Evaluation of Retinal Nerve Fiber Layer Thickness in Eyes With Hypertensive Uveitis

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**IMPORTANCE** Uveitic glaucoma is among the most common causes of irreversible visual loss in uveitis. However, glaucoma detection can be obscured by inflammatory changes.

**OBJECTIVE** To determine whether retinal nerve fiber layer (RNFL) measurement can be used to detect glaucoma in uveitic eyes with elevated intraocular pressure (IOP).

**DESIGN, SETTING, AND PARTICIPANTS** Comparative case series of RNFL measurement using optical coherence tomography performed from May 1, 2010, through October 31, 2012, at a tertiary referral center. We assigned 536 eyes with uveitis (309 patients) in the following groups: normal contralateral eyes with unilateral uveitis (n = 72), normotensive uveitis (Uv-N) (n = 143), raised IOP and normal optic disc and/or visual field (Uv-H) (n = 233), and raised IOP and glaucomatous disc and/or visual field (Uv-G) (n = 88).

**EXPOSURES** Eyes with uveitis and elevated IOP (>21 mm Hg) on at least 2 occasions.

**MAIN OUTCOMES AND MEASURES** Comparison of RNFL values between groups of eyes and correlation with clinical data; risk factors for raised IOP, glaucoma, and RNFL thinning.

**RESULTS** Mean (SD) global RNFL was thicker in Uv-N (106.4 [21.4] μm) compared with control (96.0 [9.0] μm; P < .001) eyes and was thicker in Uv-N eyes with active (119.6 [23.2] μm) compared with quiescent (102.3 [20.8] μm; P = .001) uveitis, which in turn was not significantly different from control eyes (P = .07). Compared with Uv-N eyes, significant RNFL thinning was seen in all quadrants except the temporal in Uv-G eyes and significant thinning in the inferior quadrant of Uv-H eyes with no evidence of disc or visual field changes (P = .03). Risk factors for elevated IOP were male sex and anterior uveitis. Age, higher peak IOP, longer duration of follow-up, and uveitis-induced elevation of IOP were risk factors for glaucoma and RNFL defect.

**CONCLUSIONS AND RELEVANCE** Screening for glaucomatous RNFL changes in uveitis must be performed during quiescent periods. Thinning of the inferior quadrant suggests that glaucomatous damage, more than uveitic ocular hypertension, is in fact occurring. Measurement of RNFL may detect signs of damage before disc or visual field changes and therefore identifies a subgroup that should receive more aggressive treatment.
Elevated intraocular pressure (IOP) in uveitis is the most common cause of secondary glaucoma in clinical practice and is the third most common cause of visual loss after cataract and cystoid macula edema (CME). However, unlike loss owing to cataract and CME, glaucomatous visual loss is irreversible. The prevalence of elevated IOP in a survey of 1736 adult patients with uveitis was 8.6% and, of those, 28.8% had glaucoma. Although inflammation may elevate IOP, corticosteroid treatment is also responsible in about 60% of these patients.

Detection and monitoring of glaucoma may be influenced by uveitic changes. For example, CME and diffuse retinal changes such as those seen in birdshot chorioretinopathy and multifocal choroiditis may affect visual field (VF) test results. Inflammatory optic disc swelling may also obscure assessment of the glaucomatous optic disc.

Reduced retinal nerve fiber layer (RNFL) thickness is a good marker for diagnosing early damage in primary open-angle glaucoma and eyes in which glaucoma is suspected. Reduced RNFL thickness not only precedes VF loss but is also reliable and reproducible, enabling more frequent assessment and better trend analysis.

Nonetheless, the effect of inflammation on the RNFL needs to be ascertained before considering its use for glaucoma detection in patients with uveitis. Certain ocular structures, such as the macula in anterior uveitis and the absence of clinically detectable CME, were reported to be thickened in acute exacerbations, leading to the postulation that the inflammation is not confined to the anterior segment despite the clinical appearance.

