Frequency doubling technology perimetry in non-arteritic ischaemic optic neuropathy with altitudinal defects

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Aim: To determine if frequency doubling technology perimetry (FDT) is more sensitive to optic nerve injury in non-arteritic ischaemic optic neuropathy (NAION) than standard automated perimetry (SAP).

Methods: Charts from 18 patients (20 eyes) with NAION with altitudinal defects who underwent a complete neuro-ophthalmic examination, SAP, and FDT were reviewed. The extent of damage as determined by SAP, FDT, and clinical estimation of the regional extent of optic disc pallor was compared. 10 subjects (20 eyes) with normal ocular examinations and full appearing optic nerve heads were included as a control group.

Results: FDT demonstrated more extensive visual field defects in the relatively intact hemifield on SAP (proportion of locations at 5% or worse in the total deviation plot was 8.7% (SD 6.2%) for SAP and 38.3% (39.5%) for FDT p<0.0027). 16 of 20 eyes with altitudinal NAION demonstrated diffuse optic disc pallor. 11 of these eyes with diffuse pallor demonstrated significant defects in both hemifields using FDT, while only two eyes demonstrated diffuse damage using SAP. Correspondence between the extent of optic disc pallor and the extent of visual scotoma was higher for FDT (85%) than with SAP (40%).

Conclusion: FDT appears more sensitive to axonal injury reflected by the extent of optic disc pallor in altitudinal NAION than SAP and in some patients reveals visual dysfunction in the hemifield that appeared relatively uninvoluted when evaluated using SAP.

The extent of damage to the optic nerve caused by non-arteritic ischaemic optic neuropathy (NAION) has been estimated previously using clinical ophthalmoscopy and standard achromatic perimetry and standard achromatic perimetry (SAP). However, a substantial number of retinal ganglion cells may be damaged before visual field defects are observed with conventional techniques. Frequency doubling technology (FDT) perimetry was developed to isolate the magnocellular ganglion pathway, which was thought to be preferentially damaged in glaucoma. In this capacity, FDT has demonstrated high sensitivity and specificity in the detection of visual field defects on standard perimetry in glaucoma and for compressive lesions affecting the anterior visual pathways. In addition, FDT has demonstrated more extensive visual field defects than SAP in some patients with early open angle glaucoma, in the intact hemifield of patients with normal tension glaucoma with altitudinal defects, and in resolved optic neuritis indicating that this technique may be more sensitive in the detection of ganglion cell dysfunction in these disorders.

FDT may also be more sensitive to visual dysfunction in NAION and provide a better indicator of the extent of damage when evaluating this condition. Conversely, ocular scatter associated with the larger FDT stimulus could possibly mask areas of visual dysfunction in patients with NAION. Altitudinal hemifield defects in NAION have steep slopes corresponding to the horizontal raphe. Therefore, because of ocular scatter and small fixation shifts, the larger FDT stimulus which is presented close to the horizontal meridian may fail to detect damaged locations along the horizontal raphe. Indeed, Wall et al found a similar effect when evaluating FDT in the detection of vertical hemianopias caused by chiasmal or retrochiasmal disease.

This study will compare the extent of damage detected by FDT, SAP, and the extent of optic disc pallor in patients with NAION with altitudinal defects in order to determine if FDT can detect visual dysfunction outside of the abnormal hemifield defined by conventional perimetry as a result of more diffuse ganglion cell dysfunction occurring below the threshold detectable with standard automated perimetry.

METHODS

Eighteen patients (20 eyes) who were seen in the UAB ophthalmology clinics from 1999 to 2001 diagnosed with either unilateral or bilateral NAION with altitudinal visual field loss were included in this study. The diagnosis of NAION was defined by a complete neuro-ophthalmological evaluation revealing typical signs and symptoms (for example, acute painless loss of visual acuity and/or visual field deficit, an ipsilateral relative afferent pupillary defect, colour defect, acute optic disc oedema with haemorrhages, and optic disc crowding in the unaffected eye). Only patients who demonstrated altitudinal defects on standard automated perimetry were included.

