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Conventional perimetry, short-wavelength automated perimetry, frequency-doubling technology, and visual evoked potentials in the assessment of patients with multiple sclerosis

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PURPOSE. *To evaluate the diagnostic power of conventional, achromatic, automated perimetry (CAP), short-wavelength automated perimetry (SWAP), frequency-doubling technology (FDT) perimetry, and visual evoked potentials (VEP) in a group of patients with multiple sclerosis (MS) with or without a history of optic neuritis.*
METHODS. *Thirty eyes of 15 patients (5 male, 10 female, average age 38±7 years) with confirmed diagnosis of MS underwent CAP, SWAP (Humphrey 750–II VFA, program central 30-2, full-threshold strategy), FDT perimetry (program N-30), and pattern VEPs. Sixteen eyes (53.3%) had no history of ocular involvement and a negative ophthalmologic examination. They were matched with a control group of 10 healthy volunteers (4 male, 6 female, average age 31±10 years). The mean deviation (MD) and the pattern standard deviation (PSD) of the two groups were compared (t-test). Fourteen eyes (46.7%) had, on the contrary, a history of optic neuritis. Inside this group, the MD and the PSD of the three techniques were correlated (Spearman's rank test), in order to investigate whether any significant differences might be revealed by these techniques in pointing out the total amount of visual field damage.*
RESULTS. *When comparing MS patients without signs or symptoms of ocular involvement and a control group, no significant differences were found for CAP MD, CAP PSD, and FDT PSD. Significant differences were found, on the contrary, for SWAP MD (p=0.0014), SWAP PSD (p=0.0001), and FDT MD (p=0.0001). When considering the MD and the PSD of the three techniques in the group of MS patients who had a history of optic neuritis, a significant correlation was found only between CAP MD and SWAP MD (r=0.0057), with a tendency by SWAP to reveal a higher rate of visual field loss. The other correlations were not significant. According to predefined criteria, the group of asymptomatic subjects had abnormal CAP in 1 eye (6.25%), abnormal SWAP in 9 (56.2%), abnormal FDT in 11 (68.7%), and abnormal VEPs in 7 (43.7%). The combined use of all techniques allowed us to identify silent optic nerve impairment in 15 (93.7%) eyes.*
CONCLUSIONS. *Short-wavelength automated perimetry and FDT perimetry are two non-conventional perimetric techniques that were mainly developed for the early detection of glaucomatous damage. The results of this study demonstrate their efficacy also in detecting early visual field deficits in MS patients without clinical signs of optic neuropathy. Frequency doubling perimetry, in particular, proved to be an easy, fast, and sensitive technique in the assessment of patients with MS. Our results also suggest that subclinical visual involvement in MS can be better diagnosed using multiple (neurophysiologic and psychophysical) tests. (Eur J Ophthalmol 2005; 15: 730-8)*

KEY WORDS. *Visual field, Short-wavelength automated perimetry, Frequency-doubling technology, Visual evoked potentials, Multiple sclerosis*

