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CLINICAL INVESTIGATION

Using Frequency-Doubling Perimetry to Detect Optic Neuropathy in Patients with Graves' Orbitopathy

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Abstract

Purpose: to test the ability of frequency-doubling technology (FDT) perimetry to detect dysthyroid optic neuropathy (DON).

Methods: Fifteen eyes of 15 patients with DON and 15 healthy control eyes were studied. Eligible eyes had a diagnosis of DON based on visual field abnormalities on standard automated perimetry and had visual acuity better than 20/30. FDT testing was performed using both the C-20-5 screening test and the C-20 full-threshold test. Normal and DON eyes were compared with regard to FDT mean sensitivity.

Results: Sensitivity ranges were 40.0%–86.7% for the screening test, and 53.3%–100.0% (total deviation) and 20.0–93.3 (pattern deviation) for the C-20 threshold test. The corresponding specificity ranges were 86.7–100.0, 33.3–93.3, and 26.7–100.0, respectively. The best sensitivity/specificity ratios were for one abnormal point depressed <5% in the screening test (86.7%/86.7%), one point depressed <1% in the total deviation analysis (80.0%/86.7%), and one point depressed <2% in the pattern deviation analysis (80.0%/86.7%). DON eyes presented significantly lower than normal average sensitivity in the central, pericentral, and peripheral areas.

Conclusions: FDT perimetry is a useful screening tool for DON in eyes with normal or only slightly reduced visual acuity. **Jpn J Ophthalmol** 2008;52:475–482 © Japanese Ophthalmological Society 2008

Key Words: dysthyroid optic neuropathy, frequency-doubling perimetry, Graves' orbitopathy, visual field defect

Introduction

Dysthyroid optic neuropathy (DON) is a serious complication of Graves' orbitopathy (GO), occurring in 5%–8.6%[1] of patients. It is thought to be a result of compression of the optic nerve at the orbital apex by enlarged extraocular muscles. Symptoms and signs of DON may include decreased visual acuity (VA), abnormal visual fields (VFs), altered color and brightness perception, afferent pupillary defects, and edema or atrophy of the optic nerve head.[1] When most of these symptoms and signs are present, the diagnosis of DON is straightforward. It is, however, much more difficult to establish when changes in VA are subtle, since such changes may be related to a variety of factors, including decreased corneal transparency due to exposure keratopathy.[2]

VF examination plays an essential role in the diagnosis of DON. Goldmann's manual perimetry can still be useful, but the current standard in VF examination is standard automated perimetry (SAP) using threshold testing encompassing the central either 21° or 28° of the VF.[3–6] Although strategies such as the Swedish Interactive Threshold Algorithm (SITA) program (Humphrey Systems, Dublin, CA, USA)[7] have significantly decreased the duration of SAP, it may still be too time consuming for certain patients, especially for those with GO in the congestive phase, in whom it may lead to false-positive results. There is therefore a need for tests capable of rapidly and accurately identifying patients with subtler forms of DON.

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Frequency-doubling technology perimetry (FDT, Carl Zeiss Meditec, Dublin, CA, USA) is a recently introduced modality of VF testing originally developed mainly to detect glaucomatous damage.[8,9] It makes use of the frequency-doubling illusion by which a sine-wave grating of low spatial frequency undergoing counterphase flicker at high temporal frequency appears to the observer to have twice the actual number of bars.[10] FDT perimetry is a sensitive method for detecting VF defects and is usually less time consuming than SAP. Since its introduction, FDT has been used to study a range of different conditions and seems to be of benefit to patients with neuro-ophthalmic conditions.[11–13] However, so far no study has specifically addressed cases of DON.

The purpose of this study was to evaluate the sensitivity and specificity of FDT perimetry for the detection of DON in GO patients with VA above 20/30.