Altitudinal field loss on standard perimetry was defined as a dense scotoma that respected the horizontal meridian, in which the abnormal hemifield had a minimum of 18 of 24 locations that fell outside of the 95% confidence interval on the total deviation plot, while the unininvolved hemifield had no more than six of 24 locations that fell outside the 95% confidence interval on the total deviation plot.

Patients were selected by retrospective chart review and underwent a standard neuro-ophthalmic examination, in addition to testing with standard automated white on white perimetry (SAP) using the 24-2 Swedish Interactive Thresholding Algorithm (SITA) and frequency doubling technology (FDT) perimetry within 3 months or less. All FDT and 24-2 SITA fields used in this study were performed after resolution of optic disc oedema. In order to ensure reliable visual field examinations, patients with a visual
acuity of worse than 20/60, or those who performed standard perimetry or FDT unreliably (defined as greater than 33% fixation losses, false positives, or false negatives) were also excluded. In addition, patients lacking a description of the optic disc which did not detail the extent of optic disc pallor were also excluded. The University of Alabama at Birmingham institutional review board approved the study.

SAP was performed using the Humphrey field analyser II with the SITA 24-2 thresholding program (Humphrey-Zeiss Instruments, San Leandro, CA, USA). FDT was performed using the visual field analyser with frequency doubled technology (Welch-Allyn, Skaneateles Falls, NY, USA) using the full threshold mode (N-30) with the standard manufacturer’s parameters.5

Table 1  Subject demographics

<table>
<thead>
<tr>
<th></th>
<th>NAION subjects</th>
<th>Normal controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>Number of eyes</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>59.6 (10.8)</td>
<td>58.8 (9.4)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/9</td>
<td>10/11</td>
</tr>
<tr>
<td>Hypertension*</td>
<td>45%</td>
<td>10%</td>
</tr>
<tr>
<td>Diabetes*</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>Mean time from AION (months) (range)</td>
<td>6.75 (3–14)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Testing order:
- FDT then SITA: 9/10
- SITA then FDT: 11/10

*p<0.05

To compare the extent of visual field defect in each hemifield detected by each technique, the percentage of test locations that were abnormal in each hemifield was calculated for each technique. Abnormal test locations were defined as any point that exceeded the 95% confidence interval on the total deviation plot using either task. Standard perimetry tests 52 locations, while the FDT tests only 19 locations. This method allows geographic comparison across each modality despite the differences in spatial resolution with the FDT.

To ensure that differences seen between abnormal test locations between FDT and SAP testing were not the result of differences in the normative databases for each instrument or of possible visual functional differences in eyes with small disc areas seen commonly in patients with NAION, we obtained FDT and SAP test results from 10 age matched subjects (20 eyes) with small appearing but normal optic discs (based on indirect ophthalmoscopy of a “discs at risk” appearance and disc size estimation with a direct ophthalmoscope), and normal standard SAP visual fields (PSD with 95th percentile and a normal glaucoma hemifield test) as a control group.

Table 2  Global visual field parameters (SD) for FDT and SAP in NAION and normal subjects

<table>
<thead>
<tr>
<th>Field test</th>
<th>NAION</th>
<th>Normal</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SITA MD</td>
<td>-11.01 (3.98)</td>
<td>-0.32 (0.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FDT MD</td>
<td>-9.04 (3.10)</td>
<td>0.51 (1.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SITA PSD</td>
<td>13.10 (3.98)</td>
<td>1.41 (0.14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FDT PSD</td>
<td>12.30 (4.11)</td>
<td>3.7 (0.97)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Intergroup comparisons performed using a nested ANOVA of Rosner.4

Figure 1  Extent of scotoma demonstrated with SAP (SITA) and FDT in the involved hemifield in each NAION subject with altitudinal loss. The percentage defect represents the percentage of abnormal test location found on the total deviation plot for each technique.