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INTRODUCTION

The earliest symptoms of multiple sclerosis (MS) are often represented by ocular disorders. Optic neuritis is a well known manifestation, but it is not the only one. Ocular motility disorders with sudden diplopia may also occur. Among psychophysical techniques, conventional, achromatic, white-on-white automated perimetry (CAP) is generally utilized as the golden standard when suspecting optic neuritis. Threshold tests measuring sensitivity in the central area of the visual field (VF) are usually performed when this condition occurs. They allow identification of typical perimetric defects, i.e., central and/or paracentral scotomas, which derive from optic nerve fiber damage. Conventional automated perimetry has been the clinical standard to assess the visual field for more than 25 years. This test uses a small, white flash (200 ms) of light as the target on a dim, white background. Standard VF tests are nonspecific for any ganglion cell subpopulation, so that detection can be mediated through different groups of retinal ganglion cells at the same time. In past years, some new non-conventional perimetric techniques have been introduced, whose original goal was the early detection of glaucomatous damage. Two of them have reached a large diffusion and can be performed by commercially available instruments: short-wavelength automated perimetry (SWAP) and the more recent frequency-doubling technology (FDT) perimetry. Short-wavelength automated perimetry is a modification to CAP developed independently by Chris Johnson and Pamela Sample at the University of California, San Diego (1-3) and the University of California, Davis (4-6). This technique was standardized in 1994. It uses a 440 nm narrow band 1.8° target at 200 ms duration on a bright 100 cd/m^2 yellow background. The target locations and thresholding procedures are identical to those for CAP. With these parameters, SWAP isolates the short-wavelength sensitive cones and their connections (7-9). The test is thought to be processed by the small bistratified blue-yellow ganglion cells, which account for approximately 9% of the total population of retinal ganglion cells. Longitudinal studies have stated that SWAP losses in patients with ocular hypertension are predictive of subsequent glaucomatous VF losses detectable by CAP (3, 5). Two interesting reviews illustrating the theoretical aspects of SWAP and their potential clinical applications are available in the literature, one by Chris Johnson (10) and one by John Wild (11). FDT perimetry is a more recent technique, developed by Johnson and Samuels (12). This is a fully nonstandard perimetric technique. The hardware is different from conventional perimeters. This technique is based upon the frequency-doubling illusion that occurs when viewing a grating with a low spatial frequency and a high temporal rate. The percept is double the spatial frequency of the actual physical grating. This illusion has been attributed to a subset of the magnocellular ganglion cells (M_y cells), which are nonlinear in their response properties (13, 14). Each grating target is a square subtending about 10° in diameter. Targets are presented in one of 17 test areas located within central 20° radius of VF (program C-20) or, with a shift in fixation, the range can be extended to 30° in the nasal step area (program N-30). A modified binary search thresholding strategy is used. As a glaucoma screening device, FDT perimetry proved to be as sensitive as CAP and its specificity is excellent (15-17). The above mentioned techniques have also been tested in neuro-ophthalmologic disorders (18-22), but currently no reports are available testing the diagnostic capability of CAP, SWAP, and FDT together in MS diagnosis. The aim of this study is to evaluate the effi-

TABLE I - MEAN (SD) MEAN DEVIATION VALUES OBTAINED WITH THE THREE PERIMETRIC TECHNIQUES IN EACH OF THE THREE GROUPS

	CAP	SWAP	FDT
Control group	- 1.02 ±0.71	- 2.31 ±0.84	0.15 ±0.73
Asymptomatic MS patients	- 1.20 ±1.06	- 4.43 ±1.32	- 3.40 ±1.27
Symptomatic MS patients	- 6.85 ±3.40	-11.71 ±4.23	- 4.84 ±2.11

Values are dB. CAP = Conventional, achromatic, white-on-white automated perimetry; SWAP = Short-wavelength automated perimetry; FDT = Frequency-doubling technology; MS = Multiple sclerosis

cacy of CAP, SWAP, FDT, and VEPs in the assessment of patients with MS, especially those without history of optic neuritis.

METHODS

Fifteen MS patients (5 male, 10 female, average age 38±7 years) were recruited from the Neurological Clinic of the Department of Neurosciences, Ophthalmology and Genetics of the University of Genoa, Italy. They all had a confirmed diagnosis of MS, according to Poser's criteria (23). Both eyes of each subject were included in the study and underwent pattern VEP recording and VF testing with three different perimetric techniques: CAP, SWAP, and FDT. Sixteen eyes (53.53%) had no history of ocular involvement and a negative ophthalmologic examination. Fourteen eyes (46.7%) had a history of optic neuritis. Ten healthy, age-matched volounteers (4 male, 6 female, average age 31±10 years) were enrolled as a control group and only the right eyes were considered for statistical analysis (10 eyes). Before testing, informed consent was obtained for all study participants, who underwent a complete ophthalmologic examination at the Neuro-ophthalmology Disease Center of our department. Subjects with myopia or hyperopia >3 diopters or astigmatism >2 diopters were rejected, as well as subjects with any general (other than MS) or ocular diseases that might influence perimetric results. Each technique was repeated twice, on separate days, and only the results of the second examination were taken into consideration. Conventional automated perimetry and SWAP were performed with the same perimeter (Humphrey 750 II HFA, Humphrey Systems, Dublin, CA) and the same program (central 30-2 threshold test, full-threshold strategy, testing 76 points within the central 30°). Short-wavelength automated perimetry tests were preceded by a 10-minute period of background light adaptation by the patients. FDT perime-

