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Retinal Nerve Fiber Layer Optical Texture Analysis

Detecting Axonal Fiber Bundle Defects in Patients with Ocular Hypertension

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Purpose: To apply retinal nerve fiber layer (RNFL) optical texture analysis (ROTA) to investigate the prevalence, patterns, and risk factors of RNFL defects in patients with ocular hypertension (OHT) who showed normal optic disc and RNFL configuration in clinical examination, normal RNFL thickness on OCT analysis, and normal visual field (VF) results.

Design: Cross-sectional study.

Participants: Six hundred eyes of 306 patients with OHT.

Methods: All participants underwent clinical examination of the optic disc and RNFL, OCT RNFL imaging, and 24-2 standard automated perimetry. To detect RNFL defects, ROTA was applied. The risk score for glaucoma development was calculated according to the Ocular Hypertension Treatment Study and European Glaucoma Prevention Study (OHTS-EGPS) risk prediction model. Risk factors associated with RNFL defects were analyzed using multilevel logistic regression analysis.

Main Outcome Measures: Prevalence of RNFL defects.

Results: The average intraocular pressure (IOP) measured from 3 separate visits within 6 months was 24.9 ± 1.8 mmHg for the eye with higher IOP and 23.7 ± 1.7 mmHg for the eye with lower IOP; the respective central corneal thicknesses were 568.7 ± 30.8 μm and 568.8 ± 31.2 μm. Of 306 patients with OHT, 10.8% (33 patients, 37 eyes) demonstrated RNFL defects in ROTA in at least 1 eye. Of the 37 eyes with RNFL defects, the superior arcuate bundle was the most frequently involved (62.2%), followed by the superior papillomacular bundle (27.0%) and the inferior papillomacular bundle (21.6%). Papillofoveal bundle defects were observed in 10.8% of eyes. The smallest RNFL defect spanned 0.0° along Bruch's membrane opening margin, whereas the widest RNFL defect extended over 29.3°. Age (years) (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.03−1.13), VF pattern standard deviation (decibels [dB]) (OR, 1.82; 95% CI, 1.01−3.29), cup volume (mm^3) (OR, 1.24; 95% CI, 1.01−1.53), and the OHTS-EPGS risk score (OR, 1.04; 95% CI, 1.01−1.07) were associated with RNFL defects.

Conclusions: A considerable proportion of patients with OHT who showed no signs of optic disc and RNFL thickness abnormalities on clinical and OCT examination exhibited RNFL defects on ROTA. Axonal fiber bundle defects on ROTA may represent the earliest discernible sign of glaucoma in the glaucoma continuum.

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Glaucoma is the leading cause of irreversible blindness worldwide.[1] Elevated intraocular pressure (IOP), or ocular hypertension (OHT), represents an early stage in the glaucoma continuum in which retinal ganglion cell apoptosis and axon loss is accelerated in the absence of detectable retinal nerve fiber layer (RNFL) change.[2–4] With the advent of OCT, analysis of RNFL thickness has become the prevailing standard for detecting RNFL defects in glaucoma.[5,6] Retinal nerve fiber layer optical texture analysis (ROTA) is a new algorithm devised to measure the optical texture of axonal fiber bundles.[7,8] By integrating RNFL thickness and reflectance measurements obtained from standard OCT scans, ROTA reveals the trajectories of axonal fiber bundles, uncovering the loss of the optical texture of the axonal fiber bundle in glaucoma that may not be detectable with OCT RNFL thickness analysis and red-free RNFL photography.[7,8] With the same notion, we hypothesized that eyes with OHT might

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have focal axonal fiber bundle defects that regular optic disc examination or OCT RNFL thickness analysis would miss. Because treating all patients with OHT is neither cost-effective nor efficacious,[4,9] it is vital to recognize those with axonal fiber bundle defects when assessing the risk for visual field (VF) progression and the need for treatment. Applying ROTA in this study, we investigated the prevalence, patterns, and risk factors of axonal fiber bundle defects in patients with OHT who showed no signs of optic disc or RNFL abnormalities on clinical examination and no evidence of abnormal OCT RNFL thickness or VF measurements.

Methods

Patients

Clinical and OCT data of 600 eyes from 306 patients with OHT who were recruited consecutively (after excluding ineligible participants) between February 2017 and October 2019 (assessment of eligibiltiy for study inclusion started in September 2016) from 4 study sites of an ongoing clinical trial[10] in Hong Kong that aims to determine whether provision of IOP-lowering treatment is more cost-effective upon (1) detection of progressive RNFL thinning or (2) detection of a 5-year glaucoma conversion risk score of more than 15% calculated according to the Ocular Hypertension Treatment Study (OHTS) and European Glaucoma Prevention Study (EGPS) risk prediction model[11] were analyzed in the present study. Ocular hypertension was defined as having (1) an IOP of 23 mmHg or more but less than 32 mmHg in at least 1 eye and 21 mmHg or more but less than 32 mmHg in the fellow eye, calculated from the average of 3 separate visits within 6 months; (2) normal optic disc and RNFL configuration on clinical examination; (3) no VF defects by standard automated perimetry (Swedish Interactive Threshold Algorithm standard 24-2); and (4) no RNFL thickness abnormalities on OCT (definitions of VF defects and RNFL thickness abnormalities are described next). Inclusion criteria were age of 18 years or older; best-corrected visual acuity of 20/40 or better; no history of medical, laser, or surgical treatment for IOP reduction; and open anterior chamber angles. Exclusion criteria were secondary causes of IOP elevation, ocular or systemic diseases that may cause VF loss or optic disc abnormalities, pathologic myopia, inability to perform reliable VF testing, suboptimal quality of OCT scans, previous intraocular surgery other than uncomplicated cataract surgery, and diabetic retinopathy or maculopathy. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Hong Kong Hospital Authority research ethics committee with informed consent obtained.

