

Effect of inhaled fluticasone propionate on retinal nerve fiber layer thickness in asthmatic children

Selim Dereci¹, Ozgur Pirgon¹, Mustafa Akcam¹, Kemal Turkyilmaz², Bumin Dunder³

¹Department of Pediatrics, S. Demirel University, Faculty of Medicine, Isparta - Turkey

²Department of Ophthalmology, R.T. Erdogan University, Faculty of Medicine, Rize - Turkey

³Department of Pediatrics, Faculty of Medicine, Katip Celebi University, Izmir - Turkey

ABSTRACT

Purpose: Corticosteroids are under suspicion of playing an important role in the development of retinopathy. We aimed to determine peripapillary retinal nerve fiber layer (RNFL) thinning by spectral-domain optical coherence tomography (OCT) in children being treated with inhaled fluticasone propionate due to asthma.

Methods: Thirty-eight children diagnosed with allergic asthma (mean age 9.8 ± 2.8 years, age range 6-13 years) and 40 age-similar controls were enrolled in this study. All children with asthma were taking inhaled fluticasone propionate at a dosage of 250 µg or more per day for at least 1 year. The RNFL thickness measurements were performed using Cirrus HD spectral-domain OCT 400. Central subfield thickness, cube average thickness, and cube volume were also measured.

Results: Among the 38 children with asthma and 40 healthy subjects who completed follow-up, children with asthma had similar mean peripapillary RNFL thicknesses compared with control children. The mean central subfield thickness was significantly higher than that of controls (248.8 ± 23.4 vs 237.5 ± 23.5 , $p < 0.037$). There was a positive linear relationship between cube average thickness and eosinophil count with a Pearson correlation coefficient of 0.336 ($p < 0.039$) and a negative correlation was found between central subfield thickness and disease duration ($r = -0.385$, $p = 0.017$) in children with asthma.

Conclusions: Asthmatic children have similar peripapillary RNFL measurements compared to controls on spectral-domain OCT. Raised eosinophil counts in asthmatic children were found to be significantly associated with cube average thickness.

Keywords: Asthma, Children, Fluticasone propionate, Retinal involvement, Retinal nerve fiber layer

Introduction

Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm (1). From 2001 to 2009, asthma diagnoses increased among all demographic groups, with a higher percentage of children reported having asthma than adults (9.6% vs 7.7% in 2009) (2).

Inhaled corticosteroids are currently the most effective anti-inflammatory medications commonly used in the

treatment and management of mild to moderate asthma (3). Serious side effects are uncommon, but the risk increases with the daily dose. There are 3 published reports describing ocular complications of inhaled steroid use, including ocular hypertension, chorioretinopathy, and posterior subcapsular cataracts (4-6). Moreover, intrathoracic or intra-abdominal pressure in asthmatic attacks can cause visual abnormalities or retinal involvement (7). Mechanistically, it is thought that an acute rise in intrathoracic/intra-abdominal pressure from closure of the glottis leads to intraocular venous pressure increase (8).

The introduction of spectral-domain optical coherence tomography (SD-OCT) has improved retinal image resolution (9). Enhanced depth imaging technology allows for good-quality imaging of the choroid, permitting qualitative and quantitative analysis of this layer. Optical coherence tomography (OCT) also can be used to obtain histologic sections of the retina and retinal nerve fiber layer (RNFL) thickness measurements. In this study, we aimed to evaluate peripapillary RNFL thickness in children with asthma in comparison with those of age- and sex-matched healthy controls using Cirrus spectral-domain HD-OCT.

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Corresponding author:

Ozgur Pirgon
Department of Pediatrics
Faculty of Medicine
S. Demirel University
Isparta, Turkey
ozgurpirgon@gmail.com

Patients and Methods

Subjects

Thirty-eight children (20 girls, mean age 9.8 ± 2.8 years, age range 6–13 years, disease duration 1.6 ± 1.4 years) were recruited from children who were admitted to the Pediatric Allergy Unit from April 2012 to April 2013. The study group consisted of 38 prepubertal children with asthma (diagnosed according to GINA 2006 guidelines) (10) who had used inhaled fluticasone propionate (Flexotide, GlaxoSmithKline, Middlesex, UK) 250 µg daily for more than 1 year. In all participants, fluticasone propionate was administered with the aid of an aerochamber to ensure that the therapeutic dose required was delivered to the lungs. Male or female patients >7 years of age who were diagnosed with atopic asthma by clinical manifestations and positivity at least to one aeroallergen on skin prick testing or the presence of specific immunoglobulin E (IgE) were enrolled. Exclusion criteria included chronic diseases (except asthma), corneal abnormalities, retinal diseases, strabismus, glaucoma, optic disc disorders, neurologic diseases and other disorders that cause peripheral neuropathy such as diabetes mellitus and hypothyroidism, a previous history of ophthalmic surgery or ocular trauma, family history of glaucoma, and myopia or hyperopia >3.0 D.