Patients and Methods

Between December 2004 and March 2006, 30 eyes were subjected to FDT perimetry. Of these, 15 eyes from 15 GO patients (ten women and five men) were recruited for this prospective study. In all 15 patients, Graves' disease was diagnosed by the Department of Endocrinology at our institution, based on clinical, laboratory, and imaging studies. GO was diagnosed in all of these patients by the presence of thyroid dysfunction, lid retraction, restrictive extraocular myopathy, and optic nerve dysfunction, as well as the presence of no other causes of the ophthalmic features.[14] Both orbits of each patient were scanned with a 16-slice multidetector computed tomography (CT) scanner (Brilliance 16; Philips Medical Systems, Nederland B.V., the Netherlands) without the use of sedation or intravenous contrast. All 15 patients with GO had DON documented by clinical examination, which included VA testing, the presence of afferent pupillary defects, and VF defects on SAP, as well as neuroimaging studies demonstrating apical orbital crowding from enlarged extraocular muscles. The remaining 15 eyes were from 15 healthy controls (eight women and seven men). Approval from the Institutional Review Board Ethics Committee was obtained for the study, and informed consent was obtained from all participants.

The patients underwent a comprehensive ophthalmologic examination, including best-corrected VA, applanation tonometry, pupillary reactions, extraocular motility evaluation, slit-lamp examination, evaluation of eyelid and soft tissue inflammation, measurement of the lid fissure, Hertel exophthalmometry, funduscopy, and VF evaluation. A dilated fundus examination was performed after completion of VF studies.

SAP was performed with a Humphrey field analyzer 750 (Carl Zeiss Meditec) using a 4 mm^2 Goldmann size III stimulus (0.43°) on a dim background (31.5 apostilb). The central field was measured by a threshold 24-2 test program presenting stimuli on a grid with 6° intervals encompassing the central 21° of the VF (24-2 SITA standard test). Each patient's appropriate near correction was used. Rest breaks were allowed when requested.

Fifteen patients (one eye each) were selected for the study. To be included in the study, the patient had to have at least one eye with DON documented by an abnormal SAP test result. To qualify as an abnormal VF on SAP, three adjacent abnormal points at the $P < 0.05$ level or two adjacent points with one abnormal at the $P < 0.01$ level were required.[13] Other inclusion criteria were best-corrected VA of 20/25 or better in the study eye; age above 20 years, good cooperation for performing VF, spherical refraction within ±5 D; cylinder correction within ±3 D; intraocular pressure less than 22 mmHg; and reliable VF. A reliable Humphrey VF test was defined as one with a fixation loss of less than 25%, and fewer than 25% false-positive or false-negative responses. Patients with clinical signs of glaucomatous optic neuropathy or optic disc anomaly were excluded.

The control group consisted of healthy volunteers recruited from hospital staff members with normal ophthalmic examination results, including normal SAP visual fields. A normal SAP VF was defined as a pattern standard deviation (PSD) within the 95% confidence limits and a Glaucoma Hemifield Test result within normal limits. The healthy control eyes also had a healthy appearance of the optic disc and retinal nerve fiber layer. One eye of each healthy subject was included in the analysis, and the left or the right eye was selected to match the selections in the patients with DON.

As a strict criterion of sample independence, we selected only one eye from each patient and one from each control. Following previous studies,[12,13] we estimated the sample size by hypothesizing that sensitivity and specificity for the best FDT parameters would be around 80% (confidence intervals between 60% and 100%). Based on these assumptions, calculations indicated that 15 eyes in each group would yield an adequate comparison.

FDT perimetry was performed after SAP, with an interval of at least 15 min to reduce fatigue effect. Testing was performed in a darkened room using an FDT device. Patients and controls were submitted to both the C-20-5 screening mode and the C-20 full-threshold mode. An interval of at least 5 min was allowed between the C-20-5 screening test and the C-20 full-threshold test in order to improve reliability, as suggested by Tsukamoto et al.[15]

Both strategies tested four locations in each quadrant (10° × 10° squares) and one central location (10° of arc of a central circle), totaling 17 locations tested in the central 20° of the VF. In each area tested, the FDT device presented frequency-doubling stimuli (10 × 10) with low spatial frequency, cosinusoidal grating (0.25 cycle/degree), and high temporal frequency (25-Hz counterphase flicker) on a square background.