Statistical methods

Statistical analyses were conducted using the SAS System for Windows, Release 8.00 (SAS Institute, Cary, NC, USA). Two sets of analyses were conducted. The first set of analyses compared mean percentage hemifield defects between FDT and SAP among NAION and normal subjects using a paired t test modified as described by Rosner,5 and was used to account for potential intraocular dependence. Separate analyses were performed for the involved and uninvolved hemifields. For the NAION intragroup comparisons, this approach was not possible because both eyes were included in only two of 18 subjects. Therefore, one eye of each of these two subjects was excluded from the analysis. The means of the 18 remaining eyes were compared. A comparison was performed separately excluding the right eye and the left eye for these two subjects and the results were identical. The second set of analyses compared mean percentage hemifield defect between NAION and normal subjects as measured by SAP and FDT using analysis of variance (ANOVA) with modification as described by Rosner.5 Separate analyses were performed for the involved and uninvolved hemifields.
Finally, a Spearman’s correlation coefficient (rho) was calculated to determine the magnitude of association between global indices for SAP and FDT.

RESULTS
Characteristics of patients and control subjects are outlined in table 1. There were no significant differences in age, sex, or race between patients with NAION and controls. All normal controls and NAION subjects were white. Nine NAION patients (11 eyes) underwent FDT assessment before SAP, while seven patients (nine eyes) received standard testing first. Global indices for SAP and FDT are shown in table 2. FDT underestimated mean defect when compared with SAP in agreement with previous reports comparing the techniques in glaucoma.9

The percentage areas of abnormality for the involved and uninvolved hemifields are shown in figures 1 and 2, respectively, for each eye from the NAION group. The mean percentage defect using FDT and SAP for the involved and uninvolved hemifields of the NAION patients along with the mean percentage defect in the hemifields of the normal control subjects (mean of 40 hemifields from 20 eyes) are presented in table 3. For comparisons within the NAION group in this table only data after exclusion of the right eye from the two patients from which data were obtained from both eyes is presented. The results were similar regardless of which eye was included in the analysis from these two subjects (see below). In hemifield relatively undamaged on SAP, FDT showed a greater defect area using than with SAP (p value <0.0027 left eye or right eye excluded) (fig 3). Since the NAION group had a higher proportion of patients with diabetes, an additional analysis was performed comparing FDT results in the uninvolved hemifield adjusting for the effects of diabetes which produced similar results (adjusted p value <0.049 left eye excluded, p value <0.043 right eye excluded).

Both SAP and FDT demonstrated highly significant differences in mean percentage defect in the involved hemifield from the hemifield of the normal group. There was no significant difference in the uninvolved hemifield using SAP from the values obtained in the normal controls with small optic discs (p = 0.4652); however, there was a significant difference between the average percentage defect area using FDT and the average defect area found in normal controls (p <0.0003) in this hemifield, indicating that the more extensive defects found with FDT are not the result of differences in the normative databases between the two instruments or of functional differences that might theoretically be present in subjects with small optic discs with fewer axonal fibres.

To compare the agreement between the extent of visual field defects using FDT and SAP with the degree of pallor of the optic disc, each hemifield was classified as normal or abnormal based on if the percentage of abnormal test locations fell outside of the 95% confidence interval for the corresponding hemifield from the control group. FDT and SAP results were classified as regional if the defect was confined to one hemifield, or diffuse if both hemifields were significantly abnormal; 15 out of 20 eyes with NAION selected in this study had diffuse optic disc pallor. The remaining eyes had regional pallor only, four having relative superior hemidisc pallor and two with relative inferior hemidisc pallor. All of the six eyes with superior or inferior pallor.

Table 3
<table>
<thead>
<tr>
<th>Percentage defect</th>
<th>Involved hemifield</th>
<th>Uninvolved hemifield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SITA</td>
<td>FDT</td>
</tr>
<tr>
<td>NAION (n = 18 eyes)</td>
<td>90.1 (7.9)</td>
<td>92.9 (9.8)</td>
</tr>
<tr>
<td>Normal (n = 20 eyes)</td>
<td>4.8 (5.3)</td>
<td>4.95 (7.5)</td>
</tr>
<tr>
<td>p Value (normal v NAION)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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</table>
disc pallor had corresponding altitudinal defects on both SAP and FDT perimetry. In eyes with disc pallor described as diffuse two had significantly diffuse defects on SAP while 11 had diffuse defects on FDT. Overall, eight of 20 eyes (40%) had SAP fields that corresponded to the extent and location of disc pallor, while visual fields in 17 of 20 eyes (85%) corresponded using FDT. Case examples of the visual field defects on both FDT and SAP in study eyes 10 and 17 with regional and diffuse optic disc pallor are illustrated in figures 4 and 5, respectively.