In this study, we first assessed the effect of uveitis on the RNFL. Second, we determined whether any RNFL changes were related to elevated IOP in eyes with glaucomatous uveitis (Uv-G; positive controls) and ascertained whether those changes were also present in nonglaucomatous eyes with hypertensive uveitis (Uv-H). Finally, we performed logistic and linear regression analysis to determine the risk factors for RNFL defects and the factors influencing the RNFL thickness.

Methods

We screened the medical records of consecutive patients who attended a tertiary referral uveitis clinic at Moorfields Eye Hospital from May 1, 2010, through October 31, 2012, for eligible patients. Inclusion criteria consisted of a diagnosis of uveitis, history of elevated IOP (>21 mm Hg) by Goldmann applanation tonometry on at least 2 separate occasions, and available peripapillary RNFL scans measured by the same OCT device (Spectralis HRA+OCT; Heidelberg Engineering). The scans were obtained as part of the patients’ clinical follow-up. Thickness of the RNFL was measured using circular scans located 3.4 mm from the center of the optic disc. Scans with poor quality (Q score, <20 from the printout) and eccentric location were excluded. Patients were also excluded if they had multiple scleroses, optic disc swelling, frank corneal edema, previous vitrectomy or laser retinopexy, or central or peripheral retinal scars from uveitis. Eyes with previous vitrectomy were excluded because the eyes may have experienced transient IOP fluctuations intraoperatively and in the immediate postoperative period. Eyes that had undergone laser retinopexy were excluded because the procedure ablates the retina and may have an effect on the RNFL thickness. Retinal scars may affect the RNFL in a way not attributable to glaucoma, which was the subject of this study. The Research Governance Committee of Moorfields Eye Hospital approved the data collection (protocol LIGS 10201, Causes of Visual Loss in Uveitis), and obtaining informed consent was not considered to be necessary. This study adhered to the tenets of the Declaration of Helsinki.

The patients’ medical records were examined to determine the age and sex of the patient and the type of uveitis, treatment, duration of follow-up, peak IOP, corticosteroid- or uveitis-induced elevated IOP, optic disc appearance on results of clinical examination, and Humphrey VF findings where available. Uveitis was classified as anterior, intermediate, or posterior/panuveitis according to the Standardized Uveitic Nomenclature classification. Glaucomatous disc changes were diagnosed by the presence of a vertical cup-disc ratio of less than 0.7, focal rim notching, rim thinning, or rim excavation. Glaucomatous VF changes were deemed present when the glaucoma hemifield finding was graded “outside normal limits” with a cluster of 3 contiguous points at the 5% level on the pattern deviation plot, using the threshold test strategy with the 24-2 test pattern of the field analyzer (Zeiss-Humphrey HFA; Carl Zeiss Meditec). Corticosteroid-induced IOP elevation was defined as an IOP of at least 6 mm Hg before corticosteroid treatment or greater than 21 mm Hg on at least 2 separate occasions related to treatment with any kind of corticosteroid. Uveitis-induced IOP elevation was defined as an IOP of greater than 21 mm Hg in an actively inflamed eye before corticosteroid treatment. Active uveitis relates to any evidence of ongoing disease activity determined by the presence of inflammatory cells in the anterior or posterior segment with or without CME. The peak IOP referred to the highest IOP reading ever recorded.

The eyes of eligible patients were divided into the following 4 groups: the normal contralateral eyes of patients with unilateral uveitis (control group), those with normotensive uveitis (Uv-N group), those with raised IOP and normal optic disc and/or VF (UvH group), and those with raised IOP and glaucomatous optic disc and/or glaucomatous VF (Uv-G group).

