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Screening for glaucoma in a general population with the non-mydriatic fundus camera and the frequency doubling perimeter

M. DETRY-MOREL[1], T. ZEYEN[2], P. KESTELYN[3], J. COLLIGNON[4], M. GOETHALS[2], and the BELGIAN GLAUCOMA SOCIETY

[1]St Luc University Hospital, Université Catholique de Louvain, Brussels
[2]St Rafael University Hospital, KUL, Leuven
[3]University Hospital, RUG, Gent
[4]University Hospital, ULG, Liège - Belgium

PURPOSE. *To evaluate the usefulness of non-mydriatic fundus camera (NMFu-camera) and frequency doubling perimeter (FDP) for detecting glaucoma in a general population.*
METHODS. *This prospective observational multicenter study consisted in screening for glaucoma in the populations of three Belgian cities. Intraocular pressure (IOP) was measured with non-contact pneumo-tonometer (NCT) and applanation tonometry (AT) if NCT IOP was ≥17 mmHg. Visual field was screened with FDP (C-20-5) and digitized optic disc photographs (ODPs) were taken with NMFu-camera. FDP was considered abnormal if at least one defective point was found. ODPs were graded as normal or glaucomatous by consensus of three glaucoma specialists. Optic disc and visual field results were matched per eye. Subjects with known ocular hypertension and/or treated primary open angle glaucoma were excluded from the analysis.*
RESULTS. *A total of 1620 subjects were included in the study. Their mean age was 63.2 years. AT IOP was >21 mmHg in 8.2%. A total of 98.1% of ODPs could be interpreted. Glaucomatous optic discs were detected in 3.5% of the subjects. In this group only 24% had an AT IOP ≥22 mmHg. FDP was abnormal in 44.5%. The sensitivity and specificity of FDP to identify patients with an optic disc graded as glaucomatous were 58.6% and 64.3% respectively.*
CONCLUSIONS. *The combined use of the NMFu-camera and the FDP is a feasible method for an initial glaucoma mass screening. NMFu-camera may be a useful and quick method to screen for glaucomatous damage in a community. FDP in screening strategy was revealed to be not sensitive enough when setting the cut-off value at one defective test location. IOP measurements were confirmed to be a poor tool to detect glaucomatous damage. (Eur J Ophthalmol 2004; 14: 387-93)*

KEY WORDS. *Glaucoma screening, Optic disc imaging, Frequency doubling perimetry, Frequency doubling technology, Glaucoma epidemiology, Intraocular pressure*

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INTRODUCTION

Optimal strategies for screening for glaucoma in a general population are problematic. A combination of methods detecting optic disc change and functional visual loss has been shown to be more sensitive than tonometry alone (1-5).

Among the various techniques of optic disc and nerve fiber layer evaluation, the non-mydriatic fundus camera (NMFu-camera) has proven to be a useful screening tool in detecting glaucomatous optic disc damage (6, 7). Frequency doubling technology (FDT) is based on the so-called frequency-doubling illusion phenomenon. Most previous studies supported that this phenomenon was substrated by mechanisms in the magnocellular pathway, in particular the My ganglion cells that are selectively lost in eyes with early glaucoma (8-10). Recent findings suggested an alternate temporal cortical origin of this illusion. Frequency doubling perimetry (FDP) has proved to be an efficient, rapid, and reliable method for detection of glaucomatous visual field loss (11-16).

The purpose of this study was to evaluate the feasibility and the potential of the NMFu-camera and the FDP to detect glaucomatous optic disc damage in an initial glaucoma mass screening.

METHODS

In October 1999, the populations of three Belgian cities (Brugge, Brussels, Liège) were invited by newspaper and television advertisements to present for glaucoma screening in public spaces.

The subjects were prospectively examined in this cross-sectional study according to a protocol that included a medical questionnaire, tonometry, optic nerve head examination, and computerized perimetry. All participants completed a medical and family history questionnaire seeking both risk factors for glaucomatous neuropathy and local and systemic treatments that could interfere with intraocular pressure (IOP) values.

IOP was measured with the non-contact pneumotonometer (NCT) (CanonTX-10) and controlled with the Goldmann applanation tonometer (AT) if the NCT IOP was ≥17 mmHg. Linear regression analysis on a separate sample of 100 patients has shown that a cut-off value of 17 mmHg measured by NCT has a 95% chance of giving an AT <21 mmHg (17).

