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Predicting optic atrophy in patients with anterior uveitis by computed tomography-based assessment of optic nerve diameter

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Background: *An objective assessment of factors for ocular inflammation and its sequelae and diagnostic assessment of possible development of the sequelae in early phases of uveitis are essential for early and effective treatment of endogenous uveitis.*

Purpose: *To determine whether it is possible to predict optic atrophy in patients with anterior uveitis using computed tomography (CT)-based assessment of optic nerve diameter.*

Material and Methods: *Patients with anterior uveitis underwent a routine eye examination (ophthalmoscopy, biomicroscopy, intraocular pressure (IOP) measurement, and Humphrey perimetry). In addition, they underwent CT-based assessment of optic disc diameter at 3-5 mm from the entrance into the orbit in the affected eye and the contralateral healthy eye. Patients received treatment as per the protocol.*

Results*: The percentage difference in optic nerve diameter between patients with uveitis complicated by optic neuritis and those with uveitis only for affected eyes was large (33.1%) and statistically significant. At 3 months and 6 months after initiation of treatment, mean optic disc diameter in patients with optic neuritis decreased by 37.2% and 49.1%, respectively, compared to baseline values. At 6 months, a decrease in optic nerve diameter among optic neuritis patients was observed both in those who received treatment and in those who failed to receive treatment, but was less marked in the former patients. Particularly, from 3 months to 6 months, optic nerve diameter decreased by 17.3% in treated optic neuritis patients versus 23.5% in those who remained untreated.*

Conclusion: *CT-based data on the change in the optic nerve diameter at the entrance into the orbit in patients with optic neuritis is an objective characteristic of the presence and grade of atrophic process. Early identification of the potential for development of optic atrophy in individuals with optic neuritis will make it possible to treat them early and, consequently, to prevent or stabilize the process.*

Keywords:

iidiopathic anterior uveitis, optic neuritis and atrophy, computed tomography, assessment of optic nerve diameter

Introduction

Because uveitis is a severe eye disorder prevalent among young working-age adults, with 10% to 35% of uveitis eyes developing blindness or visual impairment, the disease is a serious medical and social problem.

Endogenous uveitis is characterized by a chronic recurrent course which in 55-60% of cases results in severe organic anterior and posterior segment changes refractory to medical and surgical treatment. Optic nerve inflammation is a severe complication occurring in 14-27% of cases. Optic neuritis can result in partial or total optic atrophy, leading to permanent vision loss [1, 2].

Objective assessment of risk factors for ocular inflammation and its sequelae and conducting clinical studies in early phases of uveitis for predicting complications are essential for early and effective treatment of endogenous uveitis.

We have previously reported on the method developed for predicting optic atrophy as a sequela of optic neuritis in patients with chronic anterior uveitis [3]. The method involves computed tomography (CT)-based assessment of nerve diameter thickness in the affected and healthy eyes of patients with chronic anterior uveitis after disease recurrence and subsequent comparison of the measurements obtained with those obtained during the first episode of the disease. A percentage difference in optic nerve diameter between in the affected eye and the contralateral healthy eye of 30% or more was found to be a predictor of optic atrophy.

In a clinical study at the Filatov institute, of the 34 patients with chronic recurrent anterior uveitis, seven exhibited optic nerve thinning (a percentage difference in optic nerve diameter measured at the entrance into the orbit between the affected eye and the contralateral healthy eye of 30% or more), which enabled predicting optic atrophy in the latter patients. Of the seven patients, six received intensive metabolic therapy and therapy aiming to prevent optic disc degeneration, which resulted in the stabilization

of the condition. The seventh patient could not receive the aforementioned treatment due to family circumstances, and, in seven months, exhibited a relative central scotoma with ophthalmoscopic evidence of partial optic atrophy. The results obtained provided reason for further research to be done on a larger sample of patients with a purpose to determine whether it is possible to predict optic atrophy in patients with anterior uveitis using CT-based assessment of optic nerve diameter.

Material and Methods

This open-label, non-interventional study was conducted within the framework of the research program named "Optimizing the diagnosis, treatment and prevention of the development of ocular degenerative and inflammatory disorders" (State Registration No. 0119 U 003575). The study followed the ethical standards stated in the Declaration of Helsinki, the European Convention on Human Rights and Biomedicine and relevant laws of Ukraine. Informed consent was obtained from 54 patients who were examined and treated for idiopathic unilateral anterior uveitis in the Department of Ocular Inflammation, the Filatov Institute of Eye Diseases and Tissue Therapy, and Medical Eye Care Center of Odesa National Medical University. The inclusion criterion was the presence of unilateral idiopathic anterior uveitis. The exclusion criteria were diabetes; acute infectious, viral, or cardiovascular disease; abnormal circulation in the major ocular vessels; history of ocular surgery; or pregnancy.