Table 4 compares the mean percentage defect in each hemifield between the AION subjects with diffuse disc pallor and relatively localised disc pallor. While patients with regional disc pallor had a similar extent of damage using both SITA and FDT in the involved and uninvolved hemifields, patients with diffuse disc pallor had significantly greater defects with the FDT in the hemifield uninvolved using SAP.

DISCUSSION
Thirteen of 20 eyes in our study demonstrated more extensive defects using FDT than found with standard perimetry extending into the hemifield that was spared by standard perimetry. Furthermore, 11 of 14 eyes with diffuse pallor of the optic disc and altitudinal defects using SAP demonstrated damage in both hemifields using FDT, while all eyes with altitudinal defects on FDT had corresponding regional disc pallor, indicating that the more extensive FDT defects correspond to more extensive optic nerve atrophy.

Since we selected patients based on having altitudinal defect on standard perimetry, we cannot determine if subjects with diffuse damage on standard fields have more or less extensive defects using FDT. Unfortunately, no subjects with NAION with diffuse loss of the visual field could be included for comparison owing to poor visual acuity or unreliable visual fields. However, we have demonstrated that more extensive defects using FDT extend into the uninvolved hemifield as determined by SAP in some patients, similar to previous reports in glaucomatous optic neuropathy, and that these defects correlate to the extent of disc pallor.

We found no significant reduction in the extent of visual field defect seen with FDT in the evaluation of altitudinal field loss; thus, ocular scatter is unlikely to affect the

Figure 4  Case example from study eye No 10, a subject with greater pallor in the inferior region of the optic disc graded as inferior hemidisc pallor in the right eye (A) and corresponding superior altitudinal visual field defects on the total deviation plots for both SAP and FDT (B).

Figure 5  Case example from study eye No 17, a subject with diffuse disc pallor in the left eye (A). The visual field defect is altitudinal when tested using SAP on the total deviation plot; however, the visual field defect demonstrated using FDT is diffuse (B) and corresponds to the extent of optic disc pallor.
geographic extent of visual field defects determined by the larger FDT stimuli when presented adjacent to the horizontal meridian as has been previously suggested with visual field defects due to intracranial disease that respect the vertical meridian.

Although there is no good experimental model of NAION, it is presumed that it represents a vascular disease of the optic disc. The rapid onset, poor recovery, and crowded appearance of the optic disc, and the association with microvascular diseases, such as hypertension and diabetes, support the widely held theory that vascular insufficiency of a structurally crowded optic disc leads to infarction of the laminar and possibly the retrolaminar optic nerve. In addition, it has been suggested that the altitudinal visual field defects seen in NAION are the result of infarctions of the optic disc that lie in the watershed zone between the distribution of the posterior ciliary arteries, possibly associated with nocturnal systemic hypotension.

Traustason and colleagues classified visual field defects following NAION using SAP and found, similarly to the current study, that most subjects did not have absolute altitudinal visual field loss and that decreased threshold sensitivity was frequently found in both hemifields. The authors concluded that pure altitudinal loss rarely occurs in NAION and that even patients with “highly altitudinal” field loss still had some loss of threshold sensitivity in the other hemifield. The authors did not strictly define altitudinal field loss as we did in our study.

Two previous reports have attempted to define the role of FDT in the detection of neuro-ophthalmological disorders. Both studies included a subset of patients with NAION. Thomas et al examined 103 patients with “neuro-ophthalmic” visual disorders defined as quadrantanopic, hemianoptic, altitudinal, or central visual field defects, along with 30 normal subjects and 29 patients with glaucoma. They found that FDT was a sensitive and specific test but could not accurately categorise the visual field defects. However, neither the number of patients with altitudinal loss nor the specific diagnosis of patients with neuro-ophthalmic disorders were provided, making the results difficult to interpret for NAION.