TABLE II - MEAN (SD) PATTERN STANDARD DEVIATION VALUES OBTAINED WITH THE THREE PERIMETRIC TECHNIQUES IN EACH OF THE THREE GROUPS

	CAP	SWAP	FDT
Control group	1.64 ±0.35	2.61 ±0.36	3.75 ±1.44
Asymptomatic MS patients	2.20 ±0.61	3.75 ±0.70	4.41 ±0.88
Symptomatic MS patients	6.01 ±2.96	5.49 ±1.51	5.72 ±2.22

Values are dB. CAP = Conventional, achromatic, white-on-white automated perimetry; SWAP = Short-wavelength automated perimetry; FDT = Frequency-doubling technology; MS = Multiple sclerosis

TABLE III - COMPARISON (t-Test) BETWEEN ASYMPTOMATIC MS PATIENTS AND CONTROL GROUP FOR EACH INDEX (MD, PSD) OF EACH PERIMETRIC TECHNIQUE (CAP, SWAP, FDT)

Asymptomatic MS patients vs control group	Significance (t-test)
CAP MD	Not significant
SWAP MD	p=0.0014
FDT MD	p=0.0001
CAP PSD	Not significant
SWAP PSD	p=0.0001
FDT PSD	Not significant

MS = Multiple sclerosis; MD = Mean deviation; PSD = Pattern standard deviation; CAP = Conventional, achromatic, white-on-white automated perimetry; SWAP = Short-wavelength automated perimetry; FD = Frequency-doubling technology

TABLE IV - CORRELATIONS (Spearman'S Rank Test) AMONG CAP MD AND PSD AND THE ANALOGOUS INDICES OF THE OTHER TWO PERIMETRIC TECHNIQUES (SWAP AND FDT) IN THE GROUP OF SYMPTOMATIC MS PATIENTS

Groups	Significance
CAP MD vs SWAP MD	r=0.0057
CAP MD vs FDT MD	Not significant
CAP PSD vs SWAP PSD	Not significant
CAP PSD vs FDT PSD	Not significant

CAP = Conventional, achromatic, white-on-white automated perimetry; MD = Mean deviation; PSD = Pattern standard deviation; SWAP = Short-wavelength automated perimetry; FDT = Frequency-doubling technology; MS = Multiple sclerosis

try was performed with an FDT instrument (Welch Allyn, Skaneateles, NY, and Carl Zeiss Meditec, Dublin, CA) and the program N-30, full threshold strategy, was utilized. This program tests 19 locations (1 central location, 16 locations within 25°, and 2 additional nasal locations within 30°).

The t-test was utilized to compare the asymptomatic MS group and control group, taking into consideration the mean deviation (MD) and the pattern standard deviation (PSD) of the three perimetric techniques. Inside the group of the 14 eyes affected by optic neuritis, the MD and the PSD of CAP were correlated with the corresponding indices of SWAP and FDT (Spearman's rank test).

To qualify as a VF defect for CAP and SWAP, three abnormal points at the $p<0.05$ level or two adjacent points with one abnormal at the $p<0.01$ level were needed. For data using FDT perimetry, to meet criteria for a VF defect, we required two adjacent abnormal points at $p<0.05$ or one at the $p<0.01$ level. Visual evoked potentials (VEPs) recording utilized stimuli represented by checkerboard patterns with a rectangular luminance profile presented in a counter phase mode. The repetition frequency was 1 Hz (transient pattern VEPs). Two different fundamental spatial frequencies (SF) of 1 and 4 cycles per degree (cpd) were used. Stimuli were generated by a digital display generator driven by an IBM compatible PC, and displayed on a monitor subtending 14° from 1 m viewing distance. The screen mean luminance was 80 cd/m^2.