In the screening C-20-5 test protocol, target areas were presented at a contrast expected to be detected by 95% of healthy age-matched subjects.[16] Unseen targets were presented a second time and labeled $P \geq 5\%$ whenever the subject responded. If the second stimulus was missed, a third stimulus was presented corresponding to what would

be seen by 98% of the healthy population (missed by 2% of healthy persons). The locations of these stimuli were labeled $P < 5\%$. If, however, the third stimulus was missed, a fourth stimulus was presented corresponding to what would seen by 99% of the healthy population. In that case, the location was labeled $P < 2\%$, or, if missed, $P < 1\%$.[12,17]

The C-20 full-threshold protocol determines the minimum contrast necessary to detect the stimulus for each of the 17 target locations in the stimulus display. This is accomplished by means of a modified binary search type of staircase. If the stimulus is detected, the contrast is decreased in the following presentation; if the stimulus is not detected, the contrast is increased. Thus, the test is continued until the stimulus with the lowest contrast is detected at each test location.[13] The test provides information on threshold (dB) plots, deviation plots with a five-probability-level classification based on age-related normative reference, mean deviation (MD) and pattern standard deviation, and statistical global indices. The test also provides reliability indices (fixation, false positive, and false negative), determined through catch trials. Only reliable fields were accepted in this study, in which the VF had fewer than 33% false-positive or false-negative responses and less than 20% fixation losses.

We tested several sets of diagnostic criteria to assess the validity of FDT in detecting abnormality in eyes with DON. Using SAP abnormalities and other clinical findings such as afferent pupillary defects to define the presence of DON, we calculated the sensitivity and specificity for a number of predefined criteria. Several criteria were used for the C-20-5 screening protocol, including depression as compared to the manufacturer's internal normative database (to <5%, <2%, or <1% probability levels) as either a single point or as two defective points in either an isolated or an adjacent fashion. This enabled us to evaluate the best sensitivity and specificity criteria.[12,18] The C-20 threshold test results were subjected to similar calculations.

The C-20 threshold test was also used to compare DON patients and controls with regard to mean deviation (MD), mean sensitivity in the central area, and average sensitivity threshold in the pericentral and peripheral zones of the VF.

Sensitivity and specificity were calculated for each criterion in the traditional manner. A criterion with a high specificity, if positive, confirmed the disease, and a test with a high sensitivity, if negative, ruled out the disease.[19]

The odds ratio for having the disease was calculated for each diagnostic criterion. P values of <0.05 were considered significant. Results of statistical significance were obtained after Bonferroni's correction based on the number of comparisons within each analysis in order to avoid type 1 errors.

We used an unpaired t test to compare patients and healthy subjects. Pearson's correlation coefficients were used to evaluate the relationship between the severity of visual loss as determined by SAP mean deviation and by the FDT C-20 threshold test mean deviation. Adherence to a normal distribution was assessed using the Kolmogorov-Smirnov test. The level of statistical significance for such comparisons was set at $P < 0.05$.

Results

Data concerning age, sex, visual acuity, and SAP of eyes with DON are shown in Table 1. VA was 20/20 in 13 eyes and 20/25 in two. The mean age (± SD) of patients with DON and of healthy individuals was 51.40 ± 9.41 and 45.00 ± 7.16 (mean ± SD of the SAP mean deviation was –5.57 ± 3.12 dB). The glaucoma hemifield test was outside normal limits in 14 eyes and borderline in one. Exophthalmometry findings in the affected eyes ranged from 18 to 28 mm with a mean (± SD) of 22.67 ± 3.54 mm. Restrictive myopathy

Table 1. Age, sex, study eye, visual acuity, clinical findings, and mean deviation on standard automated perimetry in 15 patients (15 eyes) with DON

