Violation of the ISNT Rule in Nonglaucomatous Pediatric Optic Disc Cupping

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PURPOSE. To determine whether nonglaucomatous optic disc cupping in children violates the ISNT rule (which states that for normal optic discs the neuroretinal rim width is greatest in the order inferior ≥ superior ≥ nasal ≥ temporal).

METHODS. Digital ocular fundus photographs from a random cohort of children with large optic disc cups of nonglaucomatous origin were analyzed in masked fashion by using computer graphic software. The diameter and perimeter of each optic disc and optic cup and the width of the neuroretinal rim were drawn and measured. Measurements were compared to a random cohort of normal pediatric optic discs.

RESULTS. The ISNT rule was intact in 9 (16%) of 55 eyes of nonpremature children with nonglaucomatous cupping, in 6 (21%) of 28 eyes of children with a history of prematurity and nonglaucomatous cupping, and in 35 (73%) of 48 eyes with normal discs.

CONCLUSIONS. Violation of the ISNT rule occurs with greater frequency in the pediatric population with large optic disc cups of nonglaucomatous origin, compared with the pediatric population with normal optic discs. In discs with small cups, neuroretinal rim width conforms to the overall oval shape of the disc, which is usually greatest in vertical dimension, whereas discs with large cups possess greater variability of relative neuroretinal rim width around the disc; greater relative vertical cup/disc ratio versus horizontal cup/disc ratio, and lower predictability of the ISNT rule. (Invest Ophthal Vis Sci. 2010;51:890–895) DOI:10.1167/iovs.09-3837

In adults, large optic disc cups are often a sign of glaucoma. Children, however, show a lower prevalence of glaucoma than adults, 1 but may present with optic disc cupping of nonglaucomatous origin. Large disc cups in children may be diagnosed as physiologic large cups or may be associated with prematurity and periventricular leukomalacia. 2–6 Children with large optic disc cups often present a clinical dilemma on initial examination, as tests to rule out glaucoma, including intraocular pressure measurement and formal visual field analysis, can be difficult within the pediatric age group. 7

The ISNT rule has been used to help diagnose the presence of glaucoma in adults, based on the morphometric characteristics of the optic disc. 8,9 The normal optic disc usually demonstrates a configuration in which the inferior neuroretinal rim is the widest portion of the rim, followed by the superior rim, and then the nasal rim, with the temporal rim being the narrowest portion. 10 The rule states that, for normal optic discs, the neuroretinal rim width is greatest in the order inferior ≥ superior ≥ nasal ≥ temporal. Glaucoma frequently damages superior and inferior optic nerve fibers before temporal and nasal fibers, leading to thinning of the superior and inferior rims and violation of the rule. 11 Thus, violation of the rule has been shown to have predictive value in diagnosing glaucoma in adults. 8

In a child with a large optic disc cup, does violation of the ISNT rule imply that the child has glaucoma? We undertook this study to determine whether the rule would be violated in children with large optic disc cups of nonglaucomatous origin.

METHODS

Forty-nine children with large optic disc cups were examined over a 4-year period who met the selection criterion of nonglaucomatous optic disc cupping, based on previous clinical diagnosis during routine care in a comprehensive pediatric ophthalmology practice. We purposely did not stipulate measurement parameters as inclusion criteria; rather, we sought to define a typical clinical population and analyze measurement parameters as the outcome of the study. Nonglaucomatous cupping was defined as optic disc cupping in the absence of glaucoma, optic atrophy, or other optic disc anomaly, but allowed for physiologic optic disc cupping and cupping in a setting of prematurity. Patients were excluded if they had ocular hypertension; glaucoma; history of congenital anterior segment anomalies; history of trauma; prior eye surgery; history of intraocular inflammation; optic atrophy, or history of intracranial tumor, increased intracranial pressure, or optic nerve tumor; presence of optic nerve pits, optic nerve colobomas, optic disc hypoplasia, or other optic disc anomalies; cicatricial retinopathy of prematurity or peripheral retinal ablation treatment; myopia greater than 5 D; or age greater than 17 years. Optic atrophy was defined as pallor affecting the optic rim and was excluded from the cohort; all discs had neuroretinal rims of good color. In children with significant developmental delay, neuroimaging data excluded compressive optic nerve or optic chiasm lesions. In many cases, information from multiple prior visits was available to corroborate early-onset, nonproliferative optic disc cupping. Complete dilated eye examinations were performed on each child. The intraocular pressure by hand-held tonometry (Tono-Pen XL; Medtronic, Jacksonville, FL) or Goldmann applation tonometry measured 21 mm Hg or less in all children, with the exception of three children whose developmental delay and level of cooperation did not allow measurement. Two of the three children had been seen for prematurity in infancy with large cups noted, and all three had no progression of cupping over follow-up and thus were believed to have nonglaucomatous cupping.