Forty age-matched healthy children (20 girls, mean age 10.2 ± 2.6 years, age range 6–13 years) enrolled as a control group. Age- and sex-matched healthy subjects with no history of respiratory disorder, other atopic signs or symptoms, or helminthes or parasitic infection were considered as control subjects.

The institutional review board of R. T. Erdogan Medical Faculty Ethical Committee approved the study protocols. Signed informed consent forms were obtained from the parents of the children.

Total IgE and eosinophil counts

Total serum IgE level was measured using immunoenzymometric sequential assay (type 4) ELISA kits (AccuBind, Monobind Inc., Lake Forest, CA, USA) and values of over 100 IU/mL were considered high. Total eosinophil counts and the percentage of blood eosinophils were measured with an automated blood analyzer, ABX Pentra 80 (Horiba Medical, Montpellier, France), and values more than 4% were considered increased.

Eye examination

Each subject underwent ophthalmologic standard examination including measurement of visual acuity (by Snellen charts), slit-lamp examination, Goldmann applanation tonometry, central corneal thickness measurement (by Pocket Precision ultrasonic pachymeter, Quantel Medical, Clermont-Ferrand, France), and funduscopy (including detailed examination of the optic disc).

Measurements of peripapillary RNFL thicknesses

The RNFL thickness measurements were performed using Cirrus HD SD-OCT 400 (Carl Zeiss Meditec, Dublin, CA, USA).

Peripapillary RNFL thicknesses of temporal, nasal, inferior, and superior quadrants and average RNFL thickness were obtained with optic disc scan protocol based on the 6 mm C 6 mm data cube captured by the optic disc cube 200 200 scan. The OCT imaging was performed after participants' pupils were dilated to obtain higher signal quality. Scans with blinking and signal strengths <7 were excluded from the study. Central subfield thickness (CST), cube average thickness (CAV), and cube volume (CV) measurements were also based on the 6 mm a 6 mm data cube captured by the macular cube 512 128 scan.

Statistical analysis

Means and standard deviations were used as descriptive statistics. The appropriateness of the normal distribution of the data acquired was tested with the Kolmogorov-Smirnov test. For comparison of the measurement values of 2 groups, Student *t* test was applied to the values complying with the normal distribution and Mann-Whitney *U* test was applied to those not complying with the normal distribution. Pearson correlation test was used for correlation analysis. A value of $p < 0.05$ was used to indicate statistical significance. Data were analyzed by using the program Statistical Package for Social Sciences (SPSS for Windows 11.0, Chicago, IL, USA).

Results

Thirty-eight asthmatic children were enrolled in the study. Most of the patients had mild persistent asthma (87%). Mean patient age was 9.8 ± 2.8 years, and mean duration of inhaled steroid therapy was 1.6 ± 0.4 years. Thirty-six percent of patients received inhaled steroids exclusively; 21% received inhaled steroids with a short course of oral steroids. There was no difference in age, sex, weight, or height compared to controls. None was found to develop posterior subcapsular cataract, glaucoma, or increased intraocular pressure (IOP).

There were no significant differences between children with asthma and those without asthma with respect to mean superior, inferior, or temporal RNFL thickness measurements (Tab. I). Moreover, we found no difference between control subjects and asthmatic children for CV (9.5 ± 0.6 vs 9.7 ± 0.8 µm, $p = 0.163$) or CAV (278.8 ± 10.6 vs 272.56 ± 22.5 mm³, $p = 0.116$). However, IgE levels and CST measurements were significantly higher in asthmatic children than in healthy controls (248.8 ± 23.4 vs 237.5 ± 23.5 µm, $p = 0.037$).

We found no significant correlations among IgE levels, eosinophil counts, disease duration, and OCT parameters in asthmatic children. However, mean CAV measurements were positively correlated with eosinophil counts ($r = 0.336$, $p = 0.039$) and CST had a negative correlation ($r = -0.385$, $p = 0.017$) for disease duration (Tab. II).

Discussion

The retinal nerve fibers, which occur in the innermost layer of the retina, are formed by ganglion cell axons, which react to impulses from the photoreceptors to the central vision by way of the optic nerve. Axon damage is characterized by thinning of RNFL. As a result of the thinning of the RNFL, a

TABLE I - Clinical characteristics of the asthmatic children and healthy controls

	Patients	Controls	p
Age, y	9.8 ± 2.8	10.2 ± 2.6	0.539
Female/male	20/18	20/20	0.995
Disease duration, y	1.6 ± 0.4	-	-
IgE level	394.8 ± 385.6	144.5 ± 54.2	0.021 ^a
Eosinophil count, %	4.78 ± 3.09	3.43 ± 2.89	0.162
ARNFLT	96.4 ± 8.7	94.9 ± 8.4	0.451
SRNFLT	125.0 ± 13.5	123.1 ± 15.5	0.573
NRNFLT	73.6 ± 14.1	72.3 ± 11.1	0.650
IRNFLT	121.9 ± 14.8	114. ± 18.6	0.071
TRNFLT	66.2 ± 7.7	67.2 ± 9.1	0.581
CST, µm	248.8 ± 23.4	237.5 ± 23.5	0.037 ^a
CV, mm ³	9.5 ± 0.6	9.7 ± 0.8	0.163
CAV, µm	278.8 ± 10.6	272.56 ± 22.5	0.116

ARNFLT = average retinal nerve fiber layer thickness; CAV = cube average thickness; CST = central subfield thickness; CV = cube volume; IgE = immunoglobulin E; IRNFLT = inferior retinal nerve fiber layer thickness; NRNFLT = nasal retinal nerve fiber layer thickness; SRNFLT = superior retinal nerve fiber layer thickness; TRNFLT = temporal retinal nerve fiber layer thickness.

