Tomographic Identification of Neuroretinal Rim Loss in High-Pressure, Normal-Pressure, and Suspected Glaucoma

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Purpose. To identify progressive rim loss and describe patterns of regional change in various clinical presentations of glaucoma by scanning laser tomography (SLT).

Methods. A previously described analytical approach was used to identify progressive rim area loss in SLT disc images of eyes of people with ocular hypertension (OHT, n = 97), early POAG (OHT converters; n = 30), asymmetric normal-pressure glaucoma (NPG, established and suspected in contralateral eyes; n = 26), and normal control subjects (n = 32). Analysis was performed longitudinally in individual image series, and cross-sectionally within groups at different time points.

Results. Reproducibly reduced rim area was detected in 2 (6.2%) of 32 normal control subjects, 11 (11%) of 97 OHT subjects, 27 (90%) of 30 OHT converters, 16 (58%) of 26 of suspected NPG eyes, and 15 (54%) of 26 of established NPG subjects, 27 (90%) of 30 OHT converters, 16 (58%) of 26 of suspected NPG eyes, and 15 (54%) of 26 of established NPG subjects, and normal control subjects (n = 32). Analysis was performed longitudinally in individual image series, and cross-sectionally within groups at different time points.

Conclusions. There were similarities and differences in the pattern of rim loss in SLT disc images of high- and normal-pressure presentations of glaucoma. Progressive rim loss was detected in eyes without visual field defects, eyes that progressed to develop field defects, and eyes with established and more severe glaucoma. (Invest Ophthalmol Vis Sci. 2004;45: 2279–2285) DOI:10.1167/iovs.03-1243

Sequential neuroretinal rim loss in progressive glaucoma has been described quite extensively by optic disc photography1–4 but not as much by the newer technique of scanning laser tomography. Unlike disc photography,1–5,7–9 scanning laser tomography data are reproducible8 and amenable to objective and quantitative analysis in a way that could be useful for detecting glaucoma progression.10–13 Previous longitudinal photographic studies of neuroretinal rim loss have mostly been in eyes with ocular hypertension (OHT) progressing to develop visual field abnormality.1,2,4,14 At this stage of disease, the observed pattern of disc cupping is predominantly that of generalized expansion or vertical elongation. In the latter, rim loss inferiorly and superiorly exceeds nasally and temporally so that the optic disc seems preferentially affected in its poles. Cross-sectional studies agree that the cup commonly becomes vertically oval in “early” glaucoma.15–17 The nature of rim loss in more advanced glaucoma has been understood by cross-sectional studies. Jonas et al.18 have suggested that rim loss at a given stage of primary open angle glaucoma (POAG) may involve any region of the optic disc, although the location of most pronounced loss varies with the severity of disease.

Concerning the pattern of glaucomatous optic disc change seen in scanning laser tomography, two longitudinal studies are notable. Kamal et al.19 examined OHT and OHT converters19 disc images, and suggested a preponderance of change in the superior and inferior regions of the rim and cup. Burgoyne et al.20 analyzed disc images of monkeys with experimental glaucoma and identified vertical cup-disc ratio and temporal and superior peripapillary retinal height as useful regional parameters for modeling change.

We have described an analytical approach for identifying sequential rim loss in scanning laser tomography that appears reliable enough to distinguish eyes with glaucoma progression from unchanging eyes.12,13 By analyzing rim loss sector by sector, regional patterns of change within the optic disc can be identified. Based on this, we wondered whether, and in what form, glaucoma progression in various clinical presentations of the disease could be identified by scanning laser tomography. We assessed longitudinal optic disc image series of persons with suspected glaucoma with no field defects (OHT and normal-pressure glaucoma [NPG suspects]), eyes in which perimetrically confirmed high-pressure glaucoma (POAG) developed, and eyes with moderately advanced NPG. Groups were also compared cross-sectionally at the start and end of the follow-up. We then described patterns of regional rim change, compared this between groups, and examined whether identified patterns corresponded in any way to the foregoing descriptions derived by standard disc photography.

