness; EDI, Enhanced depth imaging; LA, Luminal area; OCT, Optical coherence Tomography; PVR, proliferative vitreoretinopathy; RNFL, Retinal nerve fiber layer; RPE, Retinal pigment epithelium; SA, Stromal area; SFCT, Subfoveal choroidal thickness; TCA, total circumscribed choroidal area.

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https://doi.org/10.1016/j.pdpdt.2021.102494
Received 10 May 2021; Received in revised form 19 August 2021; Accepted 19 August 2021
Available online 24 August 2021

index [6]. Systemic inflammation is also considered to be a key factor in the pathogenesis of asthma. It has been demonstrated that low-grade systemic inflammation persists in asthmatic patients even if they have no symptoms and pulmonary function tests are normal [7]. However, a relationship between asthma and choroidal parameters has until now not been established.

There are a variety of studies investigating the association between choroidal structural and vascular features, and with respiratory system diseases other than asthma, such as chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea syndrome (OSAS) [8–10], but the relationship between asthma and choroidal tissue remains unclear.

This study aimed to investigate whether there are structural changes in choroidal tissue in patients with asthma. To the best of our knowledge, this is the first study evaluating the probable association between asthma and ocular structural features, such as the choroidal vascularity index (CVI), choroidal thickness (ChT), and retinal nerve fiber layer (RNFL) thickness in adults.

2. Materials and methods

This cross-sectional, observational study was conducted in the Departments of Ophthalmology and Pulmonary Diseases of Ahi Evran University Training and Research Hospital. Prior to the study, the approval of the local ethics committee was obtained and the study was conducted following the Declaration of Helsinki ethical principles. A signed informed consent was obtained from all participants before the study. Age and sex-matched fifty-nine patients with allergic asthma and fifty healthy volunteers were involved in the study. The body mass index (BMI) of all volunteers was calculated.

The asthma patient group consisted of patients who had been previously diagnosed with asthma but had not received inhaled or systemic treatment for at least 2 months and who applied to the outpatient clinic of pulmonary diseases with symptoms of asthma exacerbation. These patients were ambulatory without any admitting indications. Each patient was questioned for symptoms and underwent physical examination followed by respiratory functions test and peripheral arterial oxygen saturation (SpO2) measurement with fingertip pulse oximetry. The asthma control test (ACT) was performed. Patients with 19 points or below according to the ACT were classified as “uncontrolled asthma”. The reason for uncontrolled asthma was irregular inhaled drug usage and not adhering to control visits with a physician. Volunteers were referred to the ophthalmology outpatient clinic for a complete ophthalmologic examination.

The inclusion criteria were a visual acuity of at least 0.8, a spherical equivalent of less than 3 diopters, intraocular pressure below 22 mmHg, and axial length <26 mm and >20 mm. Exclusion criteria were respiratory diseases other than asthma, systemic diseases such as diabetes and hypertension, smoking, systemic, inhaled or ocular medication, history of ocular surgery, glaucoma, uveitis, retinal pathologies, and dense optical media opacities.

The patients in the control group were healthy individuals who applied to the ophthalmology outpatient clinic and had no history of systemic or ocular disease except refraction errors or drug use. In the ophthalmology outpatient clinic, all participants underwent comprehensive ophthalmologic examination including corrected visual acuity using a Snellen chart, intraocular pressure measurement with a pneumatic tonometer, and biomicroscopic ocular examination. Axial lengths of the participants were measured and recorded by optical biometry (Lenstar, Haag-Streit, Switzerland).

2.1. Image acquisition and measurements

CVI and ChT measurements were performed using images obtained from the enhanced depth image (EDI) of spectral-domain optical coherence tomography (SD-OCT, Heidelberg Engineering Inc., Software version 6.3.3.0, Heidelberg, Germany). Subfoveal choroidal thickness (SFCT) and the choroidal thicknesses at 1000μm nasal (N1000) and 1000μm temporal (T1000) to the fovea were measured manually from the outer portion of the reflective line corresponding to the retinal pigment epithelium to the inner scleral border (Fig. 1-A) with the built-in caliper of the SD-OCT device software. Peripapillary retinal fiber layer (PRNFL) thickness was also obtained by a single circle centered on the optic nerve with the Spectralis OCT device. Only high-quality images with a Q value>25 were evaluated in the study. All OCT scans were carried out in the 9:00 am-11:00 am time interval to avoid diurnal choroidal variations. All OCT scans were done by the same experienced operator.