Optic disc digitalized photographs (ODPs) were taken in both eyes of the participants with the NMFu-camera (Canon CR6-45NM) and stored on optical discs.

All the optic discs were first screened by three experienced observers separately in a masked fashion. Afterwards, all the suspect optic discs were re-examined by the three observers together and graded as normal or glaucomatous by consensus. Interobserver variability was calculated on a subset of the optic discs using kappa values. Agreement was considered to be fair for $0.4 < k < 0.59$, good for $0.6 < k < 0.74$, and excellent for $k > 0.75$ (18).

Consensus was based on nonstereoscopic assessment of C/D ratios equal to or higher than 0.7, focal or diffuse narrowing of the neuroretinal rim, asymmetry of the vertical cup to disc ratio >0.2 for comparable disc areas (measured on a superimposed reticule), vessel abnormalities, or a typical disc hemorrhage. Definition of glaucomatous optic disc damage was not based on color, cup depth, or peripapillary atrophy.

Every patient was examined with the FDP in the C-20-5 suprathreshold screening mode (Zeiss/Humphrey Systems, Dublin, CA). The FDP was considered abnormal if one test location was defective at the 5% level irrespective of the reliability of the test. For timing concerns, FDP was only performed once for every participant. The test was considered reliable if any index showed ≤1 error out of three trials.

AT measurements were performed after the completion of ODP and FDP in order to optimize the quality of the ODPs and to avoid FDP defects due to artifacts. Residents in training and experienced paramedical staff, supervised by an ophthalmologist, examined all the subjects. Patients with an AT >21 mmHg, an abnormal FDP, or an ODP graded as glaucomatous were invited for a control visit in one of the university hospitals involved in the study.

The data were analyzed using the Statview program (Statview, Berkeley, CA, 1996, version 4.5 for Macintosh). Both eyes of participants were included in the analysis. Optic disc and visual field results were matched per eye.

The sensitivity and the specificity of FDP to identify patients with an optic disc graded as glaucomatous were calculated.

Detailed critical analysis of the results of the ques-

tionnaire and control visits was beyond the scope of this study.

In consideration of patient rights and patient protection, the data accumulation was in agreement with Belgian Health Ministerial recommendations.

RESULTS

A total of 1802 (mostly white) subjects were examined during the 9 screening days. Of these 1802 subjects, 118 (6.5%) persons reporting a history of ocular hypertension and/or previous medical or surgical treatment for glaucoma were excluded from the analysis to reduce any selection bias in the interpretation of the data. Hence 1620 participants (96.4%) who could complete all the different testing (tonometry, FDP, and ODPs) were included in the analysis. A total of 940 (58%) were women and 680 (42%) were men. Their mean age was 63.2 ± 10.7 years (range 22 to 97 years).

The mean NCT IOP ± SD was 16.1 ± 3.9 mmHg (range 7 to 42 mmHg). A total of 821 participants (50.7%) had a NCT IOP >17 mmHg. Among them, 8.2% had an AT IOP >22 mmHg. In the group with glaucomatous optic disc, the mean NCT IOP ± SD was 21 ± 5.7 mmHg. A total of 16 (24.2%) persons belonging to this group had an AT IOP >22 mmHg.

Due to their excellent resolution, ODPs could be successfully interpreted in 98.1% of the cases. The kappa values for interobserver variability ranged from 0.51 to 0.54 (Tab. I). Glaucomatous optic discs were identified in 65 eyes of 59 participants (3.5%). Bilateral glaucomatous optic discs were identified in six participants. An optic disc hemorrhage could be detected in 7 eyes (0.4%) with two optic disc hemorrhages noticed in two glaucomatous optic discs. Table II summarizes the results of the grading of the ODPs.

A reliable FDP was obtained in 1474 subjects (91%). At least one defective test location was found in 1156 examinations (721 participants) (in one eye in 326 subjects and in both eyes in 395 subjects) (44.5%). The mean testing time per eye was 1.16 minutes ± 49 seconds. The sensitivity and specificity of FDP in detecting the patients with an optic disc graded as glaucomatous were 58.6% and 64.3% respectively. Table III summarizes the sensitivity and specificity of FDP in detecting the eyes with glaucomatous optic discs.