Clinical Examination and Investigations

All participants underwent clinical examination of the optic disc and the RNFL by glaucoma specialists (C.K.S.L. and P.P.M.C.). Measurement of central corneal thickness (CCT) and assessment of iris trabecular contact[12] with anterior segment OCT (CASIA2; Tomey), standard automated perimetry (24-2 Swedish Interactive Threshold Algorithm standard, Humphrey Field Analyzer II-i; Carl Zeiss Meditec), and OCT imaging of the RNFL (Cirrus HD-OCT [Carl Zeiss Meditec]; Triton OCT [Topcon]) were performed at 2 clinic visits within 6 months (95.8% of patients had 2 visits within 3 months); IOP was measured from 3 clinic visits within the same 6-month period, and the mean was obtained. For each IOP measurement, 2 readings using Goldmann applanation tonometry were averaged and recorded; a third measurement was obtained if the first 2 readings differed by more than 2 mmHg, and the median was recorded. Age, CCT, VF pattern standard deviation (PSD), vertical cup-to-disc ratio (measured by OCT), OHTS-EGPS risk score, and other VF and OCT measurements were averaged from the 2 clinic visits. Axial length (IOLMaster 700; Carl Zeiss Meditec) and refraction were measured from the first visit.

Definition of Retinal Nerve Fiber Layer Thickness Abnormalities on OCT

Patients with RNFL thickness abnormalities in OCT were excluded from the study at recruitment. At the time, ROTA was not yet available, and RNFL thickness abnormalities in OCT were defined with reference to the RNFL thickness deviation map and the RNFL thickness map generated from the Cirrus HD-OCT using the optic disc cube scan (200×200 pixels in 6×6 mm^2). Because false-positive detection of RNFL thickness abnormalities in the RNFL thickness deviation map is common at the superior and inferior quadrants of the optic disc in healthy eyes with myopia because of the convergence of the superotemporal and inferotemporal RNFL bundles toward the macula,[13–15] RNFL thickness abnormalities were defined by the presence of (1) more than 20 contiguous superpixels (1 superpixel = 4×4 pixels) of RNFL thickness below the first percentile on the RNFL thickness deviation map and (2) RNFL thickness loss in the corresponding location on the RNFL thickness map (Fig S1, available at www.aaojournal.org). The RNFL thickness deviation map contained 2500 (50×50) superpixels, of which about 2000 superpixels were analyzed for detection of RNFL defects after excluding the optic disc and the parapapillary atrophy region. To distinguish RNFL defects from false-positive results, a threshold of 20 adjacent pixels was chosen. This was based on the fact that in a healthy eye, 1% or approximately 20 superpixels (i.e., 2000 superpixels $\times$ 1%) would be expected to have RNFL thickness below the first percentile. In our previous studies, we applied the 20-superpixel threshold to define RNFL defects in the RNFL thickness deviation map.[7,14] Only OCT scans with a signal strength of 6 or more were included in the analysis. Scans with motion artifact, poor centration, or missing data (e.g., blinking) were checked by the operator and discarded with rescanning performed at the same visit.

Retinal Nerve Fiber Layer Optical Texture Analysis

Widefield (12×9 mm^2) OCT data obtained from the Triton OCT covering the parapapillary region and the macula captured at the same 2 clinic visits were exported for ROTA. Only OCT scans with a signal-to-noise ratio of 30 or more were analyzed. The algorithm of ROTA has been described.[7] Retinal nerve fiber layer optical texture analysis integrates RNFL reflectance and RNFL thickness measurements with a series of nonlinear transformations to reveal the optical texture and trajectories of axonal fiber bundles. Axonal fiber bundle defects in ROTA represent altered intrinsic optical properties of axonal fiber bundles or loss of axonal fiber bundles. Retinal nerve fiber layer optical texture analysis has been shown to have a higher diagnostic performance compared with parapapillary RNFL thickness analysis and macular ganglion cell–inner plexiform layer thickness analysis for detecting RNFL defects in early glaucoma using VF testing or red-free RNFL photography as the reference standard.[7,8]

Detection and Analysis of Retinal Nerve Fiber Layer Defects in Retinal Nerve Fiber Layer Optical Texture Analysis

Like red-free photography, RNFL defects in ROTA were identified on subjective assessment of RNFL reflectivity. Different from red-free photography, the borders of RNFL defects can be delineated distinctively in a wide field with ROTA because of the enhanced visualization of axonal fiber bundle trajectories; ROTA has been shown to have high interobserver agreement and low test–retest variability for detection of RNFL defects.[7] By following the trajectories of axonal fiber bundles, the borders of RNFL defects were traced, the angular width along the Bruch's membrane opening (BMO) margin was measured, and the area of RNFL defects was calculated using a custom program developed in MATLAB (MathWorks, R2018) as previously described.[8] Axonal fiber bundles were classified by location relative to the macula and fovea. Arcuate axonal fiber bundles ran outside the macula (18° or approximately 5.5 mm) along the superior and inferior temporal retinal vascular arcades; papillomacular axonal fiber bundles projected from the macula to the optic disc except for those projecting from the fovea (5° or approximately 1.5 mm), which were labeled as papillofoveal bundles. Retinal nerve fiber layer optical texture analysis images obtained from the first and second clinic visits were examined; an RNFL defect was confirmed when it was evident in both visits. Retinal nerve fiber layer optical texture analysis images from the first visit were used to measure the area, angular width, and location of RNFL defects within the 10 × 7-mm^2 region of analysis, as previously described.[8] Images with RNFL defects then were overlaid after aligning the BMO center and foveola of each eye with affine transformation (Fig S2, available at www.aaojournal.org) to generate the RNFL frequency distribution topography (Fig 3).

Perimetry

Standard automated perimetry was performed with the Humphrey Field Analyzer II-i (24-2 Swedish Interactive Threshold Algorithm standard). A reliable VF test showed fixation loss of 20% or less and false-positive errors of 15% or less. Unreliable tests were repeated on the same day. A VF defect showed 3 or more nonedge contiguous locations with $P < 0.05$ (except for the 6 nasal locations), with 1 or more locations with $P < 0.01$ on the same side of the horizontal meridian in the pattern deviation plot and glaucoma hemifield test results classified outside normal limits, and the defect was confirmed on 3 consecutive visits.