The result of the OCT was reported as being within normal limits if the patient’s measurement fell within the top 5% to 95% of the population’s normative database, borderline if it was 1% to less than 5%, and outside normal limits if it was 0% to less than 1% (Figure 1). The mean thickness was given in the inferior, superior, nasal, and temporal quadrants, and the global thickness represents the mean of the 4 quadrants.
We compared all categorical variables using the χ² test. We used the unpaired t test and Mann-Whitney test to compare means in parametric and nonparametric data, respectively. One-way analysis of variance with Bonferroni correction and the Kruskal-Wallis test were used to compare parametric and nonparametric values, respectively, in more than 2 groups. We used multivariate linear and logistic regression to determine the factors affecting the RNFL thickness and risk factors for RNFL defects. P < .05 is considered significant. Results are described as mean (SD) unless stated otherwise.

The right eye showed normal values (seen in 5%-95% of the population) of retinal nerve fiber layer (RNFL) thickness. The left eye showed RNFL thinning due to glaucoma. Numbers given with quadrants represent mean RNFL thickness; the number in the center represents the global (G) mean RNFL thickness. The superior (S) and inferior (I) quadrant RNFL thicknesses fall outside normal limits (seen in <1% of the population), and the nasal (N) quadrant RNFL thickness falls in the borderline thickness (seen in 1% to <5% of the population). ILM indicates internal limiting membrane; T, temporal quadrant.
Results

We identified 344 adult patients. Thirty-three patients had no OCT scans and 2 were excluded for multiple sclerosis with optic nerve involvement. Of the remaining 309 patients, 82 eyes were excluded for poor-quality scans owing to dense vitritis, dense cataract, corneal scar, or vitreous hemorrhage (29 eyes); eccentric scans (12 eyes); or the presence of disc swelling, peripapillary retinal scars, choroidal neovascularization, previous vitrectomy or laser retinopexy, and other types of optic neuropathy (41 eyes). Therefore, we included 536 eyes of 309 patients in the analysis.

The eyes were divided into 72 control eyes and 464 with uveitis, which were further separated into the Uv-N (n = 143), Uv-H (n = 233), and Uv-G (n = 88) groups based on the above criteria. The prevalence of elevated IOP (Uv-H and Uv-G eyes) was 321 of 464 (69.2%), and 88 of 464 (19.0%) had clinical signs of glaucoma. The Table describes the clinical characteristics of the different groups of eyes.

### Table. Demographic Characteristics of the Eyes in Uveitis Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Uveitis Group</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Uv-N (n = 143)</td>
<td>Uv-H (n = 233)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>50.3 (15.1)</td>
<td>48.5 (14.2)</td>
</tr>
<tr>
<td>Sex, No. (%) of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>102 (71.3)</td>
<td>120 (51.5)</td>
</tr>
<tr>
<td>Male</td>
<td>41 (28.7)</td>
<td>113 (48.5)</td>
</tr>
<tr>
<td>Spherical equivalent, mean (SD), D</td>
<td>-0.6 (1.6)</td>
<td>-1.1 (2.0)</td>
</tr>
<tr>
<td>VF deviation, mean (SD), dB</td>
<td>-1.82 (1.90)</td>
<td>-2.39 (1.72)</td>
</tr>
<tr>
<td>Duration of follow-up, mean, y</td>
<td>6.2</td>
<td>7.0</td>
</tr>
<tr>
<td>Type of uveitis, No. (%) of eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>35 (24.5)</td>
<td>93 (39.9)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>74 (51.7)</td>
<td>100 (42.9)</td>
</tr>
<tr>
<td>Posterior/panuveitis</td>
<td>34 (23.8)</td>
<td>40 (17.2)</td>
</tr>
<tr>
<td>Mean peak IOP, mean (SE), D</td>
<td>NA</td>
<td>35.6 (0.61)</td>
</tr>
<tr>
<td>Mechanism of IOP elevation, No. (%) of eyes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid induced</td>
<td>NA</td>
<td>164 (70.4)</td>
</tr>
<tr>
<td>Uveitis induced</td>
<td>NA</td>
<td>69 (29.6)</td>
</tr>
</tbody>
</table>

**Abbreviations:** D, diopter; IOP, intraocular pressure; NA, not applicable; Uv-G, glaucomatous uveitis; Uv-H, hypertensive uveitis; Uv-N, normotension uveitis; VF, visual field. 