Case	Sex	Age	Eye	VA	External signs	Exophthal	FE	MD on SAP
1	F	50	OD	20/20	RM	21	Optic DE	–4.74
2	F	49	OD	20/20	RM	27	Normal	–7.56
3	F	46	OS	20/20	Left ET/HT	18	Normal	–0.76
4	F	52	OS	20/20	CS, RM	20	Normal	–2.55
5	F	39	OS	20/25	RM	24	Normal	–11.63
6	F	63	OS	20/20	CS, RM	23	Normal	–5.27
7	F	33	OS	20/20	RM	20	Normal	–4.6
8	M	56	OS	20/20	RM	21	Normal	–11.12
9	F	71	OS	20/20	CS, RM	18	Normal	–5.85
10	M	54	OS	20/20	CS, RM	28	Normal	–6.49
11	F	47	OS	20/20	CS, RM	24	Normal	–5.09
12	F	59	OS	20/20	CS, RM	25	Normal	–2.56
13	M	44	OD	20/25	CS, RM	18	Normal	–3.58
14	M	57	OD	20/20	CS, RM	28	Normal	–3.05
15	M	51	OD	20/20	CS, RM	25	Normal	–8.73

DON, dysthyroid optic neuropathy; SAP, standard automated perimetry; M, male; F, female; OD, right eye; OS, left eye; VA, visual acuity; CS, congestive signs; RM, restrictive myopathy; ET, esotropia; HT, hypertropia; FE, fundus examination; Exophthal, exophthalmometry; DE, disc edema; MD, mean deviation.

Table 2. Sensitivity, specificity and odds ratio with confidence intervals for several diagnostic criteria used in the C-20-5 screening test for diagnosis of 15 eyes with DON and 15 normal controls

Criteria	Sensitivity (95% CI)	Specificity (95% CI)	Odds ratio (95% CI)	*P**
One abnormal point depressed <5%	86.7% (70.3–94.7)	86.7% (70.3–94.7)	42.25 (5.2–318.0)	*<0.001*
One abnormal point depressed <2%	60.0% (43.8–65.4)	93.3% (77.1–98.8)	21 (2.6–151.9)	*0.002*
One abnormal point depressed <1%	53.3% (38.9–53.3)	100% (85.6–100)	N.A. (3.8–Inf)	*0.002*
Two abnormal points anywhere in the field, both <5%	60.0% (43.8–65.4)	93.3% (77.1–98.8)	21 (2.6–151.9)	0.005
Two abnormal points anywhere in the field, one <5% and one <2%	53.3% (37.3–58.8)	93.3% (77.3–98.8)	16 (2.0–114.6)	0.014
Two abnormal points anywhere in the field, one <5% and one <1%	46.7% (32.5–46.7)	100% (85.8–100)	N.A. (2.9–Inf)	0.035
Two abnormal adjacent points, both <5%	60.0% (43.8–65.4)	93.3% (77.1–98.8)	21 (2.6–151.9)	0.005
Two abnormal adjacent points, one <5% and one <2%	53.3% (37.3–58.8)	93.3% (77.3–98.8)	16 2.0–114.6	0.014
Two abnormal adjacent points, one <5% and one <1%	46.7% (32.5–46.7)	100% (85.8–100)	N.A. (2.9–Inf)	0.006
Two abnormal central points, both <5%	46.7% (31.0–52.1)	93.3% (77.3–98.8)	12.3 1.6–87.6	0.035
Two abnormal central points, one <5% and one <2%	40.0% (26.3–40.0)	100% (86.3–100)	N.A. (2.2–Inf)	0.008
Two abnormal central points, one <5% and one <1%	40.0% (26.3–40.0)	100% (86.3–100)	N.A. (2.2–Inf)	0.008

CI, confidence interval; N.A., not applicable; Inf, infinity.
*Fisher exact test. Significant values are in italics.

was present in all eyes with DON. The funduscopic examination revealed optic disc edema in one eye and normal findings in all others. In four patients both eyes were affected by optic neuropathy, but only one eye met the inclusion criteria. One of the four eyes of two patients with bilateral DON was the eye with optic disc edema. In the remaining 11 patients the contralateral eye showed no evidence of optic nerve dysfunction. A relative afferent pupillary defect was observed in all 11 patients with unilateral DON. All 15 orbits with DON had CT evidence of extraocular muscle enlargement and crowding at the orbital apex.

