CUMULATIVE CURVE TO DETECT NEURORETINAL RIM AREA DEFECTS IN GLAUCOMATOUS OPTIC NERVE HEADS

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Abstract

The aim of the study was to evaluate the capacity of rim area/disc area (RA/DA) cumulative curve analysis to distinguish optic nerve heads (ONHs) with a glaucomatous visual field from those with a normal visual field. One hundred and fifty-four subjects were consecutively recruited for the study. All the ONHs were analyzed by Image-net X Rev.3/51b (Topcon, The Netherlands), and all subjects were assessed by Humphrey 30-2 visual field (Humphrey Instruments, Inc, San Leandro, CA). Thirty-six equally spaced rim sectors of each optic disc were obtained from all ONHs and the median RA/DA cumulative curve was calculated. To increase the sensitivity of this analysis between early glaucoma and normal eyes, the cumulative curves were subsequently divided into two equal segments, and the slopes of their respective regression lines were compared. A significant difference (p<0.001) was found for the median 36 sector RA/DA values between glaucomatous eyes and normals. Because the cumulative curves distribution of early glaucomatous eyes were within the normal range, the cumulative curves of these cases with early glaucomatous damage were divided into two equal segments of 18 sectors, and the slopes of their regression lines were compared: a significant difference (p<0.05) was found in all these cases. Normal eyes were shown to be true negatives in 93% of cases in which no significant difference was observed between the two slopes. Analysis of the RA/DA cumulative curve from 36 sectors of optic disc is a valid method for the identification of glaucomatous disc pathology. However, further calculation of the slopes of the two RA/DA regression lines is needed to identify early glaucomatous damage.

Introduction

Computerized analysis of the optic disc provides a wealth of quantitative data as to its morphology in both normal and glaucomatous eyes. Proper statistical management of these data is needed to supply the information clinically relevant and utilizable in the diagnosis and assessment of optic disc changes in glaucoma1-3. Quantitative analysis of the rim area/disc area ratio (RA/DA) cumulative curve could allow identification of rim area size changes, resolving the difficulty of detection of optic disc defects and the distinction between global and localized damage for the diagnosis and follow-up of glaucomatous changes4-7.

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The aim of this study was to evaluate the capacity of RA/DA cumulative curves, and thus distinguish ONHs with normal visual field from those with glaucomatous visual field.

Material and methods

One hundred and fifty-four subjects were recruited consecutively. One eye from each subject was chosen randomly. Glaucoma patients were selected from the glaucoma center of the University of Genoa and were defined as having an intraocular pressure (IOP) higher than 21 mmHg without therapy on at least two examinations, open angle at gonioscopy, and typical perimetric glaucomatous defects. Normal subjects were volunteers from the University and had an IOP lower than 21 mmHg on at least two measurements, no personal or familial history of high IOP, and a normal visual field.

Optic disc appearance was not considered as a criterion for inclusion in the study because this could bias the determination.

All subjects had refractive defects of ±3 diopters (spherical equivalent), ability to obtain a mydriasis greater than 7 mm, no dioptic media opacities able to hinder good image acquisition, and no systemic and/or ocular diseases able to modify the papillary surface (diabetes, hypertension, vasculitis, other primary and/or secondary vascular diseases, optic neuropathy except glaucoma, etc.).

All subjects were assessed with Humphrey 30-2 Visual Field (Humphrey Instruments, Inc., San Leandro, CA) and Image-net X Rev.3/51b (Topcon, The Netherlands).

Humphrey Visual Field

Subjects were classified as having a glaucomatous visual field if they had: a. a 10dB or greater loss in the superior or inferior Bjerrum areas when compared with perimeter-defined age-matched controls, b. three contiguous points with a 5dB or greater loss in the superior or inferior Bjerrum areas, or c. a 10dB difference across the nasal horizontal mid-line in two or more adjacent locations, with no point on the edge except immediately above or below the nasal horizontal meridian. Only reliable fields were used, as determined by reliability parameters (less than 30% false positive and false negative responses and fixation loss of less than 10%).

All visual fields were assessed within 15 days of optic disc image acquisition.

Topcon Image-net system

Image acquisition was performed by means of the Image-net X Rev-3.51b Topcon system (Topcon, The Netherlands). This system includes two charge-coupled device video cameras with a field of view of 12° and a green separation system to further delineate the topography of the optic disc. Analogical signals coming from the two cameras travel to the red and green analogical-to-digital converters, with the resulting digital images (512x512x24 bit image memory) displayed to the operator and then saved to the optical disc. Correction for magnification errors is provided by means of Littmann formula-based correction factors implemented in the software.
The methodology has been described in detail elsewhere, as has the reproducibility and reliability of the system\(^2\). Briefly, at least three stereoscopic images of the optic nerve were taken, and the mean and standard deviations from the mean of the three RA/DA values were calculated. When the coefficient of variation was higher than 7\%, the images were discarded and a new image acquisition was performed. The operator identified four points located on the outer edge of the optic disc rim on each optic disc image using the ‘Optic Disc Analysis’ program which allows the traditional morphological parameters to be calculated\(^1\).

The RA/DA ratio was calculated in order to evaluate the cumulative distribution of the areas of the 36 equally spaced (10\(^\circ\)) sectors of each optic disc. For every sector, the data for normal and glaucomatous optic discs were separately and decrementally sorted to form a line. The 50th (median), 95th and 5th percentiles were calculated for each sector, and the values were graphically presented allowing the rapid visualization of data from normal and pathological eyes. Because the data distribution was not normal, the non-parametric Mann-Whitney test was used to compare the difference between the medians of the 36 RA/DA sectors of glaucomatous and normal eyes.

