Optical Coherence Tomography Characteristics of Eyes with Acute Anterior Uveitis*

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ABSTRACT: **Background:** Acute, as opposed to chronic, anterior uveitis is rarely associated with macular or optic nerve edema. Nevertheless, mild changes may not be visible on examination.

Objectives: To implement non-invasive ocular coherence tomography (OCT) for obtaining quantitative and qualitative data in the assessment of changes in macular morphology and peripapillary retinal nerve fiber layers in eyes with acute anterior uveitis.

Methods: This retrospective case-control study was conducted in patients with unilateral acute anterior uveitis lasting for up to one month. Patients with evidence of other ocular disease or who had undergone intraocular surgery were excluded. We reviewed the charts of 14 consecutive patients who were diagnosed with acute unilateral anterior uveitis between 2007 and 2008 at the Tel Aviv Medical Center. Data on demographic details, ophthalmic examination, macular thickness and peripapillary retinal nerve fiber layer (RNFL) thickness (as demonstrated by OCT) were retrieved. Retinal and RNFL thickness was compared between the healthy fellow eye (control) and the uveitic eye in the central and four perifoveal quadrant regions, and RNFL thickness was compared in the mean and four quadrant values by Student's *t*-test.

Results: We evaluated 28 eyes of 7 males and 7 females (mean age 37.7 years, range 20–65). The diagnoses were: idiopathic in five patients, ankylosing spondylitis in five, Crohn's disease in one patient and reactive arthritis in one. Nine patients were HLA-B27 positive. The retina and the peripapillary NFL in each area were thicker in the uveitic eyes compared to the controls. The difference was statistically significant. There was no correlation between the differences in OCT values and patients' demographic characteristics.

Conclusions: OCT demonstrated that eyes with acute anterior uveitis had thicker maculae and thicker peripapillary RNFL than controls. This finding suggests that even milder anterior uveitis may be associated with some degree of posterior segment manifestations.

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KEY WORDS: anterior uveitis, HLA-B27, macular edema, ocular coherence tomography (OCT), retinal nerve fiber layer (RNFL)

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Classic acute anterior uveitis is characterized by the presence of cells and flare in the anterior chamber. Posterior synechiae, fibrin and even hypopyon are sometimes present in the more severe cases. Macular edema is present in a small minority of patients, having been reported in 4%–9% of cases [1]. Frank optic disk swelling is also an unusual finding in isolated anterior uveitis [1]. Both macular and optic nerve head edema can be diagnosed by clinical examination, but mild cases may not be detected on fundoscopy. These subclinical cases may be diagnosed either by angiography with fluorescein that demonstrates hyperfluorescence and leakage, or by assessment of retinal thickness by ocular coherence tomography [2-5].

The aim of the present study was to determine whether acute anterior uveitis is associated with changes in the macular and peripapillay retinal nerve fiber layer as detected by OCT.

PATIENTS AND METHODS

We reviewed the medical records of all patients with monocular non-infectious acute anterior uveitis lasting for up to one month between January 2007 and December 2008. The patients were evaluated at the uveitis clinic of the Tel Aviv Sourasky Medical Center, a university-affiliated tertiary referral center. Excluded were individuals with uveitis persisting for longer than one month, patients with other ocular diseases in either eye, those who underwent any intraocular surgery, and patients with media opacities. The study was carried out according to the tenets of the Declaration of Helsinki and was approved by the local ethics committee.

Prior to their OCT examination, all patients underwent a complete ophthalmological examination, including visual acuity, slit-lamp examination and fundoscopy with dilated pupils. For OCT scanning (Stratus OCT 3000, Carl Zeiss Meditech, Oberkochen, Germany), macular thickness and fast RNFL protocols were used. All scans were done using an internal fixation target in the OCT device. Macular thickness protocol was used for retinal thickness assessment. Retinal thickness was measured in the central fovea area as well as in the four central and four peripheral perifoveal quadrants (inferior, superior, temporal,

OCT = ocular coherence tomography
RNFL = retinal nerve fiber layer

nasal). The fast RNFL protocol was used to assess peripapillary (360 degree) RNFL thickness. The RNFL data consisted of the average of three circular scans in the set. Only sets with a signal strength > 6 were used. The second (healthy) eye of each patient served as a control group and the measurements were compared between the uveitic eyes and the healthy fellow eyes. The following data were extracted from the patients' files: gender, age, visual acuity, examination findings, refraction, systemic diagnoses, and presence of HLA-B27 antigen.