The mean age of the 15 healthy controls (eight women and seven men) was 45.00 years (SD, 7.16 years; range, 32–62 years). Visual acuity was 20/20 in all 15 healthy eyes studied. All had spherical refraction within ±5 D; cylinder correction within ±3 D; intraocular pressure <22 mmHg; and reliable VF. Mean (± SD) of the SAP mean deviation was –0.56 ± 0.89 dB.

Tables 2 to 4 summarize the FDT perimetry findings. Sensitivity ranges were 40.0%–86.7% for the screening test, and 53.3%–100.0% (total deviation analysis) and 20.0%–93.3% (pattern deviation analysis) for the C-20 threshold test. Specificity ranges were 86.7%–100.0% for the screening test, 33.3%–93.3% for the total deviation analysis, and 26.7%–100.0% for the pattern deviation analysis.

After Bonferroni's correction ($\alpha = 0.004$; 12 comparisons), the odds ratio was statistically significant for one abnormal point depressed <5% ($P < 0.001$), <2% ($P = 0.002$), and <1% ($P = 0.002$) in the screening test. Using the criterion of one abnormal point depressed <5% in the screening test, we found a sensitivity to specificity ratio of 86.7%/86.7% and an odds ratio of 42.25, indicating high sensitivity for detecting DON. The remaining parameters, however, yielded a much poorer sensitivity and a very high specificity (Table 2).

In the total deviation analysis, sensitivity was 80%, specificity was 86.7%, and the odds ratio was 26 for one abnormal point depressed <1% ($P = 0.001$). The pattern deviation analysis yielded similar findings for one abnormal point depressed <2% ($P = 0.001$) (Tables 3 and 4).

Mean (± SD) of the FDT C-20 threshold test mean deviation was –5.75 ± 3.19 dB. Pearson correlation coefficient showed a strong association between FDT and SAP mean deviations ($r = 0.82$; $R^2 = 67\%$; $P < 0.001$). Comparisons between DON patients and controls with regard to mean sensitivity values disclosed significant differences between MD ($P = 0.001$) and mean sensitivity in the central ($P = 0.005$), pericentral ($P = 0.001$), and peripheral ($P < 0.001$) regions of the field using FDT perimetry (Table 5).

Discussion

While diagnosis of DON is straightforward in patients presenting severely reduced visual function, cases with subtle signs of optic nerve dysfunction often pose a challenge. Several authors have mentioned the difficulties in establishing a correct diagnosis of DON when VA is normal or only

Table 3. Sensitivity, specificity, and odds ratio with confidence intervals for several criteria used in the C-20 threshold test, total deviation plot, in 15 eyes with DON and 15 normal controls