The contrast of the patterns was 70%. VEPs were differentially recorded between an occipital and midfrontal electrode using gold cup electrodes placed on the scalp along the midline sites at Oz and Fz (international 10-20 system). The ground electrode was placed in the middle of the forehead. The interelectrode impedances, checked before, during, and after each trial, were kept below 5 KΩ. Patients were asked to put their chin on a chin-rest and to refrain from blinking and eye movements during the experimental sessions. Eye movements were monitored on a separate channel. Responses with amplitude more than 250 μV were automatically rejected. A small cross in the center of the screen was used as fixation point.

Each eye was tested separately, while the other eye was covered by a translucent patch to maintain light adaptation. Patients were tested by two trials, consisting of five separate 30-second runs, for each SF.

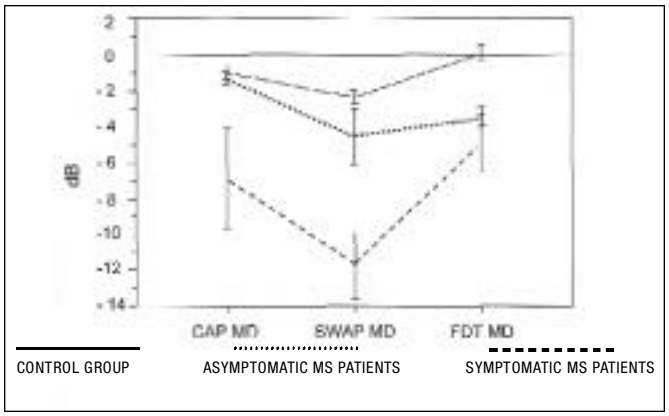

Fig 1 - *Mean deviation (MD) values obtained with the three perimetric techniques in each of the three groups (line plot)). CAP = conventional, achromatic, white-on-white automated perimetry; SWAP = short-wavelength automated perimetry; FDT = frequency-doubling technology; MS = multiple sclerosis.*

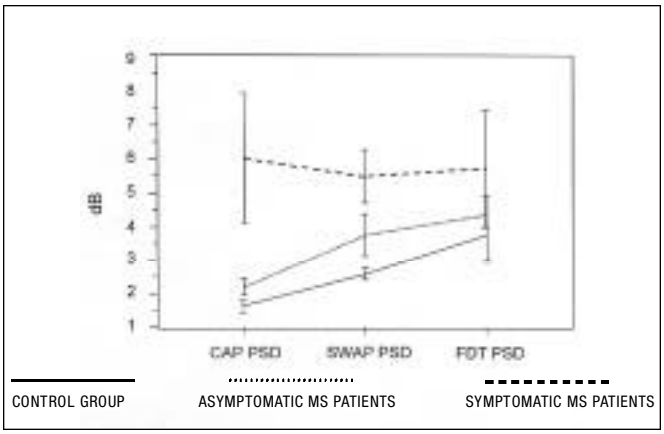

Fig. 2 - *Mean pattern standard deviation (PSD) values obtained with the three perimetric techniques in each of the three groups (line plot) CAP = conventional, achromatic, white-on-white automated perimetry; SWAP = short-wavelength automated perimetry; FDT = frequency-doubling technology; MS = multiple sclerosis.*

The responses of each run were acquired in 1000 msec epochs and stored for off-line analysis. The signals were amplified 10,000 times and bandpass filtered (1 to 100 Hz). The sampling rate was 254 Hz. We evaluated, for each SF and each eye (10 eyes in the control group, 30 eyes in the MS group), the latency values of the major positive peak (P100). Mean values and standard deviations (SD) of the electrophysiologic variables (VEPs) were computed. Limits of normal values were obtained by adding 2.5 SD to the mean latency values of control subjects, according to the recommendations of the American EEG Society.