When the cut-off value was set at two contiguous defective test locations, the sensitivity and specificity were respectively 44.8% and 75.5%.

Only 184 of 770 subjects (24%) who were invited for a control visit showed up for an appointment.

TABLE I - RESULTS OF KAPPA VALUES FOR INTEROBSERVER VARIABILITY

Interobserver reproducibility	Kappa
A vs B	0.54
A vs C	0.51
B vs C	0.53

DISCUSSION

Prevalence estimates of primary open angle glaucoma in white subjects range from 1 to 2.5% in individuals over the age of 40 years to 6.6% over 75 years. About half of all patients are unaware that they have glaucoma (7, 19).

Because the detection of glaucoma in an early stage may lead to early treatment with consequent delay or prevention of further visual impairment, population mass screening is potentially very useful. Owing to the heterogeneity and the natural history of the condition, a

TABLE II - RESULTS OF GRADING OF OPTIC DISC PHOTOGRAPHS (ODP)

ODP	One eye	Both eyes	Total participants	Grading
Normal	82*	3090	3172	1561 (96.5)
Glaucoma	53	12	65	59 (3.5)

Values are n (%)
*ODPs unreadable or graded as “glaucoma” in the other eye

TABLE III - SENSITIVITY AND SPECIFICITY OF FREQUENCY DOUBLING PERIMETER (FDP) IN DETECTING EYES WITH GLAUCOMATOUS OPTIC DISCS

Eyes	Abnormal optic disc photographs (n eyes)	FDP Normal (n eyes)	Sensitivity (%)	Specificity (%)
Glaucoma	39	28	58.2*	
Normal	1117	2027		64.5*

*Optic disc photographs

combination of tonometry, functional, and structural tests for detecting neural damage in open angle glaucoma has proved to be needed for reaching adequate sensitivity and specificity.

In addition to IOP measurement, we applied two potential screening techniques consisting of the NMFu-camera and the FDT for the identification of glaucoma in a general population.

We found that the NMFu-camera could be a rapid and efficient method for glaucomatous damage mass screening. The procedure, which could be performed without pupil dilation, was well accepted by most of the participants. Interpretable ODPs were successfully obtained in a very large majority of the participants (98%). Owing to the limitations of this technique, including the acquisition of wide angle ODPs and the absence of stereoscopic view making it impossible to measure the cup-to-disc ratios accurately, more stringent criteria were considered for optic disc assessment. Therefore we defined optic disc glaucomatous damage on the basis of consensus of the three experienced ophthalmologists instead of the more commonly used two out of three agreement (20). Interobserver agreement reflected by determination of kappa values was fair.

By this method, NMFu-camera allowed detection of glaucomatous optic discs in 3.5% of subjects without any previous history of glaucoma. Optic disc hemorrhages were found in 0.4%. These results were in agreement with some previous studies that also used NMFu-camera as a glaucoma screening tool (6, 7).

Our prevalence of 3.5% newly detected glaucomatous optic discs appeared to be relatively high compared to results of population-based glaucoma surveys whose prevalences included both newly and known diagnosed glaucomatous patients (19, 21-24). This higher observed frequency most likely can partially be attributed to the relatively older age of our subjects (mean age: 63.2 years).

Because clinically discernible structural damage to the optic nerve and nerve fiber layer mostly precedes functional glaucomatous damage and detectable visual field loss in glaucoma, we used glaucomatous ODPs as the gold standard for the calculation of the sensitivity and the specificity of FDP.

On the whole, we found abnormal visual field results in 44.5% of the participants. Based on a cut-off value set at one defective test location, we found that the diagnostic power of FDP in screening strategy (59% sensitivity and 64% specificity) was appreciably lower than previously reported with similar criteria of abnormality and did not greatly alter when considering two contiguous defective test locations as cut-off values (sensitivity 44.8%; specificity 75.5%).

With sensitivities and specificities ranging between 65% and 100%, most previous studies concluded that FDP outperformed the other functional tests in discriminating between normal and glaucomatous patients and could detect glaucomatous damage earlier than conventional static perimetry (11, 15, 16, 25-33) (Tab. IV).