Criteria	Sensitivity (95% CI)	Specificity (95% CI)	Odds ratio (95% CI)	*P**
One abnormal point depressed <5%	100% (86.9–100)	33.3% (20.3–33.3)	N.A. 1.7–Inf	0.021
One abnormal point depressed <2%	80.0% (62.5–91.3)	73.3% (55.8–84.6)	11 2.1–57.3	0.009
One abnormal point depressed <1%	80.0% (63.2–88.8)	86.7% (69.8–95.5)	26 (4.0–166.6)	*0.001*
Two abnormal points anywhere in the field both <5%	100% (85.6–100)	53.3% (38.9–53.3)	N.A. 3.8–Inf	*0.001*
Two abnormal points anywhere, one <5% and one <2%	80.0% (62.5–91.3)	73.3% (55.8–84.6)	11 2.1–57.3	0.009
Two abnormal points anywhere, one <5% and one <1%	80.0% (63.2–88.8)	86.7% (69.8–95.5)	26 (4.0–166.6)	*0.001*
Two abnormal adjacent points, both <5%	100% (85.6–100)	53.3% (38.9–53.3)	N.A. 3.8–Inf	*0.002*
Two abnormal adjacent points, one <5% and one <2%	73.3% (55.6–85.8)	73.3% (55.6–85.8)	7.6 1.6–36.6	0.009
Two abnormal adjacent points, one <5% and one <1%	73.3% (56.3–82.4)	86.7% (69.6–95.7)	17.9 (2.9–104.5)	*0.001*
Two abnormal central points, both <5%	73.3% (55.8–84.6)	80.0% (62.5–91.3)	11 (2.1–57.3)	0.009
Two abnormal central points, one <5% and one <2%	60.0% (42.9–69.2)	86.7% (69.6–95.9)	9.8 (1.7–52.5)	0.021
Two abnormal central points, one <5% and one <1%	53.3% (37.3–58.8)	93.3% (77.3–98.8)	16 (2.0–114.6)	0.014

*Fisher exact test. Significant values are in italics.

Table 4. Sensitivity and specificity of several criteria used in the C-20 threshold test, pattern deviation plot, in 15 eyes with DON and 15 normal controls

Criteria	Sensitivity (95% CI)	Specificity (95% CI)	Odds ratio (95% CI)	*P**
One abnormal point depressed <5%	93.3% (80.2–98.8)	26.7% (13.5–32.1)	5.1 (0.6–37.9)	0.330
One abnormal point depressed <2%	80.0% (63.2–88.8)	86.7% (69.6–95.7)	26 (4.0–166.6)	*0.001*
One abnormal point depressed <1%	53.3% (37.3–58.8)	93.3% (77.3–98.8)	16 (2.0–114.7)	0.014
Two abnormal points anywhere in the field both <5%	93.3% (77.7–98.8)	46.7% (31.0–52.1)	12.3 (1.6–87.6)	0.019
Two abnormal points anywhere, one <5% and one <2%	80.0% (63.2–88.8)	86.7% (69.8–95.5)	26 (4.0–166.6)	*0.001*
Two abnormal points anywhere, one <5% and one <1%	53.3% (37.3–58.8)	93.3% (77.3–98.8)	16 (2.0–114.7)	0.014
Two abnormal adjacent points, both <5%	80.0% (63.2–92.0)	46.7% (29.9–58.7)	3.5 (0.7–16.4)	0.148
Two abnormal adjacent points, one <5% and one <2%	66.7% (49.5–75.8)	86.7% (69.5–95.8)	13 (2.2–72.1)	0.008
Two abnormal adjacent points, one <5% and one <1%	40.0% (24.9–45.4)	93.3% (78.2–98.8)	9.3 (1.2–67.0)	0.043
Two abnormal central points, both <5%	46.7% (31.0–52.1)	93.3% (77.7–98.8)	12.25 (1.6–87.6)	0.035
Two abnormal central points, one <5% and one <2%	26.7% (14.5–26.7)	100.0% (87.9–100.0)	N.A. (1.2–Inf)	0.100
Two abnormal central points, one <5% and one <1%	20.0% (9.3–20.0)	100.0% (89.3–100.0)	N.A. (0.9–Inf)	0.224

*Fisher exact test. Significant values are in italics.