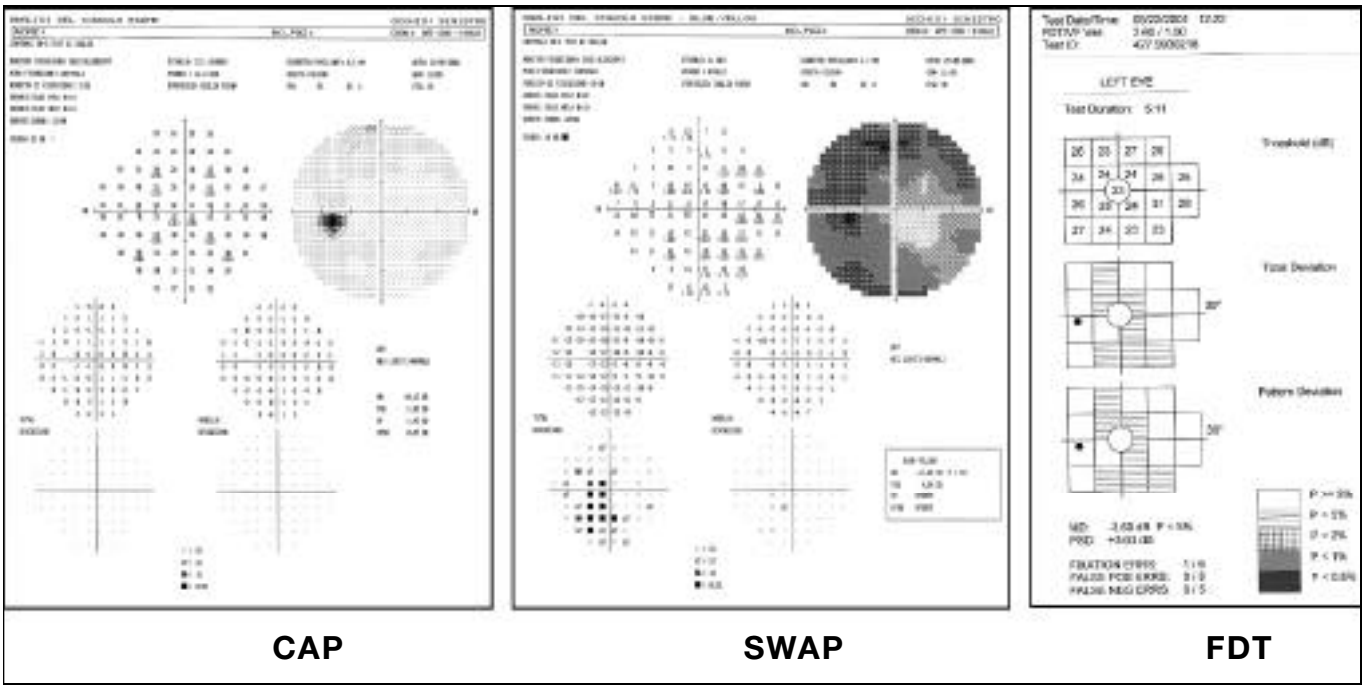

Fig. 3 - *Conventional, achromatic, white-on-white automated perimetry (CAP), short-wavelength automated perimetry (SWAP), and frequency-doubling technology (FDT) findings in the left eye of an asymptomatic multiple sclerosis patient. Conventional automated perimetry shows normal results, while the other two techniques show evident defects.*

RESULTS

There was no statistically significant difference in age between MS patients and normal controls. The mean MD and PSD values that were found in the three groups (asymptomatic MS patients, symptomatic MS patients, and normal controls) are shown in Table I and Table II. When comparing MS patients without signs or symptoms of ocular involvement and the control group, no significant differences were found for CAP MD, CAP PSD, and FDT PSD. Significant differences were found, on the contrary, for SWAP MD (p=0.0014), SWAP PSD (p=0.0001), and FDT MD (p=0.0001) (Tab. III). Figures 1 and 2 (line plots) make the interpretation of the numerical data easier. According to the above mentioned abnormality criteria, only 1 (16.2%) of the 16 asymptomatic eyes had abnormal CAP, while 9 (56.2%) had abnormal SWAP and 11 (68.7%) had abnormal FDT. In other terms, only SWAP and FDT showed significant differences between asymptomatic MS patients and normal subjects (Fig. 3). None of the 10 eyes in the control group showed abnormal results with any of the three techniques. On the other hand, the 14 symptomatic eyes had all abnormal CAP, SWAP, and FDT results. When considering the trend of the MD and the PSD of the three techniques in this group of symptomatic eyes, a significant concordance was found only between CAP MD and SWAP MD (r=0.0057) (Tab. IV), with a tendency by SWAP to reveal a higher rate of VF damage (Fig. 4). All the other correlations were not significant. Reproducible transient VEPs were obtained from all individuals, for both 1 and 4 cpd stimulation patterns. Average population latency allowed us to distinguish MS patients and controls for both SF. Significance levels were the following: $p<0.001$ for the eyes with optic neuritis and $p<0.05$ for the asymptomatic eyes.