Methods

Criteria for Selecting Subjects
The analytical approach was tested bilaterally in OHT subjects, bilaterally in asymmetric NPG subjects, the eye that “converted” in OHT converters to POAG, and unilaterally in normal control subjects. The same OHT converters and normal control subjects had been used in a previous publication to test (but not derive) the analytical approach.15 Subjects attended either the ocular hypertension and early glaucoma, or normal-pressure glaucoma research clinics at Moorfields Eye Hospi-
All had received imaging on at least four separate occasions over a minimum of 3 years. Except for NPG eyes, disc appearance was not part of the study's recruitment criteria. This study adhered to the tenets of the Declaration of Helsinki, having appropriate institutional review board approval and the subjects' informed consent.

Subjects with OHT had (1) intraocular pressure (IOP) consistently more than 21 mm Hg in one or both eyes without IOP-lowering treatment, (2) open angles on gonioscopy, (3) no defects on at least three consecutive visual field tests (Humphrey Retinal Field Analyzer 24-2 program; Carl Zeiss Meditec, Dublin, CA) with Advanced Glaucoma Intervention Study (AGIS) scores of zero, (4) refractive errors less than ±6 D, (5) no concurrent eye disease or previous intraocular surgery, and (6) age more than 40 years. Eyes of OHT converters had developed reproducible field defects, as defined by AGIS criteria (score >0), in the same location on three consecutive tests. OHT converters were taken to have early and progressive POAG.

To have asymmetric NPG, both eyes of subjects had (1) untreated mean IOP on phasing of less than 22 mm Hg, with no single reading exceeding 25 mm Hg; (2) gonioscopically open drainage angles; (3) no concurrent ocular disease or previous intraocular surgery; (4) only one eye had reproducible visual field abnormality at baseline and glaucomatous cupping compatible with the field defect (established NPG); while (5) the contralateral eye had no field defects (suspected NPG). Over the follow-up, in some eyes with suspected NPG reproducible defects developed, and they became NPG converters. Visual field abnormality in asymmetric NPG subjects was defined as for OHT converters. Abnormality was present in an eye only if its visual field received an AGIS score of 1 or more which could be verified as repeatable in the same location on three consecutive field tests. Only then was a field defect accepted as confirmed.

Eyes of normal control subjects were taken to be unchanged. Normal subjects were volunteers comprising spouses or friends of hospital patients, hospital staff, or members of external nonmedical social organizations. They had (1) IOP repeatedly less than 22 mm Hg, (2) serially normal and reliable Humphrey 24-2 visual fields with AGIS field scores of zero, (3) no concurrent ocular disease or previous intraocular surgery, (4) no family history of glaucoma, (5) refractive errors less than ±6 D, and were (6) aged more than 40 years.

Approach for Longitudinally Analyzing Rim Area for Change

This approach is described in detail elsewhere. Briefly, 30° rim area sectors were evaluated for change. The parameter of rim area was evaluated within longitudinal image series using a new experimental reference plane to define the inner edge of the rim. By this reference plane, rim area measurement variability is less and not appreciably affected by glaucoma or testing involving different operators and visits compared with conventional reference planes used in the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany). This makes variability easier to estimate and account for.

The outer extent of the rim coincided with the contour line in each subject's baseline mean topography image (JT). Mean images were derived from triplets of single topography images using the HRT software (ver. 2.01; Heidelberg Engineering). Contour lines were exported from a baseline mean topography image to other mean and single topography images in each series. Only images with mean pixel SD < 50 µm were used, and images having a grainy honeycombed appearance were excluded.