Table 5. Mean values (± standard deviation) of mean deviation and average sensitivity in three areas of the visual field in eyes with DON and normal controls in the C-20 threshold test of frequency-doubling perimetry

	DON (n = 15)	Controls (n = 15)	P*
Mean deviation	–5.75 ± 3.19	–2.05 ± 2.19	*0.001*
Average sensitivity			
Central	24.33 ± 5.06	29.20 ± 3.55	*0.005*
Pericentral	23.22 ± 4.55	28.43 ± 3.16	*0.001*
Peripheral	20.78 ± 5.13	27.23 ± 2.72	*<0.001*

*Student's t test. Significant values are in italics.

slightly reduced. That is particularly true for patients with congestive signs of GO, in whom subtle changes in VA are often thought to be related to corneal transparency abnormalities or lacrimal film dysfunction. Careful attention in excluding such factors is therefore essential in the diagnosis of the subtler forms of DON. The presence of afferent pupillary defects and optic disc edema is very helpful in doubtful cases, and neuroimaging findings may also help the clinician reach a diagnosis since enlarged extraocular muscles in the orbital apex can suggest optic nerve compression and dysfunction.

Although imaging studies can detect the severity of apical crowding, and thereby identify those at risk for DON,[1,20,21] appropriate psychophysical and electrophysiological testing is extremely important for the diagnosis and should be carried out. These tests may include color vision analysis, VF and electrophysiological tests such as visual evoked potentials (VEP), and pattern reversal electroretinography (PERG). In a study by Neigel et al.[1] involving 58 patients with DON, 64% had abnormal color vision and 66% had abnormal fields, whereas the pattern VEP was abnormal in 94%. Tsaloumas et al.[22] studied 13 eyes of eight patients with DON and found abnormal VEP before treatment in all 13 eyes, with a significant improvement after treatment with high-dose steroids or surgical decompression. The authors concluded that VEP to flash and pattern stimuli provides a useful diagnostic and monitoring tool in patients with DON. Spadea et al.[23] studied 50 GO patients with PERG and pattern VEP and found both tests to be useful in establishing an early diagnosis of DON. Acaroglu et al.[24] studied 16 patients with GO and 15 healthy controls and suggested that P-100 latencies may be significantly delayed in patients with GO, even without any clinical signs of DON. A similar result was obtained by Salvi et al.,[25] who concluded that VEPs in GO are complementary to the study of the VF study for identifying early optic nerve dysfunction in the absence of decreased VA. VEPs have been reported to have up to 96% diagnostic accuracy for DON, especially if the N75-P100 amplitude for small checks is used. However, other concomitant ocular conditions may also affect VEPs, likely resulting in a much lower diagnostic specificity of the test under normal conditions.[26,27] A recent study also found a significant false-negative rate associated with the use of VEPs in patients with DON.[28]

Despite all the above-mentioned clinical and imaging findings there remains a large number of cases in which VF examination is still of invaluable importance for the diagnosis and management of patients with DON. Goldmann's perimetry (GP) was for many years considered the gold standard of VF examination in patients with neuro-ophthalmic conditions. However, the current lack of technicians and physicians fully trained in performing GP and the advances in automated perimetry have made computerized perimetry the most commonly used method today.[4] Many authors believe that SAP can detect abnormalities earlier than manual GP because of its greater sensitivity and ability to make comparisons at each point.[4] However, despite its many advantages, SAP technology has significant drawbacks when applied to neuro-ophthalmologic patients, particularly those with severe visual loss or attention deficit. GO represents one situation when SAP is difficult to perform: because many GO patients have lid retraction and congestive signs, tear film dysfunction is a common finding. Furthermore, inferior and medial rectus restriction can make it difficult to maintain proper fixation during SAP. And, since SAP is a relatively time-consuming procedure, the above-mentioned factors frequently lead to false-positive findings.

FDT perimetry is a relatively simple method and will accomplish an examination in less than 1 min in the screening mode. Quick and user-friendly operation makes this technique attractive, especially for neurologic patients and for those for whom maintaining fixation for long periods of time is difficult. Fujimoto and Adachi-Usami[11] tested FDT perimetry in 14 patients with recovered optic neuritis (normal visual acuity) and observed a generalized sensitivity depression, while control testing with SAP revealed a depression in the central area of the VF only. Likewise, Thomas et al.[12] examined several patients with "typical" neuro-ophthalmic VF defects and found FDT perimetry to be a quite sensitive and specific detection tool. Wall et al.,[13] on the other hand, observed that the sensitivity and specificity of FDT perimetry equaled those of SAP in patients with VF defects from optic neuropathy but failed to identify patients with hemianopia.