Not surprisingly, VEP abnormalities were much more frequent (85.7% for 1 cpd and 71.4% for 4 cpd stimuli) in the symptomatic eyes of MS patients than in those without history of optic neuritis (37.5% for 1 cpd and 25.0% for 4 cpd). The use of all latency parameters (P100 latency for 1 and 4 cpd stimuli) allowed us to detect VEP abnormalities in 43.7% of the asymptomatic eyes. By comparing the sensitivity of SWAP, FDT, and VEPs in the assessment of visual dysfunction in the asymptomatic eyes, we observed that SWAP showed VF changes in three eyes that had normal FDT,

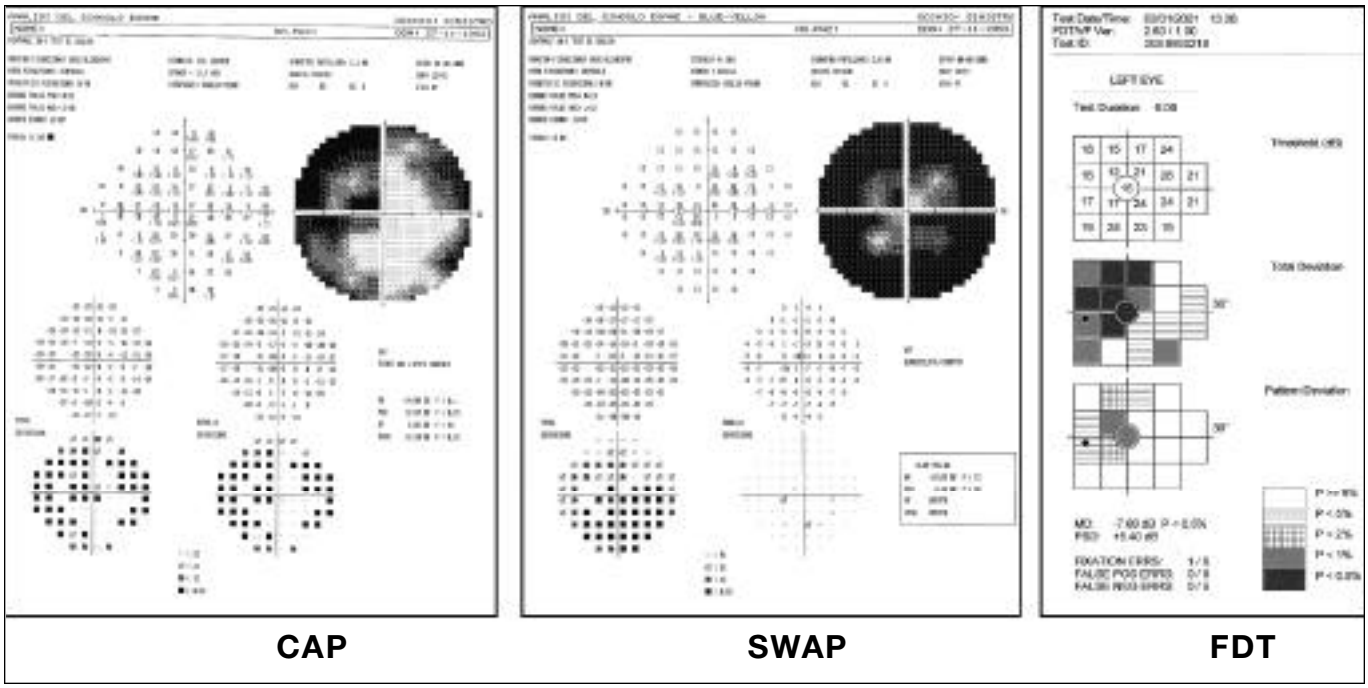

Fig. 4 - *Conventional, achromatic, white-on-white automated perimetry (CAP), short-wavelength automated perimetry (SWAP), and frequency-doubling technology (FDT) findings in the left eye of a multiple sclerosis patient with optic neuritis. All the three techniques show abnormal results. Note the higher rate of damage revealed by SWAP.*

while the opposite occurred in five eyes. VEPs were abnormal in two eyes that had normal SWAP, and in two eyes that had normal FDT. The combined use of the three techniques made it possible to detect unsuspected optic nerve impairment in 15 eyes (93.7%).

DISCUSSION

Short-wavelength automated perimetry and FDT perimetry are two non-conventional techniques for VF testing that were mainly developed for the early detection of glaucomatous damage. Thus, most investigations about the role and the usefulness of these tests are addressed to glaucoma, particularly to its early diagnosis. Few reports are available on SWAP and FDT testing in patients affected by neuro-ophthalmologic diseases. Keltner and Johnson (18, 19) evaluated the efficacy of SWAP in the assessment of patients with different neuro-ophthalmologic disorders, especially optic neuropathies: they examined by SWAP and CAP 40 patients (80 eyes). Thirteen patients (26 eyes) had recovered from optic neuritis and/or MS, 15 (30 eyes) were in various stages of treatment for pseudotumor cerebri, and 12 (24 eyes) had other miscellaneous neuro-ophthalmologic conditions. Their results