Statistics

Statistical analysis was performed with STATA version 15.1 software (StataCorp). Descriptive statistics were used to report the demographic and clinical characteristics of the study population. Biometric parameters of eyes with and without RNFL defects on ROTA were compared using linear mixed modeling with adjustment for within-subject correlation. Univariable multilevel logistic regression analysis was applied to determine the odds ratio of factors associated with RNFL defects in ROTA after adjustment for correlation between fellow eyes. P values of less than 0.05 were considered statistically significant.

Results

We screened a total of 430 patients for study recruitment. After excluding 120 patients who did not meet the inclusion criteria (30 patients had unreliable VF results despite repeated testing, 1 patient had confirmed VF defects, 25 patients had RNFL thickness abnormalities in OCT, 28 patients did not meet the IOP criteria, 8 patients had angle closure, 5 patients had suboptimal OCT quality, 4 patients had macular pathologic features, 1 patient had steroid-induced OHT, and 18 patients declined to participate in the study), 310 patients with OHT were included in the clinical trial. Among the 620 eyes of the 310 patients, 8 eyes from 4 patients and 12 eyes from 12 patients were further excluded from the study because of suboptimal ROTA quality for assessment of axonal fiber bundles. A total of 600 eyes from 306 patients with OHT were analyzed (Table S1, available at www.aaojournal.org). All eyes had no detectable RNFL defects or neuroretinal rim loss on clinical examination, no RNFL thickness abnormalities in OCT, and no VF defects on standard automated perimetry. The mean ± standard deviation age was 58.2 ± 12.9 years. The average IOP calculated from 3 separate visits within 6 months (69.0% of patients underwent 3 IOP measurements captured within 3 months) was 24.9 ± 1.8 mmHg for the eye with higher IOP and 23.7 ± 1.7 mmHg for the eye with lower IOP; the respective CCTs were 568.7 ± 30.8 μm and 568.8 ± 31.2 μm. The VF mean deviation and PSD were −1.35 ± 1.39 decibels (dB) and 1.84 ± 0.62 dB, respectively. The vertical cup-to-disc ratio was 0.55 ± 0.14. The OHTS-EGPS risk score was 15.9 ± 13.7%.

Patterns of Retinal Nerve Fiber Layer Defects

Of 306 patients with OHT, 10.8% (33 patients, 37 eyes) showed repeatable RNFL defects in ROTA in at least 1 eye. Thirty-two eyes (86.5%) showed RNFL defects involving 1 hemiretina—22 eyes (59.5%) showed superior RNFL defects, and 10 eyes (27.0%) showed inferior RNFL defects—and 5 eyes (13.5%) showed RNFL defects involving both hemiretinas. The RNFL defects largely were localized over the superior arcuate bundle and papillomacular bundle between 45° and 89° along the superotemporal BMO margin and over the inferior papillomacular bundle between 307° and 328° along the inferotemporal BMO margin as revealed from the RNFL defect frequency distribution topography generated by overlaying the 37 ROTA RNFL defect maps after aligning the BMO center and foveola of each eye (Fig 3). The superior arcuate bundle was most frequently compromised (62.2% [23 eyes]; Fig 4A), followed by the superior papillomacular bundle (27.0% [10 eyes]; Fig 4B) and the inferior papillomacular bundle (21.6% [8 eyes]; Fig 4C). Unexpectedly, 10.8% (4 eyes) showed RNFL defects over the papillofoveal bundle (Fig 4D). The total area of RNFL defects on ROTA for each eye ranged from 0.4 to 17.0 mm^2 (mean ± standard deviation, 4.1 ± 3.8 mm^2), corresponding to 0.6% to 24.3% (mean ± standard deviation, 5.9 ± 5.4%) of the 10 × 7-mm^2 region of analysis. The smallest RNFL defect spanned 0.0° along the BMO margin, whereas the widest RNFL defect extended over 29.3°. Examples of ocular hypertensive eyes without RNFL defects in ROTA are shown in Figure 5.

Factors Associated with Retinal Nerve Fiber Layer Defects

Patients with RNFL defects on ROTA were older (mean age, 64.5 ± 9.1 years vs. 57.6 ± 13.0 years; $P = 0.004$), had a smaller VF index (97.8 ± 2.0% vs. 98.5 ± 1.4%; $P = 0.010$), and had smaller average RNFL thickness (88.6 ± 8.5 μm vs. 91.3 ± 8.6 μm; $P = 0.029$) (Table 2). Age and VF PSD, which are 2 of the 5 risk factors associated with the development of glaucoma in the OHTS and the EGPS,[16,17] were positively associated with the odds of RNFL defects (Table 3). For each year increase in age, the odds in association with RNFL defects increased by 8% (95% confidence interval [CI], 1.03–1.13; $P = 0.003$); for each dB increase in VF PSD, the odds increased by 82% (95% CI, 1.01–3.29; $P = 0.048$). Increased IOP (odds ratio, 1.23; 95% CI, 0.98–1.56 for