Where age and cooperation allowed, digital fundus photography of the optic discs (Topcon retinal camera TRC; Topcon Medical Systems, Inc., Paramus, NJ) was performed. Forty-two of 49 children with large cups allowed digital fundus photography. Children ranged in age from

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The ISNT Rule in Nonglaucomatous Cupping 891

1 year, 4 months to 16 years, 5 months. Since in many cases fellow eyes did not correlate with each other in obeying the ISNT rule (Table 1, the Results section), both eyes of each patient were included in the data analysis if the eyes otherwise met the inclusion criteria. Eighty-three images of discs with large cups were analyzed (cup/disc ratio, >0.50). The images were compared with 48 images of normal optic discs in children with small to medium cups (cup/disc ratio, <0.45). The cohort of normal discs was derived from photographs taken for focal retinal defects in healthy patients or patients who had disease in the opposite eye not affecting the optic nerve. Eyes with diffuse macular defects were excluded, but photographs from normal fellow eyes were included. Eyes with small localized retinal pigment epithelial defects or congenital hypertrophy of the retinal pigment epithelium were included. The optic disc image analysis included no identifiable patient information. Parental consent was given for examination, the study was approved by the local institutional review board (IRB), and the research adhered to the tenets of the Declaration of Helsinki.¹²

Optic disc images were analyzed with the measuring software component of a digital imaging system (IMAGEnet; Topcon Medical Systems, Inc., Paramus, NJ). The measurements are calibrated for the particular camera and working distance used, to give reproducible anatomic measurements. All digital photographs and measurements were taken from the same camera. Measurements were obtained by projecting an enlarged digital image of the optic disc on the computer monitor and drawing with a cursor over the image the linear distance or circular area to be measured. The drawing was completed with the operator masked as to the remainder of the data and masked to the measurement results. The drawings were performed in the following order: the vertical disc diameter from 12 to 6 o'clock; the horizontal disc diameter from 3 to 9 o'clock; the temporal disc margin to fovea distance, done by drawing a line from the temporal end of the horizontal disc diameter line to the center of the fovea; the disc area, done by drawing a continuous curve tracing the optic disc margin fully around from 12 o'clock to 12 o'clock; the optic cup area, done by drawing a continuous curve tracing the optic disc margin fully around from 12 o'clock to 12 o'clock; the horizontal cup area, done by drawing a line from the temporal end of the horizontal cup diameter line to the center of the fovea; the temporal disc margin on the cup, done by drawing a continuous curve tracing the optic disc margin fully around from 12 o'clock to 12 o'clock; the optic cup area, done by drawing a continuous curve tracing the internal margin of the optic disc rim fully around from 12 o'clock to 12 o'clock; the vertical cup diameter from 12 to 6 o'clock, starting at 12 o'clock on the circular cup curve drawn already and ending at 6 o'clock on the circular cup curve; the horizontal cup diameter from 3 to 9 o'clock on the circular cup curve; the neuroretinal rim width, measuring from the drawn interior (cup) curve to the drawn exterior (disc margin) curve at the 12, 3, 6 and 9 o'clock disc diameter lines. The placement of the neuroretinal rim width lines was thus already determined based on the closed disc and cup curves and the disc diameter lines. When the location of the optic disc margin was selected, the position of the outer limit of the disc neural tissue was used, not including any pigmentary changes adjacent to the disc. The location of the outer border of the optic cup (inner margin of the optic rim) was determined by the contour of the cup, not specifically by the pale color of the cup, using the stereoscopic disc viewer and blood vessel contour when needed. The edge of the cup was determined by the location of the smallest radius of curvature of the disc contour, at the transition zone from the cup to the nearly planar rim, which was seen as the position of maximum change in the angle of the blood vessels traversing to and over the rim, a strategy that was especially useful in cases of gradually sloping cups. Blood vessels adjacent to the internal border of the neuroretinal rim were not included as part of the rim. Assessment of the precise location of the rim was meant to substantiate the clinical decision-making on which the ISNT rule is generally based, using the gold standard of planimetric photography. Reproducibility of measurements was validated by repeatedly measuring the superior rim width from disc margin curve to cup curve on the digital projection of a sample eye 30 times and finding a mean of 0.403 ± 0.005 mm and an SE of measurement (SD) of 0.087%. Once the drawings for a disc had been completed, the measurements were obtained (IMAGEnet software; Topcon Medical Systems, Inc.) and recorded. The vertical cup/disc ratio was calculated as the vertical optic cup diameter divided by the vertical optic disc diameter; the horizontal cup/disc ratio was calculated as the horizontal optic cup diameter divided by the horizontal optic disc diameter; the rim/disc ratio was calculated as the rim width at a given meridian (inferior, superior, nasal, or temporal) divided by the average of the vertical and horizontal disc diameters.