STATISTICAL ANALYSIS

All measured parameters, including the mean RNFL thickness, the average RNFL thickness in the four quadrants, the central retinal thickness and the retinal thickness in the four perifoveal quadrants were generated automatically in the analysis. All retinal and RNFL parameters were compared between the uveitic and healthy fellow eyes. The Wilcoxon signed Rank test was used to compare the clinical findings of the healthy and the uveitic eye of each patient. Changes in continuous clinical parameters were compared between genders and between idiopathic and HLA-B27-associated uveitis by the Mann-Whitney non-parametric test. Association between age and change in continuous clinical parameters was evaluated by Spearman's correlation coefficient. The statistical analysis was performed by the SPSS for Windows software, version 14.0.

Table 1. Patient demographics (N=14)

Age (yrs) **Mean ± SD (range)**	**37.69 ± 13.62** **(20–65)**
Gender Male (N, %) Female (N, %)	 7 (50%) 7 (50%)
Uveitis type Idiopathic (N, %) HLA-B27+ (N, %)	 5 (35.7%) 9 (64.3%)
Uveitis side Left (N, %) Right (N, %)	 7 (50%) 7 (50%)

Table 2. Paired comparisons of macular thickness and NFL thickness in the uveitic eyes vs. healthy control fellow eyes

	Healthy eye			Uveitic eye			Wilcoxon signed rank test
	Mean (μ)	N	SD (μ)	Mean (μ)	N	SD (μ)	*P* value
CFT	214.79	14	24.54	231.21	14	23.44	< 0.0001 *
Sup quad	281.71	14	24.41	314.79	14	18.60	< 0.0001 *
Nasal quad	284.93	14	23.12	312.79	14	20.49	< 0.0001 *
Inf quad	283.86	14	20.50	309.07	14	19.29	< 0.0001 *
Temp quad	267.64	14	27.68	298.57	14	22.40	< 0.0001 *
Mean	279.54	14	23.25	309.79	14	14.20	< 0.0001 *
Sup RNFL	109.11	9	16.09	128.56	9	17.52	0.074
Nasal RNFL	65.89	9	16.97	81.78	9	23.53	0.027*
Inf RNFL	127.00	9	18.85	145.22	9	18.05	0.004*
Temp RNFL	75.44	9	22.93	82.33	9	25.67	0.063
Mean RNFL	94.41	9	10.76	109.48	9	14.94	0.004*

* $P < 0.05$
CFT = central foveal thickness, RNFL = retinal nerve fiber layer

RESULTS

The study group comprised 28 eyes of 14 patients – 7 males and 7 females with unilateral acute anterior uveitis. The mean age of the patients was 37.7 years (range 20–65). The mean visual acuity was 6/15 (6/6.5–6/60) in the uveitic eyes and 6/7 (6/6–6/12) in the healthy fellow eyes (controls). The diagnoses were as follows: idiopathic in five patients, ankylosing spondylitis in five, Crohn's disease in one patient and reactive arthritis in one. All these seven patients were found to have the antigen HLA-B27. Two patients were found to have the antigen HLA-B27 but did not have a systemic disease. The demographic data are summarized in Table 1.

All 14 patients had a macular scan and 9 also underwent a peripapillary RNFL scan. The retinal thickness was found to be significantly larger in the uveitic eyes compared to the controls in all macular areas tested; the mean central retinal thickness was 231.21 ± 23.44 μ in the uveitic eyes vs. 214.79 ± 24.54 μ in the healthy eyes. The mean perifoveal thickness in the uveitic eyes was 309.79 ± 14.2 μ vs. 279.54 ± 23.25 μ in the healthy eyes ($P < 0.05$) [Table 2] .

The RNFL thickness was also larger in the uveitic eyes: the mean RNFL thickness was 109.48 ± 10.76 μ in the uveitic eyes vs. 94.48 μ in the healthy fellow eyes [Table 2]. The mean RNFL thickness in the uveitic eyes was larger than in the healthy eyes ($P < 0.05$) The RNFL thickness in the uveitic eyes was also significantly larger than in the non-uveitic eyes in the inferior and nasal quadrants. The difference between the thickness of the superior and temporal quadrants was not statistically significant [Table 2].