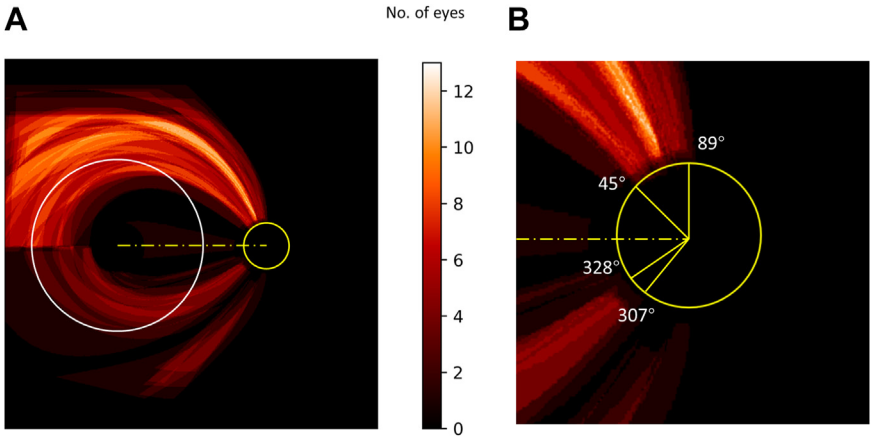

Figure 3. Images showing retinal nerve fiber layer (RNFL) defect frequency distribution topography. **A**, The RNFL defect frequency distribution topography was generated by overlaying the RNFL optical texture analysis defect maps of 37 eyes with ocular hypertension after alignment of the Bruch's membrane opening (BMO) center and foveola. The white circle indicates the macula (18°), and the yellow circle indicates the approximate BMO margin, which was estimated from the BMOs of the 37 eyes with RNFL defects using the smallest circle that intersected all the RNFL defects. The foveola–BMO center axis, a reference line to define the meridional locations along the BMO margin, is shown as a yellow dotted line. **B**, Retinal nerve fiber layer defects largely were localized over the superior arcuate bundle and papillomacular bundle between 45° and 89° along the superotemporal BMO margin and over the inferior papillomacular bundle between 307° and 328° along the inferotemporal BMO margin.

each 1-mmHg increase; $P = 0.077$) and increased vertical cup-to-disc ratio (odds ratio, 1.40; 95% CI, 0.99–1.99 for every 0.1-unit increase; $P = 0.056$) also were associated with an increased odds of RNFL defects, albeit with borderline significance. Central corneal thickness was not associated with RNFL defects ($P = 0.387$). The OHTS-EGPS risk score distributions for eyes with and without RNFL defects are summarized in Figure 6. For each percentage unit increase in OHTS-EGPS risk score, the odds of RNFL defects increased by 4% (95% CI, 1.01–1.07; $P = 0.004$).

Supplementary Analysis

In a supplementary analysis, we excluded eyes with abnormal RNFL thickness deviation maps that were considered false-positive results because they had normal RNFL thickness maps. Among 497 eyes of 279 patients with normal RNFL thickness deviation maps and normal RNFL thickness maps, 9.0% of patients (25 patients, 28 eyes) showed RNFL defects in ROTA. The pattern of RNFL defects (Fig S7, available at www.aaojournal.org) and factors associated with RNFL defects (Table S4, available at www.aaojournal.org) were similar compared with those derived from the criteria requiring both the RNFL thickness map and RNFL thickness deviation map to define RNFL defects.

Discussion

Using ROTA, RNFL defects were uncovered in 10.8% of patients with OHT who showed normal findings on clinical examination of the optic disc and RNFL, RNFL thickness measurements in OCT, and VF test results. Although the IOP in eyes with RNFL defects was only slightly higher than those without RNFL defects (Table 2), the axonal fiber bundle losses detected by ROTA likely reflect glaucomatous RNFL defects because (1) they were located in regions commonly affected by glaucoma, such as the superior arcuate bundle (Fig 3); (2) they were linked to an increase in VF PSD and a decrease in VF index (Table 3), indicating damage beyond age-related loss; and (3) they were associated with cupping, an optic disc feature that is characteristic of glaucoma (Table 3). Our study underscores the value of ROTA in detecting early axonal fiber bundle defects in patients with OHT that are not discernible via standard clinical examination and investigations. By determining the pattern and region of RNFL defects, assessing the risk for VF loss, and identifying patients in danger of glaucoma progression for IOP-lowering treatment, ROTA can help personalize glaucoma treatment.

Determining the Pattern and Location of Retinal Nerve Fiber Layer Defects

Retinal nerve fiber layer defects in OHT previously were investigated using red-free fundus photography before the era of OCT. In the early 1970s, Hoyt and Newman[18] described cases of slit-like RNFL defects in patients with OHT using red-free fundus photography. In the 1990s, Sommer et al[19] showed that 26% of patients with OHT demonstrated wedge-shaped RNFL defects on red-free fundus photography. Because the diagnosis of glaucoma in the early days was predicated on the detection of VF defects,[18,19] eyes with elevated IOP and RNFL defects but intact VFs previously considered to have OHT would have been regarded as having glaucoma by today's diagnostic standard using OCT. We included patients with OHT who showed no detectable optic disc or RNFL defects on clinical examination or optic disc photographs as determined by glaucoma specialists and no RNFL thickness abnormalities on OCT. Yet distinctive loss of axonal fiber bundle optical texture on ROTA was found in 10.8% of patients. Although most showed RNFL defects over the superior arcuate bundle, the involvement of the papillomacular and papillofoveal bundles (Figs 3 and 4) was unanticipated because it is believed that glaucoma does not affect the central vision until the late stages. Nevertheless, our results