The Topcon fundus camera is not telecentric, and the measurements among different eyes are subject to magnification error. Adjustments for magnification error using parameters of ametropia, keratometry, and axial length were beyond the scope of this study in children, because of the constraints of age and cooperation, especially for axial length measurements. We did exclude myopic refractive errors greater than 5.00 D. Magnification errors were felt to be insignificant to the primary outcome measures of our study, in that magnification would not affect analysis of optic rim and disc shape or application of the ISNT rule. Absolute size measurements have been shown to depend on instrumentation used, and thus are interpreted based on published data for our camera system.¹⁵

We analyzed data for both fellow eyes when they were available and met inclusion criteria, to determine overall adherence and intereye variation with respect to the ISNT rule. We then randomly assigned only one fellow eye of each pair for analysis of optic disc parameters and statistical comparison of groups to assure independent data sets. Statistical comparison of means to determine level of significance was performed with unpaired Student’s t-tests. The percentage of each group obeying the rule was compared for statistical significance by χ² test.

**RESULTS**

The cohort with nonglaucomatous cupping consisted of 55 eyes in children with no history of prematurity, and 28 eyes in children with a history of premature birth at 32 weeks’ gestational age or less (but without other ocular disease or anomalies). The odds ratio of premature birth within the cohort was 1 to 1.96. Within both groups taken together, children ranged in age from 1 year, 4 months to 16 years, 5 months (mean, 9.2 years). Twenty-one eyes were myopic (3 eyes between −4 and −5 D, 4 eyes between −3 and −3.87 D, and the remaining 14 at −2 D or less spherical equivalent). Sixty eyes were plano or hyperopic to a maximum of +3.125 D spherical equivalent.

The cohort with normal discs consisted of 48 eyes in 31 patients, none of whom was premature. This cohort was older than the nonglaucomatous cupping cohort, with ages ranging from 2 years, 7 months to 17 years, 11 months (mean, 12.7 years). Twenty-three eyes were myopic (2 eyes between −4 and −5 D, 5 eyes between −3 and −3.87 D, 4 eyes between −2 and −2.87 D, and 12 eyes at −1.87 D or less spherical equivalent). Twenty-five eyes were hyperopic to a maximum of +2.25 D spherical equivalent. We expected that the nonglau-
comatous cupping population would have different demographies than the normal disc population, as applicable to clinical practice. A subset of the nonglaucomatous cupping population was more likely to present at a younger age, due to evaluation for history of prematurity.

The ISNT rule was intact in 9 (16%) of 55 eyes with nonglaucomatous cupping and no prematurity and in 2 (14%) of 14 eyes with nonglaucomatous cupping and a history of prematurity. Again, since these two groups behaved similarly with respect to violating the rule, for clarity in analysis they have been placed together and compared to the group of eyes with normal discs and small to medium cups. The rule was intact in 8 (18%) of 45 eyes with nonglaucomatous cupping and in 21 (68%) of 31 control eyes, to $P < 0.004$.