* a Calculated as analysis of variance.  
  b Calculated as unpaired t test.  
  c Calculated as Kruskal-Wallis test.  
  d Calculated as Mann-Whitney test.  
  e Calculated as a χ² test.

RNFL Thickness in Uv-N Eyes

To examine the characteristics of the RNFL in Uv-N eyes, we compared them with the control eyes. The mean global RNFL measurement was significantly thicker in Uv-N eyes (106.4 [21.4] μm) compared with control eyes (96.0 [9.0] μm; P < .001). This increase in thickness was significant except in the superior quadrant (Figure 2). Unlike control eyes, the RNFL in the temporal quad-
The Uv-N eyes with active uveitis during OCT scanning had thicker mean global RNFL (119.6 [23.2] μm) compared to the eyes with quiescent uveitis (102.3 [20.8] μm; P = .001) in the absence of clinically apparent disc swelling. We found no significant difference between quiescent Uv-N and control eyes (P = .07). Therefore, active Uv-N eyes were excluded from further analysis unless stated otherwise. The RNFL scans underwent analysis once the uveitis was controlled.

We performed a multivariate linear regression to evaluate the influence of age, sex, uveitis activity, type of uveitis, and treatment effect on the global RNFL thickness in Uv-N eyes (with active and quiescent uveitis). Only factors with P < .05 on univariate regression analysis were included in this model. Sex was not a significant factor (P = .76) and therefore excluded.

After adjusting for other factors, for every 10-year increase in age, RNFL thickness decreased by a mean of 3.4 μm (SE, 0.1 [95% CI, −6.4 to 0.5] μm; P = .02). Eyes with active uveitis during OCT scanning had an increase in global RNFL thickness of 13.6 μm (SE, 4.4 [95% CI, 4.9-22.4] μm; P < .001) compared with quiescent eyes (R² = 0.23). The other factors were not statistically significant.

**RNFL Thickness in Uv-H Eyes**

We examined the RNFL thickness in Uv-H eyes (positive controls) and compared them with Uv-N eyes to determine any RNFL changes so that we could see whether glaucomatous changes were evident in the Uv-H group. The mean global RNFL was significantly thinner in Uv-H compared with Uv-N eyes (81.4 [26] vs 106.4 [21.4] μm; P < .001), affecting the superior (87.5 [27.2] vs 123.5 [29.0] μm; P < .001), inferior (93.6 [35.5] vs 134.8 [28.0] μm; P < .001), and nasal (66.0 [24.4] vs 82.2 [25.3] μm; P < .001) quadrants. However, no statistically significant difference in temporal quadrant RNFL thickness was identified (78.1 [34.2] vs 85.1 [23.1] μm; P = .6). We then compared the Uv-H and Uv-N eyes. The inferior quadrant was significantly thinner in Uv-H than Uv-N eyes (124.1 [17.3] vs 131.3 [27.8] μm; P = .03). We found no significant difference in the global measurements or the remaining quadrants.

The Uv-H eyes were further divided by OCT classification of the RNFL thickness as borderline/outside normal limits (54 eyes [23.2%]) or within normal limits (179 eyes [76.8%]). The borderline/outside normal limits group had at least 1 quadrant of thickness falling below the 5th percentile of the normative database and deemed to have an RNFL defect on OCT. The former compared with the latter group belonged to older patients (53.7 [11.0] vs 47.4 [14.5] years; P = .003) and those who had a higher mean peak IOP (38.4 [11.5] vs 34.0 [7.4] mm Hg; P < .001) and a higher proportion with uveitis- rather than corticosteroid-induced IOP elevations (23/54 eyes [42.6%] vs 41 of 179 eyes [22.9%]; P = .049).