We then correlated the differences between the healthy and uveitic eyes to various parameters. There was no correlation between the type of uveitis (idiopathic or HLA-B27) and the difference in retinal and RNFL thicknesses, nor was there any correlation between the patients' age and the difference between the uveitic and control eyes.

The difference in retinal thickness between the uveitic and healthy eyes when evaluated in males and females did reach a level of significance ($P < 0.05$) in some of the parameters: there was a difference in the superior, nasal and inferior parafoveal macular areas, with women having significantly more thickening in the uveitic eyes compared to men.

CASE REPORT

A 51 year old woman with ankylosing spondylitis and no previous eye problems was referred to the emergency room because of non-clearing anterior uveitis of her right eye lasting 2 weeks. On examination her visual acuity was 6/9 in the right eye and 6/7 in the left. She had conjunctival infection, multiple small keratic precipitates, cells +3 and flare +3 with fibrin formation and posterior synechiae. On fundus examination the macula and optic nerve looked normal. The left eye showed normal anterior and posterior segments. OCT showed that her right macula had a normal foveal contour but mildly thickened perifoveal retina [Figure 1A] compared to the left macula [Figure 1B].

The RNFL analysis was within normal limits in both eyes but the thickness in each point was larger in the right eye than in the left one, as seen in the graphs comparing the thickness in both eyes [Figure 2].The mean RNFL thickness was 114.13 µ in the uveitic eye and 81.26 µ in the healthy eye.

DISCUSSION

Acute anterior uveitis is rarely associated with clinically detectable macular or optic disk edema. We were able to detect significant changes in retinal and peripapillary nerve fiber layer thicknesses on OCT in the affected and the fellow eye.

Fluorescein angiography had been considered the gold standard for diagnosing macular edema, but OCT, a non-invasive procedure, was reported to have a sensitivity of 96% and specificity of 100% compared to fluorescein angiography [4] and has now become the main tool for diagnosis and follow-up of macular changes.

Trail [8] reported macular thickening in eyes with unilateral moderate-to-severe anterior uveitis with visual acuity deterioration to < 6/9, fibrin, hypopyon or posterior synechia. The mean difference in retinal thickness between the affected and the healthy eyes was 11.2%. Of their 15 patients 14 were HLA-B27 positive.

We did not limit our study cohort to patients with severe anterior uveitis but nevertheless were surprised to find that in all patients the macular thickness in the affected eye was higher than in the fellow eye. In addition, all patients who underwent OCT of the optic nerve head RNFL were found to have RNFL thickening in the uveitic eye.

According to available data on normal optic disks [9] there was no statistically significant asymmetry between fellow eyes, and therefore we were able to use the healthy eyes as the control group. One may argue that since uveitis may be a systemic disease, the second, presumably healthy, eye may also be involved. In these cases our results may even have a stronger power, and had we compared the macula and RNFL thickness to healthy age-matched controls the differences may have been larger.

We did not find any correlation between the presence of retinal and RNFL thickening and the etiology of uveitis (idiopathic or HLA-B27 positive), nor to the parameter of age. We did, however, find a significant difference between males and females, with more females demonstrating macular thickening, but not RNFL thickening, compared to males. Nevertheless, due to the small number of patients in the subgroups this should be taken with caution.

We assume that the pathogenesis of the macular changes we observed is similar to that of uveitic cystoid macular edema and is associated with a breakdown in the blood-aqueous and blood-retinal barriers and an increase in vascular permeability [10]. Cases of frank macular edema probably represent the more severe end of the same spectrum of macular changes in intraocular inflammation.