Descriptive ratios for optic disc parameters are listed in Table 3. Ratios of one optic disc component to another component within the same disc are not affected by magnification errors and allow for conclusions to be drawn. We do not report absolute measurements in Table 3, because of the inability to adjust for magnification errors, but will detail them in the text to better illustrate how the data were configured. Eyes with nonglaucomatous cupping had clinically larger discs than eyes without large cups (mean disc area $3.352 \pm 0.176$ mm² versus mean disc area $2.370 \pm 0.355$ mm², $P < 0.0001$). Despite the larger optic disc size measurement in eyes with nonglaucomatous cupping, the optic disc-to-fovea distance (calculated as the temporal disc margin-to-fovea distance plus one half of the horizontal disc diameter) was similar in eyes with nonglaucomatous cupping compared with eyes without large cups (mean, $4.819 \pm 0.309$ mm, versus mean, $4.630 \pm 0.507$ mm; $P < 0.1$ NS). Mean inferior, superior, nasal, and temporal rim widths in millimeters were, respectively, $0.399 \pm 0.073$, $0.372 \pm 0.075$, $0.359 \pm 0.081$, and $0.198 \pm 0.079$ in eyes with nonglaucomatous cupping and $0.702 \pm 0.090$, $0.600 \pm 0.104$, $0.529 \pm 0.083$, and $0.406 \pm 0.090$ in eyes with normal discs (all $P < 0.0001$).

### Table 2. Distribution of Eyes by Rim Meridian Measurement Position, Ordered Greatest to Least

<table>
<thead>
<tr>
<th>Measured Rim</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eyes with Nonglaucomatous Cupping (n = 83)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>35 (42)</td>
<td>28 (34)</td>
<td>20 (24)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Superior</td>
<td>27 (35)</td>
<td>26 (31)</td>
<td>24 (29)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Nasal</td>
<td>21 (25)</td>
<td>27 (33)</td>
<td>29 (35)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Temporal</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>10 (12)</td>
<td>71 (86)</td>
</tr>
<tr>
<td><strong>Eyes with Normal Discs (n = 48)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>41 (85)</td>
<td>7 (15)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Superior</td>
<td>6 (13)</td>
<td>36 (75)</td>
<td>6 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nasal</td>
<td>1 (2)</td>
<td>5 (10)</td>
<td>40 (85)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Temporal</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>46 (96)</td>
</tr>
</tbody>
</table>