We performed a multivariate logistic regression analysis to explore the effect of age, duration of follow-up, peak IOP, and cause of elevated IOP on the risk for an RNFL defect on OCT findings in Uv-H eyes. After adjusting for the other factors, every 1-mm Hg increase of peak IOP increased the risk for an RNFL defect by 5% (odds ratio [OR], 1.05 [95% CI, 1.00-1.09]; P = .03). Furthermore, for every 1-year increase in age, the risk for an RNFL defect increased by 3% (OR, 1.03 [95% CI, 1.01-1.06]; P = .02).

**Risk Factors for Uv-H and Uv-G Eyes**

To isolate the risk factors of Uv-H (Uv-H vs Uv-N groups), we examined the following clinical properties: age, sex, mean duration of follow-up, and type of uveitis. Only 2 properties were found to be significant in a multivariate logistic regression analysis. Men were twice as likely to develop Uv-H as women (OR, 2.1 [95% CI, 1.3-3.4]; P = .002), and the risk for Uv-H in anterior uveitis was increased 2-fold compared with other types of uveitis (2.3 [1.4-4.0]; P = .001).

When we examined the risks for glaucoma due to Uv-H (Uv-G vs Uv-H groups), we found that older patients (57 vs 49 years; P < .001), longer duration of follow-up (10 vs 7 years; P = .003), higher peak IOP (40.8 vs 35.6 mm Hg; P < .001), and uveitis- rather than corticosteroid-induced IOP elevations (45 of 88 [51.1%] vs 64 of 233 [27.5%] eyes; P = .001) were significant risk factors for glaucoma. Sex and the type of uveitis were not significant risk factors.

Finally, to see which cause of elevated IOP increased the risk for glaucoma, we compared eyes with uveitis- and corticosteroid-induced IOP elevations in the Uv-H and Uv-G groups. The mean peak IOP in uveitis-induced IOP was 7.3 mm Hg higher (95% CI, 4.7-9.8; P < .001), and the patients were older (mean of 52.3 vs 46.9 years, respectively; P = .01) than among the eyes with corticosteroid-induced IOP elevations. Therefore, the risk for glaucoma in uveitis-induced IOP elevation increased 2.3-fold compared with corticosteroid-induced IOP elevation (OR, 2.26 [95% CI, 1.37-3.74]; P = .002).

**Treatment of Elevated IOP**

The Uv-G eyes received a mean of 3.1 glaucoma drops compared with Uv-H eyes (2.6 drops; P < .001). Oral acetazolamide was also used in 26 of 88 Uv-G eyes (29.5%) compared with 50 of 233 Uv-H eyes (21.5%), although this difference was not statistically significant. Twenty of 88 Uv-G eyes (22.7%) had to undergo trabeculectomy or glaucoma drainage devices implantation for IOP control compared with 12 of 233 Uv-H eyes (5.2%) (P < .001).

**Discussion**

The prevalence of elevated IOP and glaucoma in our cohort of eyes with uveitis were approximately 70% and 20%, respectively, which is almost double those of 41.8% and 9.6%, respectively, in a report by Herbert et al22 from 342 eyes of 257 patients with uveitis. This difference is due to the difference in case selection. We had higher prevalences because patients with elevated IOP are at higher risk for glaucoma and needed screening with OCT.

The mean global RNFL thickness of 96.0 (9.0) μm in our control eyes was close to that in previously studied normal eyes,23 which was 97.2 (9.7) μm, and we compared this thick-
ness with that found in our Uv-N eyes. We found the RNFL to be thicker in Uv-N eyes regardless of the type of uveitis when compared with control eyes. This increase in thickness was especially seen in eyes with active inflammation compared with quiescent disease, which in turn was not statistically different from that of control eyes. These findings support previous reports of increased thickness of ocular tissues in exacerbations of acute uveitis\(^{17,18}\) and suggest that monitoring for RNFL changes in uveitic eyes should be performed during quiescence. Although some studies have found increased thickness of the RNFL in eyes with anterior uveitis,\(^{24-26}\) we found this increase in other types of uveitis.