The literature contains similar findings of increased retinal thickness after uneventful phacoemulsification and intraocular

Figure 1. Retinal thickness analysis map of the right eye **[A]** and the left eye **[B]** in patient #1

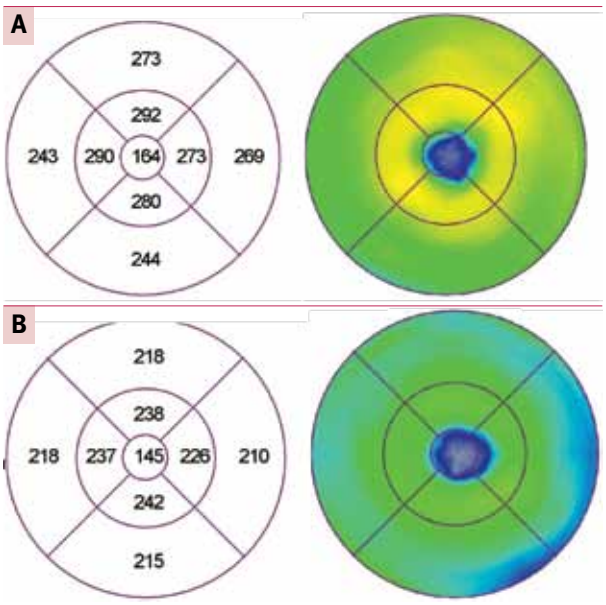
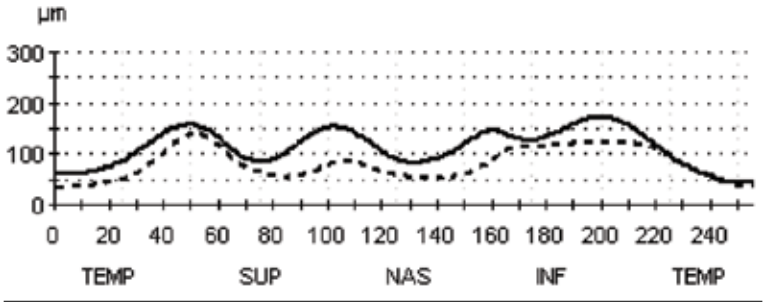


Figure 2. Retinal nerve fiber layer map of patient #1. The peripapillary RNFL is thicker in the right eye when compared to the left healthy eye



lens implantation [11,12], supporting our hypothesis that even relatively mild ocular inflammation may cause some degree of blood-retinal barrier disruption and retinal edema.

In conclusion, the OCT imaging modality allows a non-invasive investigation of microscopic macular and peripapillary RNFL changes that are not yet detectable in a standard clinical evaluation, enabling us to demonstrate that even milder ocular inflammation might cause posterior segment changes. Further research including a prospective study with long follow-up after the resolution of the inflammation is required.

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Capsule

A selective jumonji H3K27 demethylase inhibitor modulates the pro-inflammatory macrophage response

The jumonji (JMJ) family of histone demethylases comprises Fe^{2+}- and α-ketoglutarate-dependent oxygenases that are essential components of regulatory transcriptional chromatin complexes. These enzymes demethylate lysine residues in histones in a methylation-state and sequence-specific context. Considerable effort has been devoted to gaining a mechanistic understanding of the roles of histone lysine demethylases in eukaryotic transcription, genome integrity and epigenetic inheritance, as well as in development, physiology and disease. However, because of the absence of any selective inhibitors, the relevance of the demethylase activity of JMJ enzymes in regulating cellular responses remains poorly understood. Kruidenier et al. present a structure-guided small molecule and chemoproteomics approach to elucidating the functional role of the H3K27me3-specific demethylase subfamily (KDM6 subfamily members JMJD3 and UTX). The liganded structures of human and mouse JMJD3 provide novel insight into the specificity determinants for cofactor, substrate and inhibitor recognition by the KDM6 subfamily of demethylases. We exploited these structural features to generate the first small molecule catalytic site inhibitor that is selective for the H3K27me3-specific JMJ subfamily. We demonstrate that this inhibitor binds in a novel manner and reduces lipopolysaccharide-induced pro-inflammatory cytokine production by human primary macrophages, a process that depends on both JMJD3 and UTX. These results resolve the ambiguity associated with the catalytic function of H3K27-specific JMJs in regulating disease-relevant inflammatory responses and provide encouragement for designing small-molecule inhibitors to allow selective pharmacological intervention across the JMJ family.

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The man of action has to believe, the inquirer has to doubt; the scientific investigator is both

C.S. Pierce (1839-1914), American philosopher, logician, mathematician and scientist, sometimes known as "the father of pragmatism"