Anterior uveitis was diagnosed using International Classification of Diseases, 10th Revision (ICD-10) criteria and based on the Standardization of Uveitis Nomenclature (SUN) criteria, categorizing uveitis along several dimensions: course, laterality, anatomic location of the inflammation, morphology, and presence of active infection [4].

Optic neuritis was diagnosed in 18 of the 54 patients with anterior uveitis.

All patients underwent a routine eye examination (ophthalmoscopy, biomicroscopy, intraocular pressure (IOP) measurement, and Humphrey perimetry). Best-corrected visual acuity (BCVA) was assessed at 6 m using charts composed of Ukrainian letter optotypes. Standardization of the 2005 SUN working group classification was used to classify the uveitis and grade the uveitis activity [5, 6]. In addition, CT scans were used to measure the optic disc diameter at 3-5 mm from the entrance into the orbit in the affected eye and the contralateral healthy eye during the first episode of the disease and during disease recurrence.

The IOP was normal in all patients. Patients received treatment as per the protocol adopted by the Ethics Commission of the Filatov institute (2012) and approved by the National Academy of Medical Science of Ukraine Protocol (2018) on the basis of United States Public Health Service (USPHS)/ Infectious Diseases Society of America (IDSA) Guidelines for the Prevention of Opportunistic Infections in Persons Infected with Human Immunodeficiency Virus. Treatment involved antibiotics, non-steroidal anti-inflammatory drugs, immune suppressors, corticosteroids, and biological immune response modulators. Treatment duration was 10 days or less for patients with uncomplicated anterior uveitis, and 14 ± 3.4 days or less for patients with anterior uveitis complicated by optic neuritis.

Statistical analyses were conducted using Statistica 10.0 (StatSoft, Tulsa, OK, USA) software. Student t-test for independent and dependent samples was applied to assess associations between study parameters.

Results

Table 1 presents the mean percentage difference in optic nerve diameter measured at the entrance into the orbit for the affected eye and the contralateral healthy eye for 36 patients with uncomplicated uveitis and 18 patients with uveitis complicated by optic neuritis.

The mean percentage difference in optic nerve diameter for healthy eyes was rather small (0.3%). Of note that, in patients with uncomplicated anterior uveitis, the mean optic nerve diameter for healthy eyes was the same that for affected eyes (4.164 ± 0.068 мм). The percentage difference in optic nerve diameter between patients with uveitis complicated by optic neuritis and those with uveitis only for affected eyes was large (33.1%) and statistically significant. All patients were treated with a course of anti-inflammatory therapy, but 5 of the 18 patients with optic neuritis in the presence of anterior uveitis failed to receive a course of metabolic therapy and therapy aiming to prevent optic disc degeneration due to various reasons.

It should be noted that, at baseline, the percentage difference in optic nerve diameter measured at the entrance into the orbit in these subgroups was insubstantial both for healthy eyes and affected eyes (1.1% and 2.83%, respectively), which indicates that the groups were well matched with respect to these characteristics.

At 3 months and 6 months after initiation of treatment, mean optic disc diameter in patients with optic neuritis decreased by 37.2% and 49.1%, respectively, compared to baseline values (P = 0.000 for both comparisons). At 6 months, a decrease in optic nerve diameter among optic neuritis patients was observed both in those who received treatment and in those who remained untreated, but was less marked in the former patients (Table 3). Particularly, from 3 months to 6 months, optic nerve diameter decreased by 17.3% in treated optic neuritis patients (P = 0.000) versus 23.5% in those who remained untreated (P = 0.020).

In addition, at 3 months, the difference in optic nerve diameter was insubstantial (3.4%) and not statistically significant (P = 0,449) both for the former and the latter patients. At 6 months, mean optic nerve diameter in the treated optic neuritis patients was thinner than at 3 months, but 11.3% thicker than in those who remained untreated (P=0.027).