2.2. Choroidal vascularity index measurement

EDI-mode images were processed with an open source software (ImageJ version 1.53i, National Institutes of Health, USA) according to the method described by Agrawal et al. [11] (Fig. 2). First, the scale of the image was set and the image was converted to an 8-bit type and binarized with the auto local thresholding tool (Niblack’s method) (Fig. 2). A reference line parallel to the retinal pigment epithelium (RPE) was drawn (1500 μm of total length, centering on the fovea), then the subfoveal total circumscribed choroidal area (TCA) region between the RPE and CSJ was selected, using the polygon selection tool. This first image was added to the region of interest (ROI) manager tool. Later, the image was reconverted to a Red-Green-Blue color type, the threshold color was selected as white, and the image was added to the ROI manager again. White pixels corresponded to the stromal area (SA) and dark pixels to the vascular luminal area (LA). Both images in the ROI manager were merged and the thirth image was added to the ROI manager tool again. Automatic measurement of the first image represented the TCA and the measurement of the last image represented the SA. The LA was found by subtracting the SA from the TCA. The CVI was calculated as the ratio of the LA to the TCA.

ChT and CVI Measurements were performed separately by two experienced ophthalmologists (MY and OAP). Measurements with a difference of more than 10% were considered inconsistent and excluded from the study.

Peripapillary retinal nerve fiber layer (RNFL) thicknesses of global, nasal, temporal, inferonasal, inferotemporal, superonasal, and superotemporal regions were also obtained from the SD-OCT software (Fig. 1-B).

3. Statistical analysis

IBM SPSS Statistics version 22.0 software was used for the statistical analysis. A Chi-square test was used to compare categorical variables. The normality of the data was evaluated using the Shapiro-Wilk test. Independent Samples t-test and Mann Whitney U test were used to compare the variables of two groups. The correlation between the data was evaluated by Spearman and Pearson correlation tests. P values <0.05 were accepted as statistically significant.

4. Results

The right eyes of a total of 59 asthma patients (20 males, 39 females) and right eyes of 50 healthy control subjects (19 males and 31 females) were evaluated. There was no significant difference between the groups in terms of age, gender, BMI, and axial length (p>0,05 for all) (Table 1). There was a significant difference between the groups in terms of subfoveal CVI and ChT(p:0,043 and p:0,034, respectively), whereas there was no significant difference in terms of nasal and temporal choroidal thicknesses (p:0,068 and p:0,065 respectively) RNFL measurements (p>0,05 for all quadrants) (Table 2). No significant correlation was found between BMI values and CVI, ChT and RNFL thicknesses within and between groups (p>0,05 for all).

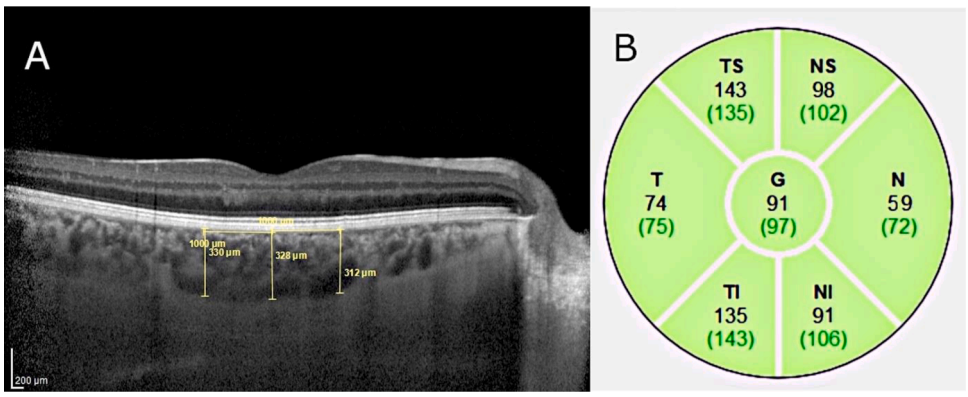

Fig. 1. Choroidal thickness measurements at 3 points of subfoveal, nasal and temporal 1000 µm distance to the fovea (A) Peripapillary retinal nerve fiber layer thickness measurements (B).