Wall and colleagues examined 97 patients with sensory neuro-ophthalmic disorders (29 of which had NAION) and 42 normal subjects in order to determine the sensitivity and specificity of FDT in neuro-ophthalmic disorder. Overall, FDT and standard perimetry had similar specificity, and sensitivity to standard perimetry in the detection of sensory neuro-ophthalmic disorders. In contrast with our study, the extent of defect using FDT was similar to that of standard perimetry. Based on these findings, the authors concluded that FDT probably does not selectively isolate the M cells. However, subjects with NAION in this previous study were not independently analysed, so it is difficult to compare these results with the finding in our study. Furthermore, the authors did not exclude patients with poor vision or mention criteria for reliability using either visual field modality. Also, testing order was not varied, so test fatigue may have had an effect.

This study demonstrates that isolated altitudinal hemiretinal dysfunction following NAION occurs rarely and that the damage in NAION may extend beyond the presumed watershed zone of compromised microcirculation of the optic disc as demonstrated by standard perimetry. While axonal loss reflected by the extent of optic disc pallor in NAION correlated with FDT more than with standard perimetry, the extent of pallor was estimated clinically by a single observer in a retrospective analysis. These subjective estimates would better be obtained using multiple observers. Similar to finding in glaucomatous optic neuropathy with hemifield defects, FDT revealed visual dysfunction in the hemifield that appeared relatively uninvolved when evaluated using standard techniques. However, since the cases were defined by standard perimetry, comparisons of the discriminatory ability of FDT and standard perimetry are not valid. Future studies with entry criteria based on optic disc characteristics alone would be desirable.

ACKNOWLEDGEMENTS
Supported by National Eye Institute K23 Grant EY13959-01 and the Eyesight Foundation of Alabama.

REFERENCES

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**Table 4** Extent of visual field defect in the involved and uninvolved hemifield using SAP (SITA) and FDT in NAION subjects with regional and diffuse disc pallor (intergroup comparisons performed using a nested ANOVA of Rosner)

<table>
<thead>
<tr>
<th>Extent of disc pallor</th>
<th>Number of subjects</th>
<th>Percentage defect</th>
<th>Involved hemifield</th>
<th>Uninvolved hemifield</th>
<th>p Value (FDT v SITA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional</td>
<td>5</td>
<td>95.4 (10.3)</td>
<td>95.6 (9.7)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Diffuse</td>
<td>15</td>
<td>89.3 (6.7)</td>
<td>91.9 (9.8)</td>
<td>0.2692</td>
<td></td>
</tr>
</tbody>
</table>
A study of PITX3 gene mutation in five families has improved our understanding of heritable cataracts. Genetic researchers have identified a unique, recurrent mutation at chromosome 10q25 to account for posterior polar cataract (CPP4) that occurs across ethnic groups. The study also indicates a bigger role for PITX3 in the development of the lens of the eye than the rest of the anterior segment, as all subjects with the mutation had cataracts.

This PITX3 mutation occurred in four unrelated large families with autosomal dominant posterior polar cataract, three English and one Chinese, and segregated with family members affected by cataracts. Two of the families had members with anterior/segment mesenchymal dysgenesis (ASMD). The mutation is a 17 base pair duplication in exon 4 of the PITX3 gene that results in a frameshift at codon 220 and altered protein product with 94 extra amino acid residues. The fifth family, of Hispanic origin, had a novel mutation in exon 4—650delG—which segregated with cataract. Neither mutation occurred in 100 healthy controls.

All family members had a full clinical examination and were genotyped. Amplification of DNA of the PITX3 region was followed by direct sequencing of the amplification products. Cataract is the commonest form of blindness. More than 14 distinct loci have been identified in humans for 11 different types of autosomal dominant congenital cataracts. Mutation in the gene for developmental transcription factor PITX3 is one more in an array of mutations in eye proteins causing the condition.