Discussion

The analysis of literature on the course of uveitis complicated by optic neuritis and resulting in optic atrophy and vision loss indicated the value given to a search for methods for predicting optic atrophy in an attempt to enable

Table 1. Difference in optic nerve diameter at the entrance into the orbit for the healthy eye and affected eye in patients with anterior uveitis only and those with both anterior uveitis and optic neuritis

Healthy or affected eye	Anterior uveitis only, n=36	Anterior uveitis and optic neuritis, n=18
Healthy eye	4.164 ± 0.068 100.0%	4.150 ± 0.079 99.7%
Affected eye	4.164 ± 0.068 100.0%	5.544 ± 0.223* 133.1%

Note: *, significance of difference in the mean value (P value = 0.000).

Table 2. Change in the diameter of the optic nerve near its entrance into the orbit in patients with optic neuritis as a complication of anterior uveitis

Diameter of the optic nerve near its entrance into the orbit (mm)		
Baseline (), n=18	3 months, n=18	6 months, n=18
5,544 ± 0.223 100,0%	3.483 ± 0.279* 62,8%	2.822 ± 0.273* 50.9%

Note: *, significance of difference in the mean value (P value = 0.000).

Table 3. Changes in the diameter of the optic nerve near its entrance into the orbit in treated and untreated patients with optic neuritis as a complication of anterior uveitis

Treated or untreated patients	Time points	
	3 months	6 months
Untreated patients, n=5	3.400 ± 0.308 - 100.0%	2.600 ± 0.200 P = 0,0196 76.5%
Treated patients, n=13	3.515 ± 0.273 - 100.0%	2.908 ± 0.253 P = 0.000 82.7%

early pathogenetic treatment and prevent a negative outcome. Numerous studies have demonstrated that peripapillary nerve fiber layer (RNFL) thickening is a risk factor for partial optic atrophy [7]. Given these findings, it was to proposed to predict the RNFL thickening loss following optic neuritis on the basis of a strong association found between optic nerve Magnetization Transfer Ratio (MTR) after an episode of optic neuritis and the degree of axonal damage [8].

Others have proposed to use biochemical inflammatory markers as criteria for predicting the outcome of optic neuritis. Zheng and colleagues [9] generated an optic nerve crush model in mice in which the optic nerve upregulated toll-like receptor 4 (TLR4) following injury. They found that the protein expression levels of TLR4, interleukin (IL)-6 and tumor necrosis factor (TNF)-α were significantly increased after optic nerve injury. Talla and colleagues [10] aimed to determine if phosphorylated neurofilament heavy chain (pNF-H) released into the bloodstream is a noninvasive indicator of neurodegeneration in experimental optic neuritis. They concluded that elevated serum pNF-H levels are a useful marker of neurodegeneration of the optic nerve in isolated experimental optic neuritis. Petzold and Plant [11] investigated the diagnostic and prognostic value of a biomarker for neurodegeneration, the neurofilament heavy chain (NfH) in patients with immune-mediated optic neuropathies. They found that high serum NfH-SMI35 levels were related to poor visual outcome.

Impaired expressions of pro-inflammatory and anti-inflammatory cytokines have an important role in the pathogenesis of optic neuritis, which it is reasonable to take into account when developing methods for the prediction of optic atrophy.

A group of Ukrainian researchers [12] proposed predicting optic atrophy by determining IL-10 levels in tear samples from the affected eye and serum gelatinase B/matrix metalloproteinase 9 (MMP-9), with a serum MMP-9 level exceeding 98.6 ng/ml required to predict partial optic atrophy. Ponomarchuk and colleagues [13] took into account that optic atrophy is characterized also by functional impairment of the visual system and they proposed to determine optic atrophy objectively based on electrical-phosphene data. Others [14] believed that a disadvantage of the above method was that electrical-phosphene data were related to a single point of the eye globe. They proposed a method to determine the grade of optic atrophy by using the mean value of phosphene-based threshold of electrical sensitivity determined in four quadrants.

Therefore, the CT-based method we proposed for predicting the development of optic atrophy in patients with anterior uveitis (a) involves the objective determination of optic nerve diameter, (b) takes into account the pathogenesis and clinical findings of this complication, (c) may be an option depending on the diagnostic capabilities of the medical center and (d) may be used either alone or in conjunction with other methods.

Conclusion

In general, the results presented indicate that the data on the change in the optic nerve diameter at the entrance into the orbit in patients with optic neuritis is an objective characteristic of the presence and grade of atrophic process. A notable limitation of the method proposed is that it may only be applicable in patients with unilateral uveitis. These findings also allow to conclude that early identification of the potential for development of (with early preventive treatment for) optic atrophy in individuals with optic neuritis will make it possible if not to prevent then certainly to stabilize or slow down this pathological process.

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Disclosures

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