All values are mean ± SD.

^aSignificant.

decrease in visual acuity may occur. Various neurodegenerative diseases can affect RNFL thickness (11-14). The present study demonstrated that there was no significant difference in peripapillary RNFL thickness between childhood asthmatic patients vs control subjects during inhaled steroid treatment, although asthmatic children had higher RNFL thickness than did healthy children.

A direct relationship between topical corticosteroids, systemic corticosteroids, and elevated IOP has been recognized for more than 5 decades. Generally, it is well-known that steroids can cause an elevation of IOP when they are administered topically or systemically over a long period of time (15). The extent to which these corticosteroids influence IOP remains controversial. Alsaadi et al (16) showed no increase in IOP in children between the ages of 5 and 15 years, with no family history of glaucoma, at a treatment with inhaled fluticasone propionate dose of 250 µg daily for ≥6 months in comparison to healthy nonasthmatic patients. In the present study, there was no difference between asthmatic children and control subjects for CV measurement that was related to IOP. Inhaled fluticasone propionate at 250 µg once daily for more than 1 year was safe and effective for long-term asthma treatment, with no evidence of clinically adverse retinal involvement.

A thin central cornea and increased IOP have been identified as major risk factors in the development of glaucoma

TABLE II - Correlations among immunoglobulin e levels, eosinophil count, disease duration, and optical coherence tomography parameters in children with asthma

	IgE level	Eosinophil count	Disease duration
ARNFLT			
<i>r</i>	0.053	0.195	-0.106
<i>p</i>	0.753	0.240	0.527
SRNFLT			
<i>r</i>	-0.017	0.070	-0.060
<i>p</i>	0.921	0.674	0.723
NRNFLT			
<i>r</i>	0.085	0.114	-0.016
<i>p</i>	0.610	0.497	0.925
TRNFLT			
<i>r</i>	0.023	0.229	-0.299
<i>p</i>	0.889	0.167	0.069
IRNFLT			
<i>r</i>	0.042	0.184	-0.017
<i>p</i>	0.804	0.269	0.918
CAV			
<i>r</i>	0.026	0.336 ^a	-0.224
<i>p</i>	0.879	0.039 ^a	0.177
CST			
<i>r</i>	-0.196	-0.041	-0.385 ^a
<i>p</i>	0.239	0.807	0.017 ^a
CV			
<i>r</i>	0.304	0.199	0.147
<i>p</i>	0.064	0.231	0.379

ARNFLT = average retinal nerve fiber layer thickness; CAV = cube average thickness; CST = central subfield thickness; CV = cube volume; IgE = immunoglobulin E; IRNFLT = inferior retinal nerve fiber layer thickness; NRNFLT = nasal retinal nerve fiber layer thickness; SRNFLT = superior retinal nerve fiber layer thickness; TRNFLT = temporal retinal nerve fiber layer thickness.

^aSignificant.

and ocular hypertension (17). However, in a recent study, the intermittent use of intranasal budesonide in the treatment of allergic rhinitis, at an average daily dose of 100 µg over a period of 2 years, was not associated with ocular side effects such as cataract, glaucoma, corneal ectasia, or abnormal tear function in 150 children aged between 8 and 15 years (18). Ozkaya et al (18) reported the effects of long-term treatment with inhaled fluticasone propionate spray on some ocular functions in pediatric patients with asthma. They observed that long-term intermittent treatment for 3-6 years with inhaled fluticasone propionate spray, as much as average 320 µg daily, in children with asthma was safe for some eye outcomes, including cataract formation, corneal ectasia, ocular hypertension or glaucoma, and central corneal thickness (19). In our study, none of the asthmatic children developed posterior subcapsular cataract, glaucoma, or increased IOP.

Corticosteroids by nasal spray or inhalation may cause ocular hypertension in susceptible patients. The degree of thinning correlates with severity of temporal macular thinning. These patients may require different peripapillary RNFL thickness thresholds for future glaucoma evaluations. This study indicates that use of inhaled fluticasone propionate in children with asthma is probably safe as far as not inducing peripapillary RNFL thickness. Our findings suggest that long-term intermittent treatment for 6-18 months with inhaled fluticasone propionate spray, as much as average 250 µg daily, in children with asthma seems to be safe for some eye outcomes.

Disclosures

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Conflict of interest: None of the authors has conflict of interest with this submission.

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