The ISNT Rule and Differentiation of Normal From Glaucomatous Eyes

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Objective: To determine whether the ISNT rule (that normal eyes show a characteristic configuration for disc rim thickness of inferior ≥ superior ≥ nasal ≥ temporal), widely used for clinical evaluation of the optic nerve head, can differentiate normal from glaucomatous eyes.

Methods: All subjects underwent complete eye examination, including achromatic automated perimetry, simultaneous stereoscopic disc photography, and confocal scanning laser ophthalmoscopy. Subjects with normal eyes had no evidence of glaucoma or ocular hypertension and had normal perimetry measurements. Subjects with glaucoma had a reproducible visual field defect. One eye from each subject was randomly enrolled. The ISNT rule was assessed by masked evaluation of disc photographs at the 3, 6, 9, and 12 o’clock positions.

Results: Sixty-six subjects with normal eyes (33 black and 33 white individuals) and 43 with open-angle glaucoma (15 black and 28 white individuals) were enrolled. The ISNT rule was intact in 52 (79%) of 66 normal eyes and 12 (28%) of 43 glaucomatous eyes (P<.001). Multiple logistic regression indicated that the odds ratio for glaucoma associated with violation of the ISNT rule was 6.04 (95% confidence interval, 1.74-20.95) after adjustment for age; race was not a confounder of this association.

Conclusion: The ISNT rule is useful in differentiating normal from glaucomatous optic nerves and is unaffected by race.

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optic disc appearance based on clinical examination, and normal automated achromatic perimetry results. Absence of glaucomatous optic neuropathy was defined as a vertical cup-disc asymmetry between eyes of less than 0.2, a cup-disc ratio of 0.6 or less, and an intact neuroretinal rim without notching or excavation. A normal visual field had a pattern standard deviation within the 95% normal limits and a glaucoma hemifield test result within the 99% normal limits on a reliable visual field.

Subjects with glaucoma had open angles on gonioscopy and repeatable achromatic visual field loss consistent with glaucoma. Glaucomatous visual field loss was defined as a pattern standard deviation outside the 95% normal limits or a glaucoma hemifield test result outside the 99% normal limits or both.

Simultaneous optic disc stereophotographs were evaluated during masked review by a committee of 3 observers (N.H., C.O., and J.M.L.). The observers evaluated optic nerve neuroretinal rim thickness at the inferior, superior, nasal, and temporal positions (ie, at the 3, 6, 9, and 12 o’clock positions). A decision regarding thickness of the rim and the ISNT rule was reached by consensus. The rule was considered to be intact if there was a gradual decrease or no change in rim width at these positions relative to the following order: inferior $\geq$ superior $\geq$ nasal $\geq$ temporal (Figure). The central retinal vessel trunk was not considered part of the neuroretinal rim.

If the ISNT rule was not intact, the consensus group was required to determine whether the inferior rim thickness was greater than or equal to that of the superior rim.

Statistical analysis was performed using JMP or SAS statistical software (SAS Institute Inc, Cary, NC). The unpaired, 2-tailed $t$ test or nonparametric Wilcoxon rank sum test was used to compare the distributions of continuous variables between groups; the $\chi^2$ test or the Fisher exact test was used to compare categorical variables. Multiple logistic regression analysis was used to investigate the association between glaucoma and adherence to the ISNT rule while adjusting for covariates. $P<.05$ was considered statistically significant. Results are presented as mean±SD unless otherwise indicated.

One hundred nine eyes of 109 subjects were enrolled. Sixty-six (33 white and 33 black) subjects were used as normal controls and 43 (28 white and 15 black) had glaucoma. Patient demographic and ocular characteristics are described in Tables 1, 2, and 3. Subjects with normal eyes were younger than those with glaucoma (46.1±13.6 vs 61.3±10.7 years; $P<.001$) (Table 1). Sex distribution (P=.55) and refractive error (P=.37) were similar between the 2 groups. Normal eyes had a shorter axial length than eyes with glaucoma (23.6±0.9 vs 24.1±1.1 mm; $P=.01$).

The ISNT rule was intact in 52 (79%) of 66 normal eyes and 12 (28%) of 43 glaucomatous eyes ($P<.001$) (Table 1). Among subjects with normal eyes, the proportion of subjects adhering to the ISNT rule did not differ by race (25 [76%] of 33 black subjects vs 27 [82%] of 33 white subjects; $P=.76$ by Fisher exact test) (Table 2). Among white participants, the ISNT rule was intact more often in normal eyes (27/33 [82%]) than in glaucomatous eyes (10/28 [36%]) ($P<.001$) (Table 3). Similarly, among black participants, the ISNT rule was intact in 25 (76%) of 33 normal eyes compared with 2 (13%) of 15 glaucomatous eyes ($P<.001$) (Table 3). The odds ratio (OR) for glaucoma associated with violation of the ISNT rule in black participants (OR, 20.3; 95% confidence interval [CI], 3.7-110.0) exceeded that in whites (OR, 8.1; 95% CI, 2.5-26.2), but the sample sizes were small and Breslow-Day test results indicated that the ORs were not significantly different, suggesting that race was a confounder and not an effect modifier.

Of the 14 normal eyes that violated the ISNT rule, 7 had an inferior rim that was thinner than the superior rim. Of the remaining 7 eyes, 5 had a nasal rim that was thicker than the inferior rim and 2 had a temporal rim...
that was thicker than the superior rim. Analysis of the vertical rim alone by diagnostic group demonstrated that the inferior rim was generally thicker than or equal to the superior rim for both normal (59/66 [89%]) and glaucomatous (26/43 [60%]) eyes. This difference between the groups was statistically significant (\( P < .001 \)).