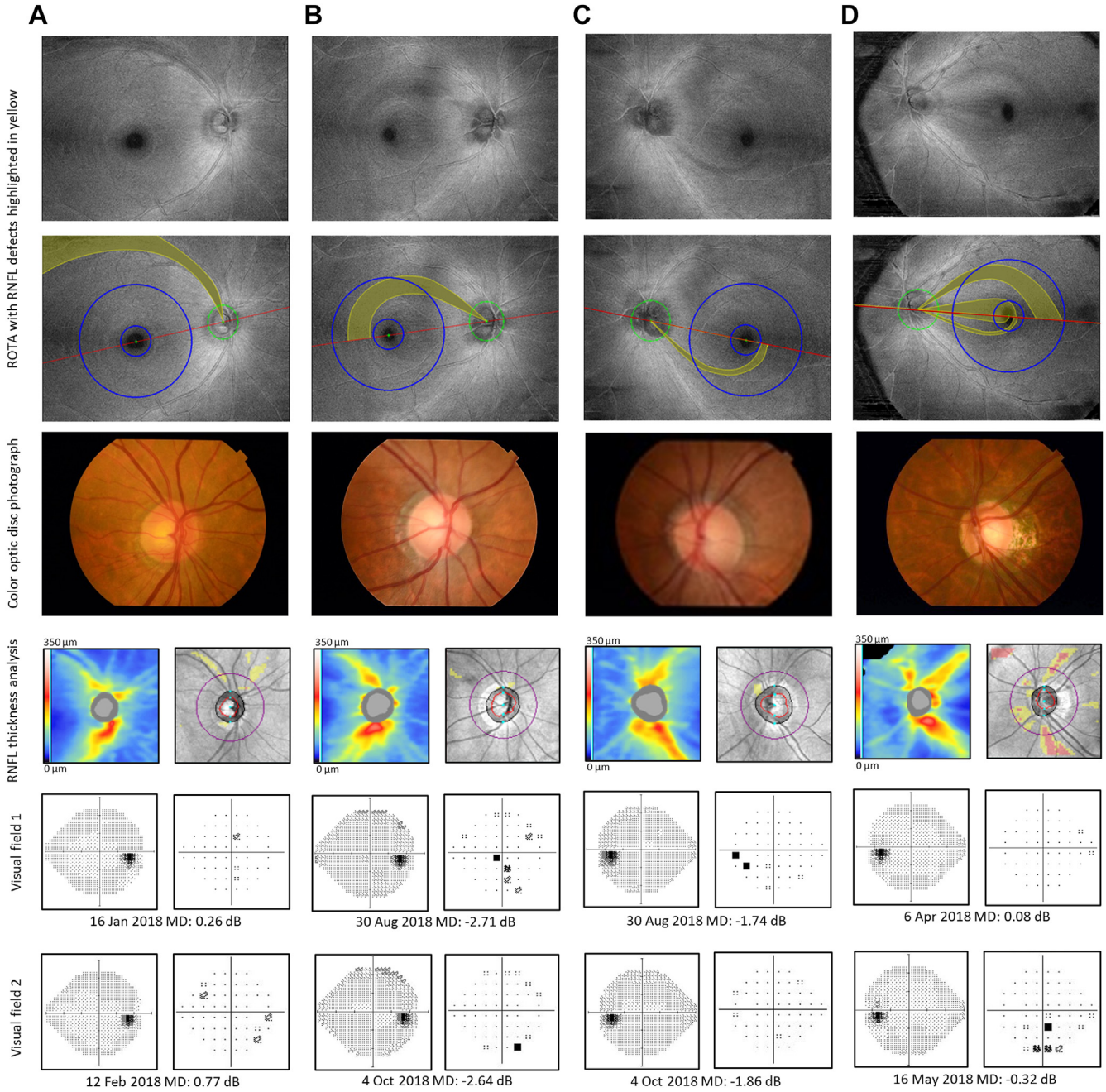

Figure 4. Images showing retinal nerve fiber layer (RNFL) optical texture analysis (ROTA) detecting different patterns of RNFL defects in patients with ocular hypertension. In the first and second rows, ROTA reveals RNFL defects involving (**A**) the superior arcuate bundle, (**B**) the superior papillomacular bundle, (**C**) the inferior papillomacular bundle, and (**D**) the superior papillomacular bundle and the superior and inferior papillofoveal bundles. The regions of RNFL defects are marked in yellow, the Bruch's membrane opening (BMO) margin is marked in green, the outer circle in blue outlines the macula (18° or approximately 5.5 mm), the inner circle in blue outlines the fovea (5° or approximately 1.5 mm), and the foveola—BMO center axis is marked in red. In the third row, color optic disc photographs show no detectable abnormalities in the optic disc configuration and no observable RNFL defects. In the fourth row, OCT reveals no RNFL thickness abnormalities detected in the RNFL thickness maps (left) or the RNFL thickness deviation maps (right) (please refer to "Methods" for the definition of RNFL thickness abnormalities). In the fifth row, visual field greyscale plots (left) and the pattern deviation probabilty plots (right) from the first and second visits show no repeatable visual field defects. dB = decibel; MD = mean deviation.

correspond with a recent study that showed that more than 70% of eyes with early glaucoma (i.e., VF mean deviation, ≥ -6 dB) showed papillomacular bundle defects and close to 17% revealed papillofoveal bundle defects.[8] Eyes with papillomacular or papillofoveal bundle defects entail a more vigilant follow-up and consideration of additional IOP reduction because they carry a high risk of central visual loss. To our knowledge, our data provide an initate account to