For any image series, limits of variability per sector (VARLIM) were calculated according to

\[ \text{VARLIM}_a = Y \cdot \frac{\sqrt{2(\delta^2 - X^2)}}{n - 1} \]

where, \( a \) is the sector number (corresponding to the order of a sector's location on the disc circumference between 0° and 360°), \( \delta \) is the sector rim area difference between pairs of intravisit single topography images, \( i \) is the ith value of \( \delta \), \( X \) is the mean of observations of \( \delta \), \( n \) is the number of observations of \( \delta \), \( Y \) is the value of the \( t \) statistic for degrees of freedom for \( \delta \), corresponding to a chosen two-tailed probability. A probability level of 0.10 corresponding to a 90% limit of variability was used based on previous findings.

Rim area data from each mean topography image were expressed as a rim area profile. A rim area profile is a plot of a disc’s 30° rim area sectors (in square millimeters) by their angular locations around the disc circumference (0°–360°, with 0° temporal, 90° superior, 180° nasal, and 270° inferior), as shown in Figures 2, 3, and 4. An eye's longitudinal image data were plotted as sequential rim area profiles in a common graph, each symbol- and color-coded to represent rim area measurement at a specific point in time.

Limits of variability define the extent of measurement variability for an image series with respect to the baseline measurement of rim area. The lower limits of variability for rim area sectors were plotted relative to the baseline rim area profile, with the region beneath the lower limits termed the zone of change. Any rim area sector that diminished, exceeded its lower limit of variability, and entered the zone of change was considered to have changed more than variability alone. This was tentatively taken to represent glaucomatous change. Only sector change repeatedly exceeding variability in two of three sequential tests was considered as progression. Data from any number of visits over time, as expressed in sequential rim area profiles, can be simultaneously assessed and weighed against their own variability estimates. An eye was considered to have confirmed progression if at least one of its rim sectors showed repeatable change meeting this criterion.

Statistical Analysis

First, an analysis was performed of the individuals’ longitudinal image series and then cross-sectionally of group data at baseline and final follow-up.

Analyzing Longitudinal Image Series by the Analytical Approach. In analyzing individuals, we analyzed each image series for change using the analytical approach. The frequency distribution of change in 30° sectors in each diagnostic category was plotted in schematic diagrams of the optic nerve head. In diagrams, sectors straddling the superior (60–120°) and inferior (240–300°) vertical meridians were taken to represent the superior and inferior disc poles, respectively. The sectors straddling the horizontal meridian temporarily (330–360°, 0–30°) and nasally (150–210°) were termed temporal-horizontal and nasal-horizontal sectors, respectively. In eyes with reproducible field defects, the location of abnormality in the Humphrey field grid was described as nasal or temporal, or superior or inferior, as defined by the AGIS field template. Paracentral abnormality affecting any of the four field locations next to fixation was noted.

Cross-sectional Analysis of Diagnostic Groups at Baseline and Final Follow-Up. In the analysis of groups, the median of rim area values was calculated for each sector in each diagnostic group. Each group’s sectors’ median values were then subtracted from the normal control group’s median values, sector for sector. This gave each diagnostic group a value for rim area deviation from normal (results refer to this just as “deviation”) for each sector. The magnitude of deviations was plotted in schematic diagrams of the optic nerve head for two time points: at baseline and at final follow-up. The probability of accepting the null hypothesis that a particular deviation was significantly different from normal was calculated by the Mann-Whitney test and expressed as probabilities per sector in schematic diagrams of the optic nerve head. \( P \leq 0.05 \) was considered statistically significant and to reflect true deviation from normal. Smaller probabilities for a sector indicated that it was less probable that the null hypothesis of true deviation from normal would be rejected. Statistical analysis was conducted on computer (SPSS ver. 9 for Windows; SPSS Inc., Chicago, IL).
RESULTS

Demographics of Subjects

Three hundred eighty longitudinal image series of 185 subjects were analyzed by the analytical approach: (1) both eyes of 97 OHT subjects, (2) both eyes of 26 asymmetric NPG subjects, (3) the eye that “converted” in 30 OHT converters to POAG, and (4) one randomly chosen eye in each of 32 normal control subjects. Subjects’ demographics and ocular parameters are shown in Table 1. Disc area was found not to be significantly different between groups ($P > 0.05$), although there was a trend toward NPG discs being larger than in other groups. Only eyes with established NPG had field defects at baseline. At final follow-up, visual field mean deviation (MD) in established NPG was worse than in ocular hypertension converters ($P = 0.003$, Mann-Whitney test). Other between-group comparisons showed no differences ($P > 0.05$). There were five NPG converters. Their visual field indices were not significantly different from those of OHT converters ($P > 0.05$, Mann-Whitney test).