Black subjects with glaucoma in our study were significantly more myopic and had eyes with greater axial length compared with black subjects with normal eyes (\( P = .03 \) and \( P = .001 \) for refractive error and axial length, respectively) (Table 3). This difference was not seen in white subjects (\( P = .64 \) and \( P = .70 \) for refractive error and axial length, respectively) (Table 3).

The mean optic disc area measured by confocal scanning laser ophthalmoscopy was significantly larger in subjects with glaucoma (\( P < .001 \)). The mean optic disc area was 1.82±0.40 mm\(^2\) (range, 0.95-2.91 mm\(^2\)) in subjects with normal eyes and 2.27±0.60 mm\(^2\) (range, 1.49 to 3.82 mm\(^2\)) in those with glaucoma (Table 1).

Multiple logistic regression analysis was performed to examine the relationship between the diagnosis of glaucoma and the ISNT rule while adjusting for potential confounders. We found significant associations of glaucoma diagnosis with violation of the ISNT rule (OR, 6.04; 95% CI, 1.74-20.95; \( P = .005 \)), larger disc area (OR, 10.75; 95% CI, 2.33-49.67; \( P = .002 \)), and increasing axial length (OR, 2.55; 95% CI, 1.21-5.35; \( P = .01 \)) after adjusting for potential confounding due to age and race.

To achieve greater homogeneity of age between the subjects with normal eyes and those with glaucoma, we further analyzed the data, restricting the subject population to 69 individuals aged 43 to 66 years. This in-
cluded 39 subjects with normal eyes (17 black and 22 white individuals, median age [range], 52 [43-60] years) and 30 subjects with open-angle glaucoma (14 black and 16 white individuals, median age [range], 55 [43-60] years). Median ages did not differ significantly between the 2 groups (P=.14). The ISNT rule was intact in 32 (82%) of 39 normal eyes and 8 (27%) of 30 glaucomatous eyes (P<.001). In multiple logistic regression modeling adjusted for age and race, we found significantly elevated ORs for glaucoma associated with violation of the ISNT rule (OR, 7.8; 95% CI, 2.1-28.6) and larger disc size (OR per unit increase, 15.0; 95% CI, 2.5-89.7).

**COMMENT**

The ISNT rule was originally described by Jonas et al, who used rim area measurements of normal eyes, calculated from projected optic disc photographs. Later, retinal nerve fiber layer thickness was measured at the optic disc borders histomorphometrically and was found to follow the same rule. This morphometric characteristic is not followed in patients with glaucoma. The present study confirms the work of Jonas et al and the utility of the ISNT rule in clinical practice in black and white subjects.

Several studies have demonstrated a higher prevalence of open-angle glaucoma with higher rates of blindness in persons of black African ancestry compared with European-derived populations. Racial differences in ocular anatomy include larger disc and cup areas in black subjects with similar neuroretinal rim area, yielding an overall larger cup-disc ratio. Girkin et al reported that most differences in optic disc topography between black and white subjects with normal eyes became nonsignificant after adjustment for reference plane height and for optic disc area as measured by confocal scanning laser ophthalmoscopy. Girkin and colleagues demonstrated that racial differences in optic disc structure had little impact on the relative ability of subjective and objective methods to discriminate between glaucomatous and normal optic discs. One could therefore expect the neural rim to follow the ISNT rule regardless of race. In the present case study, race and age were treated as potential confounders, and multivariable logistic regression techniques were used to control for the potential effects of imbalances in these variables between groups.

The nasal sector of the optic nerve is more difficult to evaluate owing to obscuration of the rim by the exit of large retinal vessels. We tested the hypothesis that the inferior-superior rim relationship alone would simplify the detection of a suspicious optic disc. However, this turned out not to be the case. In future studies, evaluation of the temporal disc region compared with the other 3 rim sectors may increase specificity in detecting glaucomatous optic discs because the vertical rim is frequently affected before the horizontal rim.

Several studies have found equal optic disc sizes in both normal and glaucomatous eyes, while others have demonstrated larger disc areas in glaucomatous eyes. Optic disc area in the present study was greater in the glaucomatous eyes than in the normal eyes for both races, as well as in the combined racial group. The ISNT rule remained a predictor of a glaucoma diagnosis after controlling for multiple factors including disc area.

Despite the fact that there is axonal loss with age, it remains controversial whether age affects the neuroretinal rim area. It is unlikely that the greater age of the patients with glaucoma significantly affected the relative rim thickness at the different locations. In the multivariate analysis on the age-matched groups (n=69), the ISNT rule kept its diagnostic ability in detecting glaucoma.

The present study has several limitations. The sample size is relatively small, and in a larger cohort violation of the ISNT rule could be correlated with visual field status and disease severity. Although glaucoma was defined strictly based on functional criteria, in the evaluation of normal eyes we could not avoid the inclusion of optic nerve information typically obtained during a routine eye examination. One could argue that this bias would favor inclusion of normal eyes that adhere to the ISNT rule, yet the fact that more than 20% of our normal eyes violated the ISNT rule suggests that this potential bias was minimal. The reality of glaucoma structure and function research is that the visual field, intraocular pressure, and optic disc are always examined in every patient entering any imaging or visual function study. Our definition of normal eyes used previously published standard criteria that include an optic disc examination in addition to functional testing. We intentionally excluded glaucoma suspect eyes and eyes with preperimetric glaucoma to facilitate the comparison between normal and glaucomatous eyes. Future studies should address the use of the ISNT rule for these individuals. Finally, our results can be applied only to patients with a similar range of refractive error.

The present study suggests that the ISNT rule is a clinically useful method to aid in glaucoma diagnosis and risk assessment in clinical practice. Although differences in optic nerve anatomy exist between black and white subjects, our results suggest that the ISNT rule can be applied equally to white and black individuals.

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**REFERENCES**