**Table 3. Comparison of Optic Disc Parameters in Nonglaucomatous Discs with and without Large Cups**

<table>
<thead>
<tr>
<th>Eyes with Nonglaucomatous Cupping (n = 45)</th>
<th>Mean ± SD</th>
<th>95% CI</th>
<th>Eyes with Normal Discs (n = 31)</th>
<th>Mean ± SD</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cup/disc vertical</td>
<td>$0.627 \pm 0.063$</td>
<td>0.609–0.646</td>
<td></td>
<td>$0.285 \pm 0.087$</td>
<td>0.253–0.317</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cup/disc horizontal</td>
<td>$0.704 \pm 0.021$</td>
<td>0.683–0.726</td>
<td></td>
<td>$0.407 \pm 0.095$</td>
<td>0.372–0.442</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inferior rim/disc*</td>
<td>$0.195 \pm 0.038$</td>
<td>0.184–0.206</td>
<td></td>
<td>$0.403 \pm 0.055$</td>
<td>0.384–0.423</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Superior rim/disc*</td>
<td>$0.181 \pm 0.035$</td>
<td>0.171–0.191</td>
<td></td>
<td>$0.345 \pm 0.063$</td>
<td>0.323–0.367</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nasal rim/disc*</td>
<td>$0.176 \pm 0.044$</td>
<td>0.163–0.189</td>
<td></td>
<td>$0.305 \pm 0.044$</td>
<td>0.288–0.318</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Temporal rim/disc*</td>
<td>$0.097 \pm 0.041$</td>
<td>0.085–0.109</td>
<td></td>
<td>$0.233 \pm 0.053$</td>
<td>0.215–0.252</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vertical orientation of disc†</td>
<td>$1.089 \pm 0.084$</td>
<td>1.063–1.114</td>
<td></td>
<td>$1.126 \pm 0.106$</td>
<td>1.087–1.164</td>
<td>&lt;0.1 (NS)</td>
</tr>
<tr>
<td>Horizontal orientation of cup‡</td>
<td>$1.126 \pm 0.094$</td>
<td>1.098–1.154</td>
<td></td>
<td>$1.474 \pm 0.242$</td>
<td>1.385–1.562</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CI, confidence interval.
* Rim width/(0.5 × vertical disc diameter + 0.5 × horizontal disc diameter).
† (Vertical disc diameter)/(horizontal disc diameter).
‡ (Horizontal cup/disc ratio)/(vertical cup/disc ratio).
As desired by the design of the study, eyes with nonglaucomatous cupping (Table 3) had larger cup/disc ratios (mean vertical cup/disc ratio, 0.627 ± 0.063) than did eyes with normal discs (mean vertical cup/disc ratio, 0.285 ± 0.087). Analysis of the results shows that the mean rim/disc ratio in each of the four primary meridians obeyed the ISNT rule for both groups, even though individual discs did not obey in high proportion. A preponderance of vertical optic disc orientation, meaning that the vertical disc diameter was greater than the horizontal disc diameter, was found both in eyes with nonglaucomatous cupping (40/45 discs, or 89%) and in eyes with normal discs (29/31 discs, or 94%). The ratio of vertical disc diameter to horizontal disc diameter calculated for each disc and averaged showed a mean in each group of greater than 1, measuring 1.089 ± 0.084 for the cupping group and 1.126 ± 0.106 for the normal disc group, to P < 0.1, not significantly different in magnitude. Although the optic discs were on average vertically oriented, the cup/disc ratios were on average horizontally oriented, meaning that the horizontal cup/disc ratio was greater than the vertical cup/disc ratio, more so in the normal disc group than in the cupping group. The horizontal cup/disc ratio was less than the vertical cup/disc ratio in none of the 31 eyes with normal cups and in only 3 of 45 eyes with nonglaucomatous cupping. The horizontal cup/disc ratio divided by vertical cup/disc for each disc showed a significantly smaller mean in the cupping group (1.126 ± 0.094) than in the normal disc group (1.474 ± 0.242), to P < 0.0001.

**DISCUSSION**

The ISNT rule is widely used for the clinical evaluation of optic discs to help diagnose glaucoma. Since optic nerve damage typically occurs in glaucoma before visual field defects are evident, morphometric examination of the optic disc remains a critical component of patient assessment. The nasal rim is often last to be affected by glaucomatous cupping, leading to the violation of the rule in glaucoma. The rule has received frequent attention among ophthalmic educators teaching glaucoma diagnosis. The ISNT rule has been shown to be violated preferentially in adult patients with glaucoma compared with patients without glaucoma. Harizman et al. using stereo photographs found the rule intact in 79% of 52 normal adult eyes but in only 28% of 43 glaucomatous eyes. They concluded that the rule is useful in differentiating normal from glaucomatous eyes. Sihota et al., using scanning laser tomography, found the rule intact in 71% of 136 normal eyes and in 68% of 63 eyes with early nonglaucomatous cupping. The horizontal cup/disc ratio divided by vertical cup/disc for each disc showed a significantly smaller mean in the cupping group (1.126 ± 0.094) than in the normal disc group (1.474 ± 0.242), to P < 0.0001.

The ISNT rule has been shown to be violated preferentially in adult patients with glaucoma compared with patients without glaucoma. Harizman et al. using stereo photographs found the rule intact in 79% of 52 normal adult eyes but in only 28% of 43 glaucomatous eyes. They concluded that the rule is useful in differentiating normal from glaucomatous eyes. Sihota et al., using scanning laser tomography, found the rule intact in 71% of 136 normal eyes and in 68% of 63 eyes with early nonglaucomatous cupping. In the latter study, the higher adherence to the rule in the glaucoma cohort may be due to less advanced glaucoma or the finding that optic disc tomography may overestimate rim width compared with planimetric photography or direct visualization. Nonetheless, both these studies and a study by Wang et al. confirm the general adherence to the rule in the normal population, leading to the conclusion that violation of the rule raises the suspicion of glaucoma.