Longitudinal Analysis of Individual Image Series

Two of 32 normal control eyes had repeatable change in at least one rim area sector, giving an estimated false-positive rate of 6.2%.

Of 97 OHT subjects, repeatable rim loss was identified in one eye each of 11 (11%) subjects. By definition, all had no field defects at baseline and final follow-up. Figure 1A shows that changed sectors were most frequently identified in the inferior pole ($240–300°$), followed by superiorly ($60–90°$), and nasally ($150–210°$). Three (27%) of 11 had rim loss nasally–horizontally ($150–210°$), but temporal–horizontal change was rare. Figure 2 is an example of superior–temporal rim loss. Figure 3 shows diffuse rim loss.

Repeatable rim loss was identified in 27 of 30 OHT converters. Figure 1B shows that rim loss was most frequently in the inferior pole ($270–300°$), followed by superotemporal loss between $30°$ and $90°$. Forty-two percent (13/31) had rim loss nasally–horizontally ($150–210°$), but rim loss temporally–horizontally ($330–360°$, $0–30°$) was rare. Twenty-three (77%) of 30 converters had nasal visual field defects, whereas 2 (6.7%) of 30 had paracentral field defects.

In suspected NPG, rim loss was identified in 15 (58%) of 26 eyes. In 5 (19%) of 26 eyes reproducible field abnormality developed over follow-up, and these eyes were considered NPG converters. Visual fields of the other 21 of 26 eyes remained normal throughout. Figure 4 shows widespread temporal rim loss and concurrent inferior and inferonasal change in a suspected NPG eye that retained normal visual fields. Figure 1C shows that rim loss in suspected NPG was most frequently in the inferior pole ($270–300°$) and temporally–horizontally ($0–30°$). Nasal rim loss was relatively uncommon.

Of NPG converters, repeatable rim change was confirmed in three of five eyes. One of five eyes had tentative change which, for lack of follow-up data, could not be confirmed. Three (60%) of five NPG converters exhibited paracentral defects at conversion.

In established NPG, 14 (54%) of 26 of eyes had repeatable rim loss. Figure 1D shows that rim loss was most frequent inferotemporally ($300–360°$) and temporally–horizontally.

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OHT, ocular hypertension; Converters, ocular hypertension converters; NPG suspect., suspected NPG; NPG estab., established NPG. Data are expressed as mean and standard deviation (SD).
with large and significant deviations tended to be clustered around the superior and inferior poles (Figs. 5D, 6D), but sectors clustered around the temporal–horizontal sector also showed large and significant deviations. Seventeen (65.3%) of 26 eyes with established NPG had paracentral field defects. These defects were located superiorly only in 11 (64.7%) of 17, inferiorly only in 5 (29.4%) of 17, and concurrently in both hemispheres in 2 (11.8%) of 17. In suspected NPG, rim sector deviations were smaller, and fewer were significant compared with established NPG.

All OHT, OHT converter and suspected NPG eyes had normal fields at baseline. However, suspected NPG eyes (Fig. 5C) had more rim sectors with large or moderate deviations and significant deviations, especially in the disc poles, compared with OHT (Fig. 5A) or OHT converters (Fig. 5B) at baseline (1) and at final follow-up (2) (Figs. 5, 6). This suggests that suspected NPG discs were more cupped than OHT or OHT converter discs at baseline, despite their fields being similar. At final follow-up, suspected NPG discs still appeared more cupped than OHT converters, despite all OHT converters having developed field defects and most suspected NPG eyes (21/25; 81%) having retained normal fields. Reanalysis after removing the 5 of 26 NPG converter eyes yielded a similar result.