Unlike our study, most previous studies used the Humphrey Field Analyser in a full threshold strategy with computerized perimetry as the gold standard for glaucomatous damage for most subjects. By comparing two functional tests, the diagnostic precision of FDP will be consequently higher.

The majority of previous studies examined glaucomatous patients and glaucoma suspects, frequently excluding subjects with a visual acuity less than 20/30

TABLE IV - DIAGNOSTIC PRECISION OF FREQUENCY DOUBLING PERIMETER (FDP) FOR GOLD STANDARD TEST

Authors	Sensitivity (%)	Specificity (%)	FDP strategy	Gold standard
Burnstein (2000)	86	83	Screening	HVF/GHT
Casson (2001)	78	89	Screening	HVF
Cello (2000)	85	90	Full threshold	OD/HVF
Fabré (2000)	72.2	100	Screening	OD/HVF
Johnson (1999)	65	85	Full threshold	OD/HVF
Khong (2001)	100	69	Screening	OD/HVF
Mansberger (2002)	11	87	Screening	OD
North (2002)	70	90	Screening	OD/HVF
Paczka (2001)	84	100	Screening	OD/HVF
Patel (2000)	80	93	Screening	HVF/GHT
Quigley (1998)	91	94	Screening	HVF
Trible (2000)	39/86/100*	95	Screening	OD/HVF
Yamada (1999)	92	93	Screening	OD/HVF

*Early/moderate/severe glaucomatous damage
HVF = Humphrey visual field; GHT = Glaucoma Hemifield Test; OD = Optic disc

or early cataract formation and including normal controls. As a consequence, FDP will have a higher diagnostic precision in screening a selective compared to a general population, as was the case in our study.

Trible et al also showed that FDP had a lower sensitivity and specificity for the detection of early glaucoma (32). Whether our results reflect the same profile of early glaucomatous damage in our study population needs further confirmation.

Both the inexperience of persons at this testing situation and above all, the possible existence of nonglaucomatous associated diseases could have influenced the high proportion of false positives observed in our screening program. Conversely, the hypothesis that FDP defective tests may precede undetectable abnormalities by ODP review cannot be ruled out and would explain the low specificity obtained in our study.

Finally, an AT IOP ≥22 mmHg could be detected in 8.2% of the participants but only in 24.2% of those with a glaucomatous optic disc. Once more, this finding confirms the low sensitivity of IOP measurement in the detection of glaucoma (34).

This study has several limitations. We lacked standard automated visual field and clinical examination control, and could not repeat abnormal initial FDP tests because this screening program was applied to a large population in a reduced period of time.

Concomitantly, the absence of stereoscopic viewing of the ODPs, impeding the quantification of the cup-to-disc ratios, and the possible underlying errors in the photographic determinations, which may have an inappropriate negative impact on the FDP assessments, also limited the validity of our results. Indeed the need for consensus between experienced observers is not appropriate for a screening procedure in countries or programs in which there is a lack of ophthalmologists and of glaucoma specialists. More importantly, however, the low response rate of control visits (24%) did not allow us to draw meaningful conclusions on the accuracy of these two methods for detecting glaucoma in the examined community.

Our study population was also probably biased by self selection, with probable over-representation of subjects interested in glaucoma.

In summary, this study showed that the combined use of the NMFu-camera and the FDP is a feasible approach for an initial glaucoma mass screening. By allowing performance of optic photographs successfully in the large majority of participants in a short time, the NMFu-camera can be a useful method to screen for glaucomatous optic damage in a general population. However, this technique, which is limited by the difficulties in interpreting the optic disc photographs, cannot be easily generalized to all countries and screening programs. Using cup/disc ratios

by superimposing a reticule on a magnified image, instead of using expert opinion, is a probably more valid option for mass screening.

Although superior to IOP measurements, which were confirmed herein to be a poor tool to detect glaucomatous damage, FDP in screening strategy was not sensitive enough when the cut-off value was set at one defective test location in a large population study.

Reprint requests to:
M. Detry-Morel, MD
St Luc University Hospital
Department of Ophthalmology
Avenue Hippocrate, 10
B-1200 Brussels, Belgium
detry@ofta.ucl.ac.be

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