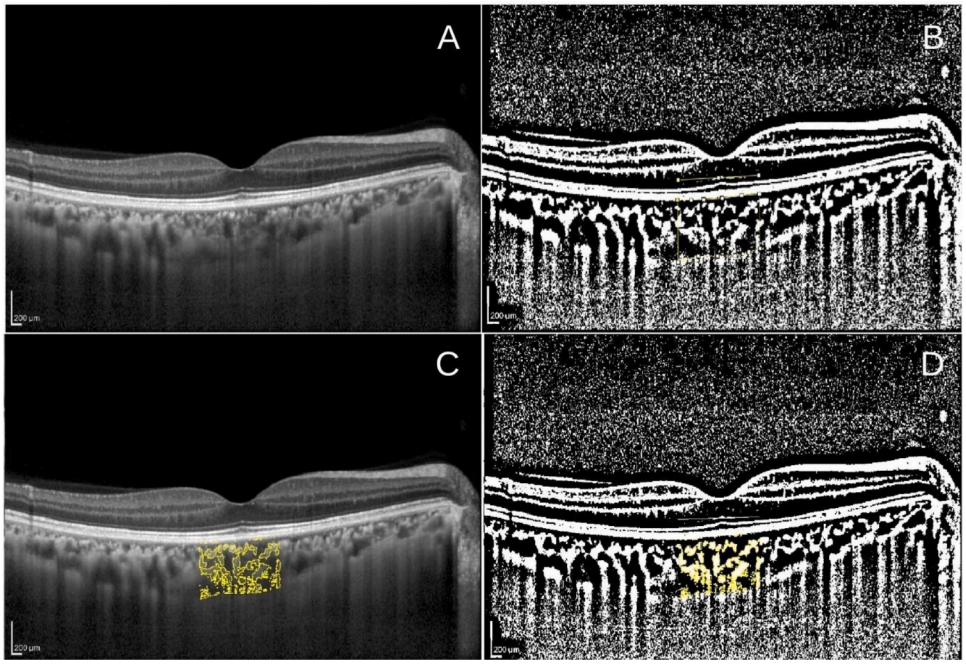

Fig. 2. Enhanced depth imaging (EDI) mode horizontal OCT image of the macula region (A) Binarized photo of the same region showing reference line of 1500 µm length above the RPE, and subfoveal selected choroidal area (B) Subfoveal choroidal region, white pixels correspond to the stromal area (SA) and the dark pixels to the luminal area (LA) (C and D). The measurement of image B gives us the total circumscribed choroidal area (TCA) and the measurement of image D gives SA or LA (depends on the color threshold settings).

Table 1
Demographic and clinical characteristics of the groups.

	Control (mean±sd)	Asthma (mean±sd)	p-value
Gender (male/female)	21/29	20/39	>0,05[a]
Age (years)	44,3 ± 8,3	47,2 ± 11,9	>0,05[b]
Body mass index (BMI)	28,3 ± 3,9	28,9 ± 4,8	>0,05[b]
Axial length (mm)	23,54 ± 1,14	23,34 ± 0,78	>0,05[b]
Spherical Equivalent (SE)	-1,04 ± 0,13	-0,98 ± 0,09	>0,05[b]
BCVA	20/20	20/20	>0,05[b]
IOP (mmHg)	14,8 ± 2,7	15,3 ± 2,9	>0,05[b]
FEV1/FVC (%)	84,51 ± 4,62	76,12 ± 5,66	<0,01[b]
FEV1 (lt)	3,34 ± 0,42	2,42 ± 0,74	<0,01[b]
SpO_2 (%)	98,84 ± 0,96	95,59 ± 1,84	<0,01[b]

[a] Chi-square test [b]Independent samples t-test

In the asthma patients group, mean arterial pulse oximeter SpO2, forced expiratory volume (FEV1) and FEV1/FVC(%) values in respiratory functions tests were; 95,59±1,84; 2,42±0,74 and 76,12 ± 5,66, respectively. We found weak correlations between SpO2 and subfoveal, nasal 1000 and temporal 1000 ChT values and CVI (r:0,262 p:0,006; r:0,251 p:0,009; r:0,216 p:0,026; r:0,286 p: 0,003, respectively). But

Table 2
Choroidal vascularity index (CVI), choroidal (ChT), and retinal nerve fiber layer (RNFL) thicknesses of the groups.