The results of our study indicate that the ISNT rule is also violated in nonglaucomatous cupping in children. We found a preponderant adherence (73%) to the rule in discs without large cups, similar to the studies just described, but a low adherence (18%) to the rule in children with nonglaucomatous large optic disc cups. Our population was limited to children, who form a good substrate in which to detect and study nonglaucomatous cupping, as glaucoma itself is much less common in children than in adults. Our population of children with nonglaucomatous cupping included a proportion of patients with a previous history of premature birth at <32 weeks’ gestation. Prematurity may influence disc morphology, causing the ISNT rule to be violated.

Previous studies examining the adherence to the ISNT rule have analyzed only one eye of each patient to generate a statistically independent sample. By restricting the data analysis to one eye, the studies would be unable to answer the question of how frequently intereye asymmetry occurs related to adherence to the rule. Asymmetry in optic disc appearance, especially cup/disc ratio, is one criterion that helps to alert to the possibility of glaucoma, but may not be as important in applying the rule if violations of the rule occur at a certain random frequency in normal eyes. In the previous studies, normal eyes had a 52% to 79% adherence to the rule, which means that 21% to 48% violated the rule. These were healthy eyes that presumably violated the rule due to normal variation, not disease. If violation of the rule in healthy eyes occurs randomly among different patients, then it is possible that random variation also occurs between eyes of the same patient, leading to one eye obeying the rule and one eye violating the rule. Assuming, for example, independence of each fellow eye regarding adherence to the rule and a theoretical value of 70% adherence to the rule for each fellow eye, it follows that in only 49% (0.7 × 0.7 × 100%) of patients would both eyes be expected to adhere. We found that the intereye difference was frequent (65%), even in normal eyes (Table 1).

An important characteristic of the large cup cohort in our study was their clinically large disc size, compared with normative data and with the normal discs in our study. Large disc size is known to be associated with large cup size. Moreover, as a geometric principle, as disc diameter increases, a constant neuroretinal rim area may be achieved with a narrower rim (similar to stretching dough into a bigger circle, such that the amount of dough remains the same, but the donut becomes thinner and longer). Thus, large discs may have narrow rims without loss of axons. We found significantly narrower rims as a proportion of disc size in our large cup group. We speculate that the fact that the rims are narrower allows their configuration to be less constrained by the shape of the optic disc itself and may result in more variability in rim width, leading to less adherence to the ISNT rule. In discs with small cups, to the contrary, the neuroretinal rim occupies more of the disc and must conform to a greater degree to the normally greater vertical dimension (vertical disc diameter/horizontal disc diameter) of the disc, such that the inferior and superior rims are wider than the nasal and temporal rims.

Nonglaucomatous optic discs with large cups may not be subject only to increased variability in rim width, but our results suggest that there may also be an overlying predictable alteration in the relative circumferential shape of the optic cup versus the optic disc in these discs. We found that the horizontal cup/disc ratio divided by vertical cup/disc for each disc was significantly smaller and closer to 1 for the cupping group and significantly greater than 1 for the normal disc group. As the cup shape more closely approximates the disc shape (a value of 1 would indicate full proportionality), then the rim widths at the four cardinal meridians may also be more similar to each other, and any normal variation in rim width more likely to cause violation of the ISNT rule. Jonas et al. calculated and commented on the quotient of horizontal to vertical cup/disc ratio in his planimetric analysis of normal adult eyes. They found a ratio of 1.19 ± 0.16 in eyes with sloping cups; and a ratio of 1.14 ± 0.09 in eyes with punched out cups, which were the eyes with the largest discs and largest cups.

Our eyes with large cups, despite their difference in cup shape compared with the normal discs, nonetheless also showed a ratio of greater than 1 in all but 3 (6.7%) of 45 eyes, obeying the principles in Jonas et al. Mardin et al. also confirm the finding that vertical cup diameter enlarges more than horizontal cup.
diameter with increasing disc size in a series of healthy adult disc regions examined by planimetry, laser scanning tomography, or nerve fiber polarimetry.