When examining individual Uv-H eyes, approximately 20% of them had an RNFL defect on OCT. The clinical features of these eyes were similar to those of Uv-G eyes whereby they belonged to an older group and had a higher peak IOP, longer follow-up, and uveitis-induced IOP elevations. These similarities suggest that if the Uv-H eyes with RNFL defect on OCT had a longer follow-up, they would also develop glaucomatous disc changes and VF loss. The similarity also supports previous reports that more eyes with a corticosteroid-induced hypertensive response developed glaucoma than those without a corticosteroid-induced response.\(^{4,22}\)

Unlike primary open-angle glaucoma, in which the RNFL thickness is significantly decreased in all quadrants,\(^{27}\) we found that the temporal quadrant seems to be spared in uveitic glaucoma. This finding may be explained by the fact that the macula, which is directly continuous to the temporal quadrant of the peripapillary RNFL, has a propensity to develop CME in uveitis. Even in anterior uveitis without clinically apparent CME, the macula has been found to be thickened.\(^{17,18}\) Consequently, although significant RNFL thinning is seen in the temporal quadrant in primary ocular hypertension,\(^{28}\) we found significant thinning in the inferior quadrant in Uv-H. Therefore, we propose that RNFL thinning affecting the inferior quadrant may be suggestive of glaucomatous changes in eyes with uveitis.

Risk factors for raised IOP were male sex and anterior uveitis. Being older and having higher peak IOP and uveitis-induced IOP elevation were risk factors for glaucoma and RNFL defect. The risk for elevated IOP was increased 2-fold in anterior uveitis compared with intermediate or posterior uveitis, possibly as a direct effect of inflammation on the trabecular meshwork, compromising the aqueous outflow system. Men were also twice as likely to develop Uv-H as women. However, the exact causative relationship remains unclear and may be linked to other sex-related issues not explored in this study. Although no reports link sex and the risk for elevated IOP or a corticosteroid-induced response,\(^{4,22}\) reports relate male sex as a risk factor for complications and poor visual outcome in juvenile idiopathic arthritis–associated uveitis.\(^{29,30}\) No other report has linked sex and elevated IOP in nonjuvenile idiopathic arthritis–related uveitis. Owing to the small number of cases in some of the subtypes, we were unable to explore the relationship of IOP and specific causes and focused on the anatomical site of inflammation.

We aggressively manage Uv-H to keep the IOP at less than 21 mm Hg, but when glaucomatous changes occur in Uv-G eyes, we aim for a target IOP of 12 to 14 mm Hg. Therefore, more IOP-lowering drops were used and more Uv-G eyes underwent glaucoma surgery compared with Uv-H eyes. This study suggests that once RNFL changes occur in Uv-H eyes, these patients already have nerve damage and therefore these eyes should be more aggressively managed to reduce the IOP to 12 to 14 mm Hg, as we manage the IOP in primary open-angle glaucoma.

The lack of data on pachymetry measurements in our cohort as a result of the retrospective design is a limitation because, although we have excluded patients with frank corneal edema on examination, IOP measurement with Goldmann applanation tonometry may be influenced by corneal thickness.\(^{31}\) Additional information such as gonioscopic findings, sequential IOP reading, and sequential OCT scans are beyond the scope of this retrospective study.

Conclusions

Screening for glaucomatous RNFL thinning with OCT should be performed during uveitis quiescence to reduce the masking effect of RNFL thickening associated with active uveitis. Thinning of the RNFL seen in the inferior quadrant should raise the possibility of progression to glaucoma in eyes with Uv-H. Therefore, RNFL scanning may provide vital clues in early treatment decisions among patients with uveitis and facilitate in their IOP management to prevent progressive visual loss due to glaucoma.