	Control (mean±sd)	Asthma (mean±sd)	p-value
Subfoveal CVI (%)	69,50 ± 4,2	67,85 ± 5,10	0,043[a]
Subfoveal ChT(µm)	343,24 ± 64,97	321,79 ± 72,3	0,034[b]
Nasal 1000 ChT (µm)	319,18 ± 65,4	298,96 ± 63,45	0,068[b]
Temporal 1000 ChT (µm)	329,63 ± 63,32	310,81 ± 64	0,065[b]
RNFL Global (µm)	102,88 ± 8,59	102,02 ± 8,82	0,608[a]
Temporal RNFL (µm)	74,71 ± 11,93	72,49 ± 12,48	0,251[b]
Nasal RNFL (µm)	77,69 ± 14,66	77,88 ± 13,92	0,702[b]
Nasalsuperior RNFL (µm)	111,86 ± 21,72	113 ± 23,12	0,873[a]
Temporalsuperior RNFL (µm)	142,24 ± 15,42	141,67 ± 17	0,799[a]
Nasalinferior RNFL (µm)	121,33 ± 26,72	118,63 ± 25,85	0,553[b]
Temporalinferior RNFL (µm)	149,78 ± 19,65	144,81 ± 23,45	0,423[a]

[a] Independent samples t-test [b] Mann-Whitney U-test

there was no correlations between FEV1, FEV1/FVC and CVI, ChT and RNFL thickness measurements.

We found a weak negative correlation between asthma duration

(18,99±7,96 years) and choroidal vascularity index (r:-0,414 p:0.001), but we did not find a correlation between choroidal thicknesses, RNFL thickness and asthma duration.

5. Discussion

Asthma is a multifactorial disease in which both environmental and genetic factors contribute to its development. Patients suffering from asthma are usually asymptomatic or have mild symptoms, except for asthma exacerbation periods. Allergic asthma is the best-recognized asthma phenotype [1].

In our study, significantly lower CVI levels and significantly thinner subfoveal choroidal thickness was found in asthma patients compared to healthy controls. Additionally, slightly thinner RNFL thicknesses and thinner N1000 and T1000 choroidal thicknesses were found, although these were not significant.

Choroidal vascularity index measurement is a recently described imaging method that enables us to distinguish which part of the choroidal tissue is mainly affected by systemic and ocular disorders [12]. The effects of the various systemic and ocular diseases on choroidal thickness have been extensively investigated in recent studies and it is shown to be affected by choroidal blood flow, and factors such as age, inflammation, oxidative stress, hypertension, and hypoxia [2].

Asthma is a chronic systemic inflammatory respiratory disease involving complex interactions between multiple inflammatory cells and mediators [13]. High levels of various cytokines, such as IL-18, IL-6, TNF-α, leukotrienes, and chemokines have been found in blood samples of patients with asthma [7]. These cytokines increase interactions between platelets, endothelial cells, erythrocytes, and leukocytes and stimulate the formation of circulating cellular aggregates and atherosclerotic vascular plaques. Moreover, the inflammation leads to an increase in peripheral arterial stiffness and a decrease in the small artery elasticity index. [5,14]. These vascular disorders may have deleterious effects on the choroid vessels. Yakut et al. showed a significant increase in blood flow resistance indices and an increase in blood flow velocity of the posterior ciliary arteries (both nasal and temporal) and the central retinal artery. Ciliary arteries are the main blood suppliers of the choroid. The authors stated that these changes might be related to atherosclerosis and vasoconstriction. However, the blood flow volume could not be measured [10].

With recent advances in choroidal imaging modalities, the role of the choroid in some ocular diseases has been elucidated. Based on recent studies, it has been shown that patients with age-related macular degeneration (AMD), both with dry and exudative types, have reduced CVI levels [15–17]. AMD is the leading cause of legal blindness in developed countries [15]. The Beaver Dam Eye Study suggested that the incidence of exudative and dry-type AMD increases in patients with respiratory dysfunctions such as asthma and emphysema [18]. Also in animal experiments, it was observed that the clinical course of wet macular degeneration in asthmatic mice was more severe [19]. There seems to be a relationship between asthma and AMD, but the mechanism remains unclear. Asthma and AMD are diseases considered in the spectrum of complement activation [20]. Activation of the complement cascade is considered to be a key factor in the pathophysiology of both asthma and age-related macular degeneration [21]. A review study claims that activation of the complement system is associated with thinning of the choriocapillaris, a choroidal layer adjacent to the RPE, hence complement activation can also lead to a decrease in the choroidal vascularity index as was found in our study [22]. We suggest that in addition to complement activation, lower CVI levels may be associated with AMD in patients with asthma.

Based on the studies in the literature, asthma patients have higher blood periostin levels compared to healthy subjects. Periostin is a matricellular protein that is considered to be a marker of airway inflammation and airway remodeling in asthma [23] In a review study by Yoshida et al., it was stated that periostin has a key role in choroidal fibrovascular membrane formation and is associated with a variety of ocular posterior segment pathologies such as choroidal fibrosis, diabetic retinopathy, primary epiretinal membrane, proliferative vitreoretinopathy (PVR), etc. [24] Choroidal fibrosis and membrane formation may be associated with an increase in the choroidal stromal component ratio (SA), and thus lower CVI levels.