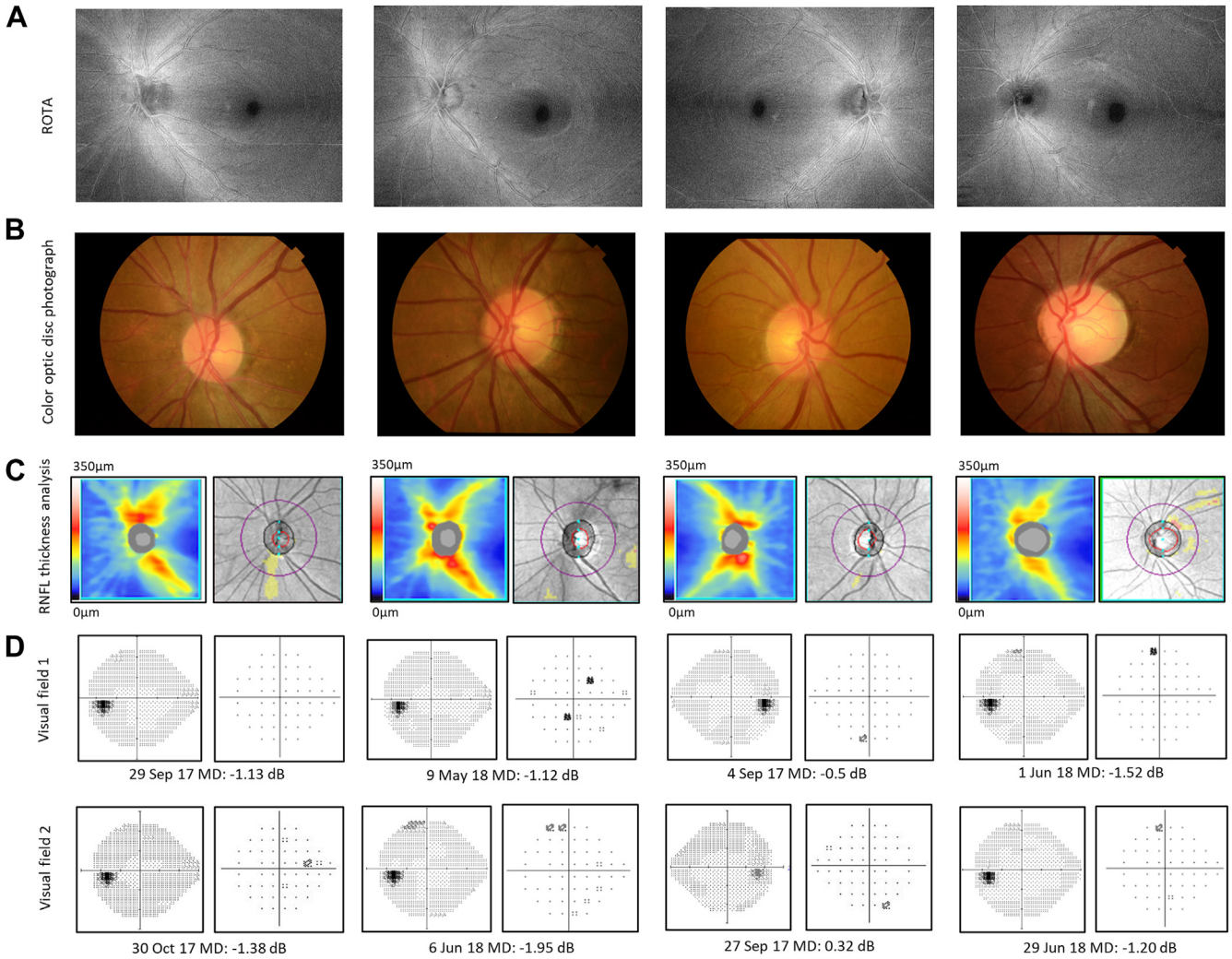

Figure 5. Examples of eyes with ocular hypertension with intact axonal fiber bundles in (**A**) retinal nerve fiber layer (RNFL) optical texture analysis (ROTA). They had (**B**) normal neuroretinal rim configuration in optic disc photographs, (**C**) normal RNFL thickness analysis in RNFL thickness maps (left) and RNFL thickness deviation maps (right), and (**D**) normal visual field greyscale plots (left) and pattern deviation probability plots (right) from the first (upper row) and second visits (lower row). dB = decibel; MD = mean deviation.

indicate that the macula can be involved in ocular hypertensive eyes that have neither optic disc abnormalities on clinical examination nor RNFL defects on OCT RNFL thickness analysis.

Assessing the Risk for VF Loss

Risk factors for the development of glaucoma in patients with OHT have been investigated in 2 landmark clinical trials: the OHTS and the EGPS.[16,17] Besides confirming elevated IOP as a risk factor for glaucoma development, the OHTS and EGPS also reported age, CCT, VF PSD, and vertical cup-to-disc ratio as independent risk factors. We examined these risk factors and showed that age, VF PSD, and the OHTS-EGPS risk score were associated significantly with RNFL defects (Table 3). We did not expect the risk factors for RNFL defects in ROTA to be identical to those in the OHTS and EGPS because our study is cross-sectional, and the end points in the OHTS and EGPS were glaucomatous optic disc changes or VF progression, not RNFL abnormalities in OCT.[16,17] Although age-related RNFL thinning has been reported,[20–23] the RNFL defects in eyes with OHT likely signify glaucomatous damage because of their associations with PSD and VF index; both are age-corrected VF measures derived to reflect glaucomatous VF decline (Table 3). This suggests that individuals with OHT and RNFL defects on ROTA are more likely to demonstrate VF loss compared with those without RNFL defects. Longitudinal studies are needed to confirm this observation.

Identifying Patients in Danger of Glaucoma Progression for Intraocular Pressure-Lowering Treatment

With the number needed to treat for patients with OHT estimated to range up to 83,[4,24,25] it is important to determine

Table 2. Comparison of Demographics and Clinical Characteristics in Patients with Ocular Hypertension with and without Retinal Nerve Fiber Layer Defect on Retinal Nerve Fiber Layer Optical Texture Analysis

Characteristic	No Defect	Defect	P Value*
No. of patients/eyes	273/563	33/37	—
Age (yrs)	57.6 ± 13.0	64.5 ± 9.1	0.004
Axial length (mm)	24.4 ± 1.4	24.3 ± 1.6	0.096
Spherical equivalent (D)	−2.10 ± 3.40	−1.77 ± 2.99	0.126
Intraocular pressure (mmHg)	24.3 ± 1.8	24.8 ± 2.3	0.057
Central corneal thickness (μm)	569.3 ± 31.2	564.4 ± 28.0	0.922
Visual field (dB)			
MD	−1.33 ± 1.39	−1.64 ± 1.35	0.279
PSD	1.82 ± 0.61	2.07 ± 0.73	0.086
Visual field index (%)	98.5 ± 1.4	97.8 ± 2.0	0.010
Average RNFL thickness (μm)	91.3 ± 8.6	88.6 ± 8.5	0.029
Vertical cup-to-disc ratio	0.54 ± 0.14	0.60 ± 0.15	0.441
Cup volume (mm^3)	0.23 ± 0.20	0.31 ± 0.25	0.124
OHTS-EGPS risk score (%)	15.4 ± 13.3	23.8 ± 16.9	0.053

dB = decibel; EGPS = European Glaucoma Prevention Study; MD = mean deviation; OHTS = Ocular Hypertension Treatment Study; PSD = pattern standard deviation; RNFL = retinal nerve fiber layer; − = not available.
Data are presented as mean ± standard deviation, unless otherwise indicated.
*Biometric parameters were compared using linear mixed modeling with adjustment for correlation between fellow eyes except for age, in which the independent *t* test was applied.