In our study FDT revealed abnormalities in most eyes with both the screening and full-threshold test, suggesting that FDT is a sensitive method to detect VF defects. When the "screening" test results were analyzed alone, the criterion of one abnormal point depressed <5% yielded high sensitivity and specificity. When different diagnostic criteria were used, however, sensitivity was much poorer, ranging from 40% to 60%. Fong et al.[29] concluded that the FDT screening strategy failed to identify hemianopic and quadrantanopic VF defects in more than half of the 15 eyes studied. Our study, however, indicates that the presence of one abnormal point depressed <5% constitutes a very sensitive and specific criterion for the diagnosis of DON. Considering the ease with which it is performed and that our patients presented relatively subtle forms of DON, the FDT screening test is potentially a useful tool for DON screening.

Gardiner et al.[30] recently evaluated different decision rules for FDT screening by applying them to groups of healthy subjects and glaucoma patients. They found that sensitivity for detecting glaucoma patients was 71.8%, 70.5%, and 61.5% for one abnormal point depressed <5%, <2%, and <1%, respectively. The corresponding specificity was 77.9%, 85.0%, and 93.6%. Although these authors used a study population different from ours, as well as a larger number of healthy subjects, their specificity results were similar and lend support to our findings. Gardiner et al.[30] report that a repeat examination to confirm the original findings would further improve the specificity with only a small reduction in sensitivity. Considering the advantages of a rapid test for patients with GO, we believe it is worth doing this examination in future studies.

Our study indicates that the full-threshold FDT test is also a effective method for detecting VF defects, even in patients with subtle or moderate forms of DON. In fact, a strong correlation between SAP mean deviation and FDT C-20 threshold test mean deviation was observed. However, although several sets of diagnostic criteria yielded high sensitivity, many were associated with poor specificity. On the other hand, the criteria of one abnormal point depressed <1% in the total deviation analysis and <2% in the pattern deviation analysis were associated with a very high sensitivity (80%), high specificity (86.7%), and an odds ratio of 26, suggesting that the full-threshold test can be used as a DON detection tool.

Since DON is relatively uncommon and our inclusion criteria were very strict, this study included a relatively small number of patients. However, sample size estimations based on previous FDT studies indicate that the sample was large enough to determine the sensitivity and specificity of FDT. Furthermore, our specificity values matched those of other studies with a larger control series. For example, the specificity of one abnormal point depressed <5% was 77.9% in Gardiner et al.[30] and 86.7% in our study. Using the C-20 threshold test, Heeg et al.[31,32] measured specificity in normal subjects and for one abnormal point depressed <1% in the total deviation analysis found specificities of 81.0% in 237 and 86% in 108 these subjects, while we found 86.7% for the same criterion. Our specificity findings are also fairly similar to findings reported by a number of other studies.[33–35]

Our study had some methodological limitations that should be pointed out. Although the diagnosis of DON did not rely exclusively on SAP, the latter was to some extent used as a "gold standard." Consequently, even if FDT perimetry performed better than SAP, the difference would be interpreted as an error. However, since our purpose was to investigate patients with DON and good visual acuity and since there is currently no best laboratory test or imaging study that can diagnose DON with certainty, it is hardly possible to exclude SAP as a major diagnostic criterion from the study design. Furthermore, since SAP is used as the current standard for detecting most optic neuropathies, we believe our observations regarding the use of FDT are valid. Studies with different design and a larger number of patients will help determine whether FDT could perform better than SAP in cases of DON.

In conclusion the current study indicates that FDT is a sensitive method for identifying patients with DON, whether the screening test or the full-threshold test is used. Since DON is a potentially vision-threatening disease, clinicians should be aware of the possible use of FDT perimetry for DON screening purposes.

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