were the following: among the 80 eyes tested, 38 (48%) had SWAP visual fields that were worse than CAP results; 29 (36%) showed no difference between CAP and SWAP visual fields; and 13 (16%) had CAP results that were worse than SWAP visual fields. Among the 26 eyes of patients with optic neuritis and/or MS, 15 (58%) had SWAP results that were worse than CAP visual fields. Ten (33%) of the 30 eyes with pseudotumor cerebri had SWAP results worse than CAP results, and 13 (54%) of 24 eyes with miscellaneous neuro-ophthalmologic conditions had SWAP results worse than CAP results. A case was also reported of a patient with pseudotumor cerebri and normal optic nerves who was found to have normal results on CAP testing and a right homonymous hemianopia on SWAP testing. The authors conclude that SWAP may be useful in detecting certain neuro-ophthalmologic deficits more readily than CAP testing, especially for optic neuritis and MS.

Fujimoto and Adachi-Usami (20) reported the case of a patient with MS who had normal Goldmann perimetry, minimal alterations revealed by CAP, and left superior homonymous quadrantanopia at SWAP test-

ing. The same authors (21) studied the VF with FDT in patients with recovered optic neuritis and tried to detect loss of magnocellular projecting cells (M cells) in the extrafovea. In their study, CAP showed depression toward the fovea, while FDT demonstrated general depression of sensitivity and especially midperipheral deficits.

The authors conclude that patients with resolved optic neuritis also have a loss of M-cell function in the extrafoveal area, and this finding is well documented by FDT results. Wall et al (22) studied the sensitivity and the specificity of FDT, compared to CAP, in neuro-ophthalmologic disorders.

They found that FDT has sensitivity and specificity similar to that of CAP for detecting VF defects in patients with optic neuropathies. However, they say, defects in patients with hemianopias may be missed because of the presence of scattered abnormal test locations and failure to detect test locations along the vertical meridian.