A limitation of our study as regards absolute size measurement comparison is the lack of correction for magnification errors. Our primary study goal was to look at the clinical application of optic disc shape in the pediatric population and derive some guidelines for interpretation of disc shape, as one often cannot obtain full intraocular pressure and visual field data from children because of their age and lack of cooperation. Magnification errors would not affect the analysis of optic disc shape. For interest, we have secondarily included in our study analysis of absolute optic disc size measurements, realizing that these data would be affected by magnification errors. Different methods to correct for ocular magnification may themselves have errors and may be especially prone to errors in eyes with lenses of high refractive power. Magnification errors were mitigated within our population by the modest refractive error in our cohort. We also note that the distance from optic disc to fovea is not clinically different in the cupping group compared with the normal disc group, a finding that would be less likely if a significant systematic magnification or ocular size bias existed between the two groups. Jonas et al. used Littmann's method to estimate corrected optic disc area from planimetric analysis of photographs of normal adult optic discs. They found an optic disc area of $2.05 \pm 0.59 \text{ mm}^2$ for discs with no cupping and $3.29 \pm 0.75 \text{ mm}^2$ for discs with punched-out cupping. These optic disc areas are relatively similar to those in our study of $2.370 \pm 0.355 \text{ mm}^2$ for normal optic discs without large cups and $3.552 \pm 0.176 \text{ mm}^2$ for those with nonglaucomatous cupping.

Another of the constraints of this study is the age of the sample. The study is most applicable to the cross section of patients seen in a pediatric eye care practice. By design, we chose to include only children (all were younger than 17 years in the nonglaucomatous cupping group and younger than 18 years in the small optic cup group). The youngest child in our study was age 1 year, 4 months. Most growth in optic nerve size occurs before 1 year of age, and so the findings should not be extrapolated to young infants. The findings of the present study might be applicable to adults. It would be useful to determine whether, in general, the ISNT rule in nonglaucomatous adults is more often violated as cups become larger.

A practical limitation of the data derives from the inability to obtain full follow-up information over decades. The static, nonglaucomatous cupping in children with large optic discs may increase the risk of development of true glaucoma later in life, which would be diagnosed at that time based on progressive deterioration in optic disc morphology or development of characteristic visual field defects. The question of whether large optic discs in general are more susceptible to glaucomatous damage is unsettled, but may relate to the pressure differential across the larger lamina cribrosa in large optic discs resulting in an “increased deformation and displacement of the central tissue in large discs.” Our data do not allow the question of ultimate progression to glaucoma to be answered.

Another limitation of the study derives from the exclusion of patients with true glaucoma from the data analysis. In our comprehensive pediatric ophthalmology practice, glaucomatous optic disc cupping was much rarer than nonglaucomatous cupping, occurring primarily in infantile glaucoma cases. We would expect children with glaucoma to show optic nerve damage similar to adult glaucoma patients and thus also violate the ISNT rule, although we did not evaluate this population in our study.

The ISNT rule has been shown to hold not only within individual optic discs, but also in aggregate when mean values of rim width are developed for normal populations. A contradictory study places mean nasal rim width as greater than mean superior rim width, but still less than inferior rim width. The authors of the latter study do not indicate whether they specifically excluded the nasal vessel trunk from the nasal rim width measurement. If they did not, then the nasal rim measurement may be greater than that found when the nasal vessel trunk was specifically excluded. It is interesting that in our cohort with large cups, the mean rim/disc ratios taken in aggregate still obeyed the ISNT rule, even though a minority of individual discs themselves obeyed the rule. The reasons for this apparent contradiction may be seen in Table 2. For example, in the cupping group, the inferior rim width was the largest more often than the rim width in any other quadrant, and so its mean was therefore also the largest; however, the inferior rim width was only the largest in 48% of eyes, meaning that it violated the rule in 52% of eyes. In the normal disc group, by comparison, the inferior rim width took the largest position in 85% of eyes, violating the rule in only 15%. Thus, although both groups demonstrated a similar aggregate position (greatest for the inferior rim, for example), the variation in position was much greater in the cupping group. This observation supports the idea that narrower neuroretinal rims in the large cup cohort are associated with greater susceptibility to variation in applying the rule.

In summary, we conclude that violation of the ISNT rule occurs in a majority of eyes in the specific pediatric population with large optic disc cups of nonglaucomatous origin. A significant increase in relative vertical cup/disc ratio versus horizontal cup/disc ratio occurs in this population, which may contribute to the reduced applicability of the rule. Despite not obeying the rule, most such eyes maintain the relation of horizontal cup/disc ratio greater than vertical cup/disc ratio and inferior rim width always greater than temporal rim width.

References