which eyes are likely to benefit from IOP-lowering treatment for cost-effective management of patients with OHT. The OHTS-EGPS risk score was designed to serve this role, but the variabilities of VF and IOP measurements have limited the precision of this risk calculation.[26] Glaucoma begins with retinal ganglion cell death and axon loss when neuroretinal rim narrowing and RNFL thinning may not be detected easily through regular clinical examination and investigations.[4] Retinal nerve fiber layer optical texture analysis is unique in unveiling the loss of the optical texture of the axonal fiber bundles that may not be visible on clinical examination or OCT RNFL thickness analysis (Fig 4). Loss of optical texture of the axonal fiber bundles on ROTA may represent the earliest detectable sign of glaucoma in the glaucoma continuum.[4] The provision of IOP-lowering treatment to patients with OHT who exhibit RNFL defects on ROTA may slow glaucoma progression and avert the development of VF defects. Our investigation has laid the groundwork to investigate whether ROTA-guided IOP-lowering treatment could be cost-effective in preventing VF progression in patients with OHT.

Limitations and Conclusions

Our study is limited by the lack of a control group to determine the prevalence of RNFL defects in healthy eyes. Taking reference from an ongoing population-based study that had examined 1189 patients older than 50 years (mean age, 63.4 years; 95% CI, 63.1−63.7 years) in Hong Kong (Tsui and Leung, ARVO 2023 E-Abstract 4308), the proportion of individuals with RNFL defects on ROTA after excluding those with glaucoma was 4.6% (95% CI, 3.4%−5.8%), which was smaller than the proportion of ocular hypertensive patients with RNFL defects (4.6% vs. 10.8%; $P < 0.001$, *z*-test), supporting the notion that the RNFL defects identified from the current study are connected with OHT. Although all ocular hypertensive eyes included in the study showed no VF defects on the 24-2 test, VF defects could be missed in eyes with papillomacular or papillofoveal bundle defects because the 24-2 VF test covers only 4 locations (2 in each hemifield) that correspond to the papillomacular and papillofoveal bundles.[8] Some eyes with RNFL defects might have shown VF defects had the 10-2 VF test been

Table 3. Univariable Multilevel Logistic Regression Analysis of Factors Associated with Retinal Nerve Fiber Layer Defects on Retinal Nerve Fiber Layer Optical Texture Analysis in Patients with Ocular Hypertension

Variable	Odds Ratio (95% Confidence Interval)	P Value*
Age (yrs)	1.08 (1.03−1.13)	0.003
Axial length (mm)	1.02 (0.74−1.41)	0.887
Spherical equivalent (D)	1.03 (0.89−1.18)	0.715
Intraocular pressure (mmHg)	1.23 (0.98−1.56)	0.077
Central corneal thickness (μm)	0.99 (0.98−1.01)	0.387
Visual field (dB)		
MD	0.83 (0.61−1.13)	0.238
PSD	1.82 (1.01−3.29)	0.048
Visual field index (%)	0.74 (0.57−0.95)	0.017
Average RNFL thickness (μm)	0.95 (0.90−1.01)	0.084
Vertical cup-to-disc ratio (per 0.1-unit increase)	1.40 (0.99−1.99)	0.056
Cup volume (per 0.1-mm^3 increase) (mm^3)	1.24 (1.01−1.53)	0.040
OHTS-EGPS risk score (%)	1.04 (1.01−1.07)	0.004

dB = decibel; EGPS = European Glaucoma Prevention Study; MD = mean deviation; OHTS = Ocular Hypertension Treatment Study; PSD = pattern standard deviation; RNFL = retinal nerve fiber layer.
*Analyses were performed using multilevel logistic regression modeling with adjustment for correlation between fellow eyes.