There are a few studies in the literature examining choroidal and RNFL thicknesses of asthmatic pediatric patients having inhaled corticosteroid treatment. A study by Dereci et al showed no significant difference between asthmatic children and control group in terms of RNFL thicknesses [25]. However, another study by Gunay et al. showed that superior, inferior, and average RNFL thicknesses of asthmatic patients were significantly lower than those of the control group whereas subfoveal thickness did not differ between the groups [26]. However, this study included patients receiving inhaled corticosteroid treatment and corticosteroid treatment has been shown to affect choroidal thickness [27]. Thus it is not possible to know exactly whether the differences between the groups were due to the treatments or the disease itself.

There is growing evidence that systemic enhanced oxidative stress plays a key role in the pathophysiology and progression of asthma [28]. Several studies revealed that oxidative stress leads to vascular endothelial damage and decreased responsiveness to nitric oxide (NO), a potent vasodilator [2]. In addition, a positive correlation was found between vessel intima-media thickness and oxidative stress in asthma [5]. A histological study by Camelo et al. showed that increased oxidative stress is associated with thinning of the choroid and retinal pigment epithelium in mice. [29] These vascular effects of oxidative stress can lead to a decrease in CVI and ChT.

Choroidal vascular resistance and perfusion pressure are controlled by the autonomic nervous system [10]. Asthmatic patients have sympathetic system over-activity especially during exacerbations [30]. Since choroid tissue is comprised substantially of vascular components, overactivity of the sympathetic system leads to vasoconstriction, and thus can lead to a decrease in CVI and ChT. Moreover, there are studies suggesting that asthmatic patients have higher levels of endothelin-1 (ET-1), a very potent vasoconstrictor, compared to healthy controls. Asthmatic patients with higher levels of endothelin-1 also experience more severe bronchial obstruction and asthma attacks [31]. Increased ET-1 levels might be associated with lower CVI and ChT.

Hypoxemia and hypercapnia have been shown to affect choroidal thickness by alterations in the choroidal blood flow, increasing oxidative stress and triggering sympathetic system activity [8]. Although asthmatic patients may have normal respiratory function except during attack periods, mild hypoxemia and hypercapnia may occur during attacks [2]. There are some contradictory findings about the effects of hypercapnia on the choroid. A very recent study indicates that short-term hypercapnia may cause a temporary choroidal thickness increase in healthy subjects [32], but in respiratory diseases with chronic hypoxia and hypercapnia, such as COPD and OSAS, subfoveal choroidal thickness was found to be significantly thinner [8,9].

Our study has some limitations. Since this was a cross-sectional study, ChT, CVI, and RNFL thickness measurements were taken only once from each patient. Therefore, we were not able to follow up on whether these parameters vary according to asthma progression. Thus we can not make any comments on whether CVI could be used to monitor asthma progression. Again, in this study, we did not include asthma patients who received inhaled or systemic drug therapy because we assumed that drugs used to treat asthma (steroids, beta-agonists, etc.) could have effects on choroid thickness and vascularity index. Therefore, we cannot provide any information about the effect of asthma treatment on these parameters. This is another limitation of our study. Likewise, we could not find a study in the literature that investigated the relationship between asthma treatment and choroidal tissue. Therefore, there is no data yet on whether asthma medications affect choroidal parameters. Another limitation of our study is the small number of the study population. Based on the results of our study, it is clear that

prospective studies with larger study populations will be needed to investigate whether CVI can be used to monitor asthma progression and to investigate the relationship between asthma treatment and CVI.

Our study demonstrated preliminary findings regarding the association between asthma and some ocular structural changes. Our study could serve as a basis and a milestone for further studies evaluating asthma and ocular parameters. Prospective cohort studies will be needed to investigate possible clinical ocular pathologies in patients with asthma.

6. Conclusion

CVI measurement seems to be a useful method for the evaluation of choroidal structural changes. Our study revealed significantly lower CVI and ChT levels in adult asthma patients who were not taking medications compared to healthy controls. Based on the results of our study, we think that there may be structural changes in the choroid in asthma patients even though they do not have any ocular symptoms. Further studies are needed to investigate the exact mechanisms contributing to our ocular findings in asthma.

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