These authors also found that defects demonstrated by both tests in patients with optic neuropathies were similar in number, extent, and shape of the defects. Thus, they conclude that FDT may not be isolating the magnocellular (M) cells with nonlinear responses to stimulus contrast (My cells) in patients with VF loss. In our study, both SWAP and FDT proved to be more sensitive than CAP in detecting mild, initial VF defects, when comparing asymptomatic MS patients and control group. Moreover, SWAP showed the tendency to reveal a higher rate of VF loss, compared to CAP, when considering VF results in patients with optic neuritis, according to the findings of Keltner and Johnson.

A possible explanation is that conventional, achromatic perimetry does not isolate the function of any specific subpopulation of retinal ganglion cells. It stimulates simultaneously most of them, without any selective property. Particularly in case of mild damage, involving a little rate of ganglion cells, their impairment might be masked by the excellent function of healthy ganglion cells. Short-wavelength automated perimetry and FDT are, on the contrary, selective techniques.

The former is processed by a subgroup of parvocellular ganglion cells, the small, bistratified, blue-yellow ganglion cells, and isolates the short-wavelength sensitive cones (S-cones).

The latter is supposed to isolate a subpopulation of the magnocellular ganglion cells (My cells). These subgroups do not have a large distribution: the former represents approximately 9% and the latter 3 to 5% of the total amount of the ganglion cells.

This could explain the fact that even a mild impairment of the function of these small groups may be detected by specific, selective tests, but may not be revealed by a non-specific test, like CAP is. Because these ganglion cell systems have fewer fibers, they may have less redundancy. A lower redundancy makes VF loss become manifest earlier.

On the other hand, the lack of agreement between SWAP and FDT findings in the group of symptomatic eyes is not surprising, because they explore, as we have just underlined, different functions. Referring to previous studies (24, 25), the abnormality rate of VEPs in asymptomatic eyes of our MS patients was comparable. However, VEPs were slightly less sensitive than SWAP and FDT. We speculate that this is likely due to the fact that VEPs explore the global function of optic nerve fibers, while SWAP and FDT, as repeatedly highlighted, have selective properties.

This finding is in agreement with the observations of other authors, who have found that even static perimetry can be more sensitive than VEPs for detecting lesions in the visual pathway (26, 27).

Unfortunately, psychophysical techniques are affected by some disadvantages: among the greatest shortcomings is their high test-retest variability, depending on a number of factors, including fatigue, learning effect, thresholds status (heavily damaged visual fields usually show higher variability), attention, and testing strategies.

The recent introduction of fast strategies for CAP and SWAP may have contributed to slightly reduce variability due to fatigue and attention degree. FDT, on the other hand, is very quick to perform (about 5 minutes per eye). Variability, however, is still the major problem for psychophysical techniques. In addition, our results showed that VEPs and perimetric techniques are not correlated in the detection of visual pathway abnormalities and that each test is capable of independently detecting optic nerve dysfunction in MS patients. This supports the view that neurophysiologic and psychophysical techniques provide manifold and complementary information, which are not directly comparable.

CONCLUSIONS

Short-wavelength automated perimetry and FDT perimetry are two non-conventional perimetric techniques that were mainly developed for the early detection of glaucomatous damage. The results of this study demonstrate their efficacy also for the assessment of patients with neuro-ophthalmologic disorders, such as subclinical optic nerve involvement in patients with MS. FDT perimetry, in particular, proved to be an easy, fast, and sensitive technique in the assessment of these patients.

The test is well accepted by the patients and is very fast (about 5 to 6 minutes per eye). Its utilization could represent the gold standard, at least for screening purposes, when utilizing psychophysical techniques in patients with MS. Short-wavelength automated perimetry is itself a sensitive technique, but is affected by some disadvantages: it is time consuming (at least some minutes for adaptation to the yellow bright screen are required for obtaining reliable results); moreover, the fatigue effect is likely higher, due to longer total procedure duration (this disadvantage, however, will be soon avoided thanks to the near at hand availability of the fast strategies). Although we are greatly encouraged by the new, non-conventional VF techniques for investigating early ocular disorders in MS, further studies on a large scale are needed before considering their implication in diagnosis and treatment. Our results also suggest that subclinical visual involvement in MS can be better diagnosed using multiple (neurophysiologic and psychophysical) tests.

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