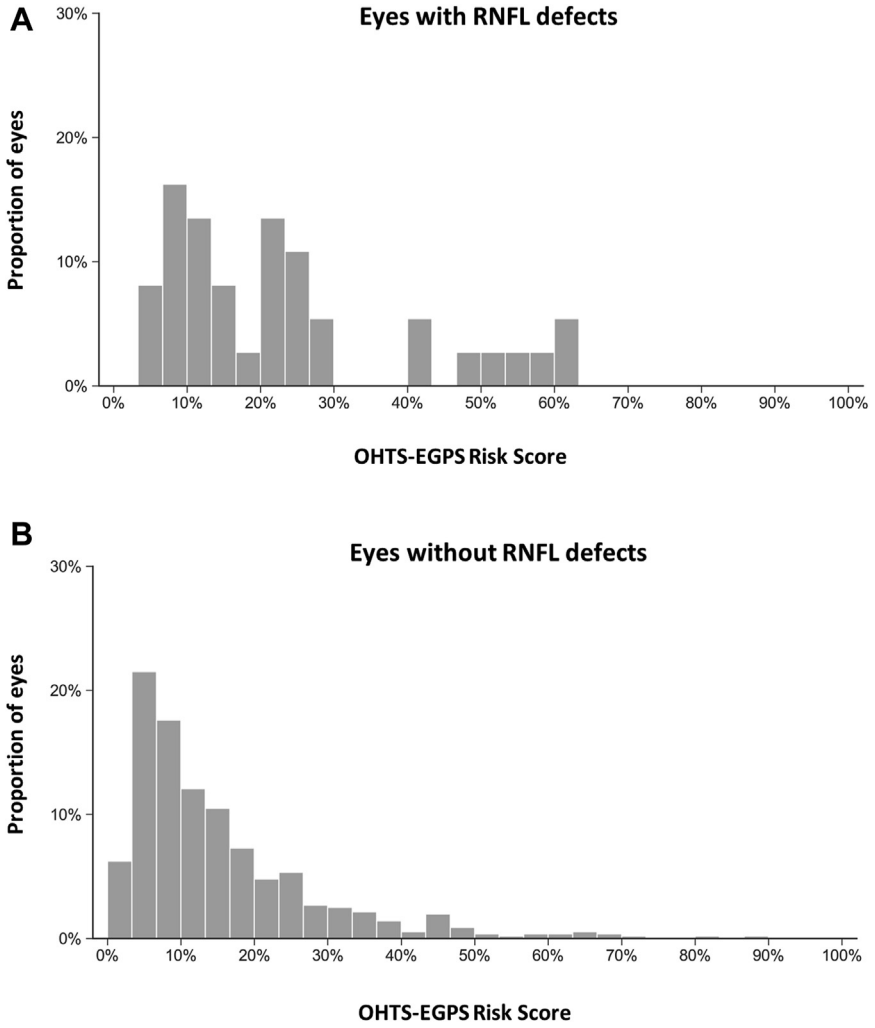

Figure 6. Histograms showing the Ocular Hypertension Treatment Study (OHTS)-European Glaucoma Prevention Study (EGPS) risk score distribution in ocular hypertensive eyes (**A**) with and (**B**) without retinal nerve fiber layer (RNFL) defects on RNFL optical texture analysis (ROTA).

included[27,28] and thus would have been excluded at recruitment. We did not include macular ganglion cell–inner plexiform layer thickness analysis in the diagnostic evaluation of OHT when we conceived the study in 2015 because evidence supporting routine OCT imaging of the macula for glaucoma detection remained sparse at the time. Finally, like red-free photography, the detection of RNFL defects with ROTA was subjective. Yet ROTA has been demonstrated to have a good inter-observer agreement, low test–retest variability, and high diagnostic performance in glaucoma detection.[7] In summary, the ability of ROTA to detect loss of optical texture of axonal fiber bundles and to discern its pattern and location with precision underlines its potential to inform the risk of VF progression and to assist treatment decision-making for patients with OHT.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The Hong Kong Hospital Authority research ethics committee approved the study. All research adhered to the tenets of the Declaration of Helsinki. All participants provided informed consent.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Leung

Analysis and interpretation: Su, Guo, Lam, Leung

Data collection: Su, Guo, Chan

Obtained funding: Leung

Overall responsibility: Su, Guo, Chan, Lam, Leung

Abbreviations and Acronyms:
BMO = Bruch's membrane opening; **CCT** = central corneal thickness; **CI** = confidence interval; **EGPS** = European Glaucoma Prevention Study; **IOP** = intraocular pressure; **OHT** = ocular hypertension; **OHTS** = Ocular Hypertension Treatment Study; **PSD** = pattern standard deviation; **RNFL** = retinal nerve fiber layer; **ROTA** = retinal nerve fiber layer optical texture analysis; **VF** = visual field.

Keywords:
Glaucoma, OCT, Ocular hypertension, Retinal nerve fiber layer defects, Retinal nerve fiber layer optical texture analysis.

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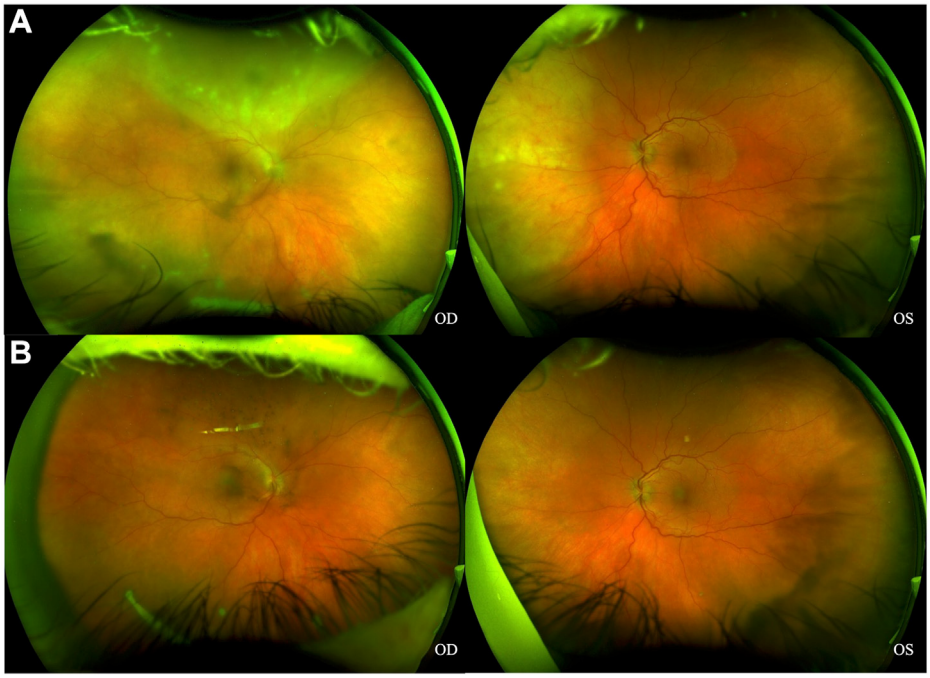
Pictures & Perspectives



Retinitis after Long-Term Corticosteroid Use

A 61-year-old man presented with acute-onset blurriness in both eyes (OU). His medical history was significant for biopsy-negative temporal arteritis and long-term systemic corticosteroid use. On presentation, visual acuity was 20/40 with 3-4+ cells in the anterior chamber and 1+ cells in the vitreous OU. Fundus examination revealed elevated optic nerve margins and peripheral retinal whitening (**A**). Laboratory work-up showed positive syphilis serology and elevated rapid plasma reagin 1:512. With the diagnosis of neurosyphilis the patient received intravenous penicillin, and vision improved to 20/20 with resolution of retinitis (**B**). This case highlights the importance of infectious work-up in new-onset retinitis, especially in immunocompromised patients. (Magnified version of Figure **A**-**B** is available online at www.aaojournal.org).

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