Cross-Sectional Analysis of Groups at Baseline and Final Follow-Up

Figure 5 shows the magnitude of rim area deviation from normal per sector for diagnostic groups at baseline (1) and at final follow-up (2). Figure 6 shows the probability of rejecting the null hypothesis of true deviation for each sector.

In Figure 5, all groups had more sectors with large (black sectors) or moderate (dark gray) deviations at final follow-up than at baseline. This was most marked in OHT converters (Fig. 5B), suspected NPG (Fig. 5C), and established NPG (Fig. 5D). There was a propensity for the disc poles to have large and also significant deviations in all diagnostic groups (Fig. 6: sectors with $P \leq 0.05$). At final follow-up, all groups had larger deviations and more sectors with significant deviations than at baseline.

In Figures 5 and 6, eyes with established NPG (Fig. 5D) had more sectors with large and significant deviations than did other groups (Figs. 5A–C). Visual fields of established NPG eyes were also more damaged (Table 1: mean MD = −6.5 dB, mean corrected pattern standard deviation [CPSD] = 9.9 dB). Sectors

FIGURE 2. Progressive rim loss in ocular hypertension. Two superior–temporal sectors, 50° to 60° and 90° to 120°, exceeded their 90% limits of variability repeatedly (arrows, top), and the cup was enlarged to become more vertically elongated. Ninety-percent limits of variability form the upper extent of the zone of change.

FIGURE 3. This optic nerve of an eye with ocular hypertension had diffuse rim loss over time, repeatably exceeding the 90% limits of variability (arrows), with only two temporal–horizontal sectors remaining without confirmed change. Many sectors have met the criterion for change by the stricter 95% and 99% statistical limits of variability. The cup is seen to enlarge concentrically.
first quantified the performance of the test to establish an acceptable and robust reference standard against which subsequent findings could be interpreted. We did this by assessing unchanging eyes and eyes with unambiguous change, for which we chose normal control subjects and OHT converters, respectively. This then provided a framework for interpreting the approach’s results in eyes whose fields were apparently normal (but suspected of changing, vis-à-vis OHT and suspected NPG) or already had confirmed abnormality (established NPG), in which change might be difficult to detect unambiguously. Difficulty reliably interpreting glaucomatous progression in fields with preexisting defects is well acknowledged.24–26

Based on longitudinally analyzing the images of normal control subjects and OHT converters by 90% limits of variability and the two-of-three criterion, and assuming no change in the former and progression in the latter, repeatable rim loss was identified with a sensitivity of 90% and a false-positive rate of 6.2%. By the same analytical approach, rim loss was identified in three of five NPG converters in whom field defects developed. In eyes with established NPG and moderately severe disease, rim loss was identified in 54%. Repeatable rim loss was also detected even in the absence of field abnormalities: in 52% (11/21) of suspect NPG eyes that retained normal fields and unilaterally in 11% (11/97) of OHT eyes. Patterns of change were then documented in the various diagnostic categories.

The longitudinal and cross-sectional analyses agreed that similar patterns of rim loss were seen in OHT and OHT converters having “early” glaucoma. Rim loss was frequently detected in the disc poles, especially inferiorly, and is consistent with a pattern of the cup elongating vertically. These findings concur with longitudinal11–13 and cross-sectional15–17 photographic studies of the disc in OHT and conversion. Preferential rim loss at or near the disc poles has been associated clinically with the common location of disc hemorrhages,27–29 localized nerve fiber layer atrophy,29 and early field defects30 and histologically with the configuration of lamina cribrosa pores.31–32 That concentric cupping may be relatively common in OHT converters1,4 was reflected in our findings, too. The not uncommon pattern of nasal rim loss seen in OHT and OHT converters suggests that cupping does not occur solely vertically. Still, the overall pattern of change would have been strongly influenced by the preponderance of rim loss in the disc poles. Also, as the normal cup tends to be horizontally