All the curves obtained from normal eyes, and those curves obtained from glaucomatous eyes which fell within the normal range, were divided into two equal parts with the same number of points (\(n=18\)), and the regression lines of these hemicurves were calculated. The RA/DA cumulative curve was then determined by comparing the slopes of the regression lines of the two partial curves.

The Excel 5.0 (Microsoft) software program was used for graphic presentation of the data, and the GraphPad Prism software (Version 2.0) for statistical analyses, including comparison of the slopes of the regression lines.

**Results**

Using the previously described criteria, 71 eyes were normal and 83 glaucomatous. No difference was found for age and disc area between normal subjects (55 ± 12.5 years [mean ± standard deviation] and 2.4 ± 0.27 mm\(^2\), respectively) and glaucomatous patients (57.1 ± 14.2 years and 2.43 ± 0.24 mm\(^2\), respectively).

A significant difference was found for global RA/DA (0.61 ± 0.05 versus 0.47 ± 0.04 [normal versus glaucomatous]), MD (-0.93 ± 0.79 versus -5.53 ± 6.96) and CPSD (0.4 ± 0.6 versus 5.9 ± 2.45).

The difference between the medians of the 36 RA/DA sectors of glaucomatous and normal eyes was significant (\(p<0.001\)) using the Mann-Whitney test (Fig. 1).

Sensitivity and specificity of RA/DA cumulative curves in distinguishing ONHs with normal visual fields from glaucomatous ones was 92.8\% and 90.1\%, respectively. (True positives were defined as glaucomatous eyes with curves that fell outside the range obtained in normal eyes. True negatives were defined as normal eyes with curves within the normal range.)

Using the above definitions, six eyes of the glaucomatous group were identified as false negatives, i.e., the RA/DA cumulative curves were within the cumulative curve distribution of normal eyes. However, in all these eyes, when the curve was divided into two equal
Fig. 1. Rim-disc area ratio (RA/DA) cumulative curves of healthy (dotted lines) and glaucomatous (continuous lines) eyes. Small continuous lines represent the 5th and 95th percentiles for glaucomatous eyes; large continuous line represents the median for glaucomatous eyes. Small dotted lines represent the 5th and 95th percentiles for normal eyes; large dotted line represents the median of healthy eyes.
parts, the slopes of the two regression lines were significantly different (at least \( p<0.05 \)) (Fig. 2).

The combination of these two methods increased the sensitivity and specificity of RA/DA cumulative curves and slope in distinguishing ONHs with normal visual fields from glaucomatous ones to 100% and 90.1%, respectively.

**Discussion**

In 1987, Flammer *et al.* suggested the formulation of perimetric indices for the interpretation of raw data provided by computerized perimetry in order to obtain useful clinical information. In 1996, both Bartz-Schmidt *et al.* and Asawaphureekorn *et al.* demonstrated, in a small number of normal and glaucomatous patients, that statistical elaboration of cumulative defect curve data resulted in a rapid and easy method to identify the presence of diffuse and localized defect areas of the disc rim. Applying this method to the present study, larger groups of glaucomatous patients at different stages of the disease yielded very favorable results, with a sensitivity of 92.8% and a specificity of 90.1% in distinguishing normal from glaucomatous eyes.

Rim area measurements taken by computerized optic disc analyzers are reported to be one of the best indicators of glaucoma-induced optic disc changes. However, when a localized defect which reduces the size of the rim area is present, the machine cannot distinguish this localized defect from a diffuse rim fiber loss. This difficulty in separating localized from global defects, which was also a shortcoming of visual field analysis, was brilliantly solved by the introduction of the cumulative defect curve.

Probably due to the large variability of ONH shape in early glaucoma patients as well, RA/DA cumulative curves were sometimes partially or totally included within the range of normal subjects. Thus, in marginal cases, evaluation of the cumulative RA/DA curve alone was not sufficient for the accurate identification of disc pathology.

In order to solve this problem, the cumulative curves of these early glaucomatous patients (six patients) were divided into two equal segments, and the slopes of their regression lines were compared. Results demonstrated that, in glaucomatous eyes with the RA/DA cumulative curve located above the 5th percentile of normal eyes, there was a statistically significant difference between the slopes of the two regression lines. This different inclination between the slopes of the regression lines of the two partial arcs indicated the presence of localized thinning of the optic disc rim. Applying this corrective data elaboration to the data from the six false-negative subjects improved test sensitivity from 92.8% to 100%.

Glaucoma was diagnosed in this study only by the presence of typical visual field changes, and not by any morphological or morphometric changes of the optic discs, in order to ensure the heterogenous sampling of glaucoma patients and potential disc pathologies. However, these inclusion criteria limited the entry of subjects with definite optic disc changes but no visual field changes, and those subjects with field defects that could not be identified as glaucomatous; for example, patients with uniform loss in differential light sensitivity or patients characterized by scattered field damage were not entered in this study. In conclusion, the potential of the RA/DA cumulative curve test to identify early disc pathology without perimetric defects needs to be investigated.
Fig. 2. A patient with early glaucoma. The graph represents one of the six curves included in the area of overlapping of the 5th-95th percentile ranges of glaucomatous and healthy eyes. When the curve was divided into two hemi-curves, the comparison of the slopes of the regression lines of the two hemi-curves showed a statistically significant difference (p<0.0001).
References