The ability of the GDx Nerve Fibre Analyser neural network to diagnose glaucoma

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Abstract  Purpose: To evaluate the neural network used by the GDx in a group of normal subjects, patients with ocular hypertension (OHT) and patients with normal-pressure glaucoma (NPG).  Methods: The GDx neural network produces a “number” that indicates the likelihood that glaucoma is present. This number was compared in three groups representing different stages of health and disease, namely, normal controls (n=101), OHT (n=102) and NPG (105). The GDx number's ability to differentiate between normal and glaucoma individuals was then investigated. We also studied the relationship between the GDx number and retinal nerve fibre layer (RNFL) average thickness and visual field status to examine how well the GDx number reflects disease severity.  Results: The GDx number was significantly different among the groups (P<0.01); it was highest in NPG and lowest in normal controls. The GDx number differentiated between glaucoma and normal with sensitivity of 92.3% and specificity of 96%. When combined with the parameter of RNFL average thickness, sensitivity and specificity were 88.5% and 100% respectively. In NPG a significant correlation was found between the GDx number and RNFL average thickness (rho=-0.88, P<0.001) and visual field mean deviation (rho=-0.64, P<0.001).  Conclusion: The GDx number is able to differentiate between groups of normal, OHT and NPG subjects. Its close relationship with RNFL average thickness and visual field status in glaucoma indicates that it is able to reflect disease severity. Furthermore, its measured ability to distinguish between normal individuals and those with glaucoma demonstrates potential for use in glaucoma diagnosis.

Introduction

Scanning laser polarimetry (SLP) has been proposed as a method for measuring in vivo peripapillary retinal nerve fibre layer (RNFL) thickness [6, 28]. It is reproducible, can differentiate between groups of normal subjects, patients with ocular hypertension and patients with glaucoma [4, 11, 15, 16, 19], and shows thinning of the RNFL with increasing age, ethnicity and eccentricity from the optic disc. SLP's ability to diagnose glaucoma has been studied extensively, and though the outcomes have varied among studies, it is broadly considered to demonstrate promise [2, 3, 16, 18, 23, 24, 27]. SLP can be performed clinically using a commercially available ocular imaging system called the GDx (Laser Diagnostics Technology, San Diego, Calif., USA).

Recently developed GDx software incorporates a trained neural network that outputs a number based on analysis of image pixels [range from 0 (normal) to 100 (advanced glaucoma)]. A back-propagation type of network with two hidden layers is used where the input layer consists of 128 input neurons representing the number of parameters and the output layer consists of a single
output neuron [29]. Trible et al. evaluated the GDx number for glaucoma diagnosis and found it to have a sensitivity of 81% and specificity of 89% [25], but did not study its significance in subjects with ocular hypertension or its relationship to conventional SLP parameters or visual fields. This is important to know in order that the method’s ability to reflect the spectrum of disease severity in clinical practice may be judged. We conducted a study to assess how the GDx number may differ between normal subjects, patients with ocular hypertension (OHT) and patients with normal-pressure glaucoma (NPG). We also studied the relationship between the GDx number and RNFL average thickness, and between each of these measures and visual field status, as represented by mean deviation (MD). In addition, the potential of the GDx number for use in glaucoma diagnosis was evaluated.

Materials and methods

Subjects

Subjects with OHT and NPG and normal controls attending the glaucoma research unit at Moorfields Eye Hospital and who had previously been imaged with the GDx were selected for this study. The normal subjects were volunteers who were spouses of patients or members of staff who met the inclusion criteria. They had visual acuity of 6/9 or better, intraocular pressure (IOP) not exceeding 21 mmHg, reproducible normal Humphrey 24-2 visual fields and no family history of glaucoma. Subjects with OHT had IOP exceeding 21 mmHg and reproducible normal visual fields on at least four consecutive separate visits. NPG patients had maximum IOP <22 mmHg and glaucomatous cupping of the optic nerve head together with corresponding reproducible visual field defects.

Tests

All visual fields were performed on the Humphrey visual field analyser (Humphrey Instrument, San Leandro, Calif., USA) using the 24-2 full-threshold program. Reliable visual fields were defined as having fixation losses of less than 20% and maximum false-positive and false-negative responses of 30%. A visual field was defined as abnormal if it had at least three locations depressed by a minimum of 5 dB, or one location depressed by at least 10 dB within a cluster of two locations [1, 13]. Visual field defects were considered reproducible if they met the criteria for abnormality and were present in exactly the same field locations in four consecutive tests. The severity of disease in NPG subjects were classified according to MD scores into early (MD <–5.00 dB), moderate (–5.0 ≤ MD <–15.0 dB) and advanced (MD ≥–15.0 dB) groups.

A GDx Nerve Fibre Analyser with software version 2.0.09 was used to image all the subjects. At each imaging session, three GDx scans were acquired and then used to calculate a mean image that was subsequently used for analysis. Only high-quality images that had passed the internal software’s automated quality control criteria were accepted. Measurements for RNFL thickness were derived from the pixelated thickness values on a circle located 1.75 disc diameters from the optic disc margin. Right and left eyes were analysed separately. In this study, we present results from the right eye only. Of the various parameters presented by the GDx software, only RNFL average thickness was selected for correlation analysis with the GDx number and disease severity. This was chosen for its simplicity and because it has been found to be a good reflector of glaucoma severity as interpreted through visual fields.

Statistics

Categorical variables were compared between the three patient groups using the Chi-square test, and quantitative variables were compared using the rank sum test. Bonferroni corrections were used throughout. We used non-parametric tests because of skewness detected in the distribution of GDx number scores and RNFL average thickness scores. Correlations between variables were assessed using the Spearman rank sum correlation coefficient. To assess the use of GDx number and average thickness in discriminating between NPG and normality, subsequent analysis was conducted that excluded the OHT patients. We randomly divided the data into a training set (75% of the data) and a validation set (25%). Two methods of classification into glaucoma or normal were then assessed. The first simply took the lower 5th centile of the GDx number of NPG patients and classified subjects as glaucomatous if they had a number higher than this. The second was that of logistic regression used to derive a linear discriminant function (LDF) using the training data. Each model was then applied to both training data and validation data.

Results

Of the 308 eyes included in this study 101 were normal, 102 had OHT and 105 had NPG. Normal controls were marginally younger than the OHT and NPG subjects, and female patients formed the majority within the NPG group (Table 1). While visual field MD and corrected pattern standard deviation (CPSD) in normal and OHT groups were comparable, in both these groups they differed significantly from the NPG group, as shown in Table 2. Of the NPG group, 24% (25/105) were classified as early, 55% (58/100) as moderate and 21% (22/105) as severe glaucoma. There was a significant difference in GDx number among the three groups (P < 0.01); it was highest in NPG and lowest in normals. A rank sum test showed that the difference between OHT and normals was statistically significant (P < 0.001). Correspondingly, the RNFL average thickness differed among the groups (P < 0.01), being lowest in NPG patients and highest in normal controls (Table 3, Figs. 1, 2). Stratification revealed that these differences were not due to differences among the groups in age or sex. In NPG patients, we found strong evidence of a trend towards increasing GDx number with worsening visual field MD (rho = –0.64, P < 0.001) (Fig. 3) and a similar trend towards decreasing RNFL average thickness with increasing GDx number (rho = –0.88, P < 0.001) (Fig. 4), indicating that RNFL thinning is reflected by increasing values of the GDx number. The lower 5th centile of the GDx number of patients with NPG in the training data was 39. When tested in the validation data set, this cut-off resulted in overall sensitivity of 92.3% and specificity of 96%. For subjects with