DISCUSSION

The analytical approach for identifying progressive rim loss was applied to images of eyes with different clinical presentations of glaucoma, as defined by IOP and visual field status. To provide a firm basis for interpreting change in these eyes, we

FIGURE 6. Schematics of the optic nerve head showing statistically significant deviations in rim area point-estimates at final follow-up (2) compared with baseline (1) for each sector in ocular hypertension, ocular hypertension converters, NPG suspects, and established NPG. Comparison between normal eyes and (A) ocular hypertension, (B) ocular hypertension converters, (C) suspected NPG, and (D) established NPG. Probability of rejecting the null hypothesis for significant deviation (P): white: P > 0.05; light gray: 0.01 < P ≤ 0.05; dark gray: 0.005 < P ≤ 0.01; and black: P ≤ 0.005. Each schematic’s aspect is as for the left eye, with left, nasal, right, temporal; 1, baseline comparison; 2, final follow-up comparison.
oval, more vertical than horizontal rim tissue would have to be lost for cupping to appear concentric in “early” disease.\(^5\)\(^{-}\)\(^{14}\)

Thus, initially, cupping that appears concentric may actually be due to vertical rim loss exceeding horizontal loss. Such a pattern of loss may not be easy to detect by subjective assessment, however,\(^5\)\(^{-}\)\(^{14}\) as illustrated in Figure 2.

Some patterns were common to all groups. As with high-pressure presentations (OHT and OHT converters with IOP > 21 mm Hg), normal-pressure groups (suspected and established) quite frequently had moderate to large and significant rim loss in the disc poles, especially inferiorly. Patterns of change were similar within high-pressure groups, whether or not field defects were present, and the same held true for normal-pressure presentations. Rim loss was identified in similar proportions of eyes with suspected NPG and established NPG (50–60% in each).

But there were some differences. Unlike high-pressure groups, rim loss in normal-pressure presentations was commonly seen temporally but not nasally, both in longitudinal and cross-sectional analyses. It could be that the relatively large and frequent temporal rim change in established NPG was due to more severe disease (mean MD = \(-6.5\) dB, mean CPSD = \(9.9\) dB), as Jonas et al.\(^17\) suggest to be the case. NPG suspects, however, had baseline fields that were normal and equivalent to those of OHT and OHT converter eyes, and yet they still had relatively frequent temporal rim loss. The temporal rim loss in NPG seemed to correlate with what was observed of their visual fields: paracentral field defects were found at conversion in 3 of 5 NPG converters, but only 2 (6.7%) of 30 OHT converters. OHT converters had predominantly nasal field defects (77%). Sixty-five percent of eyes with established NPG had paracentral field defects. Several investigators have found that field defects tend to be closer to fixation in NPG than in POAG converters,\(^35\)\(^{-}\)\(^{38}\) and in suspected NPG compared with OHT.\(^59\) We also found that sector rim area deviations from normal were larger and more often significant in suspected NPG than in OHT or OHT converters, suggesting that suspected NPG discs were more cupped at baseline and final follow-up, despite the groups having equivalent fields initially. Other investigators have reported more cupping in NPG than POAG for the same amount of field damage.\(^35\)\(^{-}\)\(^{36}\)\(^{-}\)\(^{41}\)

Using an objective analytical approach for detecting progressive rim loss, common patterns of change were observed within high- and normal-pressure presentations of glaucoma. There was agreement between the changes of pattern identified in longitudinal analysis by this approach and those yielded by some sectional analyses of the same groups over time. Apparent similarities but also differences were seen between groups, and these correlated with previously published photographic findings. Our longitudinal analysis identified progression in eyes with suspected glaucoma without visual field defects, eyes that progressed to development of definite field defects, and eyes with established and more severe glaucoma.

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