DIAGNOSTIC ABILITY OF STRATUS OPTICAL COHERENCE TOMOGRAPHY (OCT) IN PRE-PERIMETRIC GLAUCOMA DIAGNOSIS

CAPACIDAD DIAGNÓSTICA DEL STRATUS OCT PARA DETECTAR GLAUCOMAS PRE-PERIMÉTRICOS

MAYORAL F[1], POLO V[2], FERRERAS A[2], LARROSA JM[2], PUEYO V[1], HONRUBIA F[2]

ABSTRACT

Objective: To compare retinal nerve fiber layer (RNFL) measurements performed with Stratus OCT 3000 in normal, ocular hypertensive, pre-perimetric and glaucomatous eyes.
Methods: 98 normal subjects, 156 ocular hypertensives with short-wavelength automated perimetry (SWAP), 21 ocular hypertensives with altered SWAP (pre-perimetric glaucoma) and 66 glaucomatous eyes were included in the study. Diagnostic groups were classified based on intraocular pressure, optic nerve head appearance, achromatic automatic perimetry and SWAP. RNFL parameters were obtained using a Stratus OCT 3000 (Humphrey Zeiss instruments). RNFL measurements were compared among the groups.
Results: RNFL average thickness, superior, inferior and nasal quadrant thickness, and each 12 clock-hour positions except for H9, H10 and H11 showed significant differences between glaucomatous and pre-perimetric glaucoma eyes. RNFL average thickness, inferior quadrant and H10 clock-hour position showed significant differences between normal and ocular hypertensive subjects. Pre-perimetric glaucomas and ocular hypertensives showed differences in H11 clock-hour position exclusively.

RESUMEN

Objetivo: Comparar los espesores de la capa de fibras nerviosas de la retina (CFNR) medidos mediante tomografía óptica de coherencia (OCT) en sujetos normales, hipertensos oculares con perimetría automatizada de longitud de onda corta (PALOC) normal, hipertensos oculares con PALOC alterado y glaucomatosos.
Métodos: Se estudiaron 98 sujetos normales, 156 hipertensos oculares con PALOC normal, 21 hipertensos oculares con PALOC alterada y 66 glaucomatosos. Los grupos se establecieron en función de la presión intraocular, morfología papilar, perimetría automatizada convencional y la PALOC. La exploración de la CFNR se realizó mediante OCT (Stratus OCT 3000; Humphrey Zeiss instruments). Se compararon los espesores de la CFNR entre los grupos de estudio.
Resultados: El grupo de glaucoma mostró diferencias significativas con los sujetos hipertensos oculares con PALOC alterado, en el global de la CFNR, en todos los cuadrantes excepto el temporal y en todas posiciones horarias, excepto en H9, H10, H11. Entre sujetos controles y los individuos hipertensos con PALOC normal, se encontraron diferencias significativas en el espesor global de la CFNR,

Received: 14/2/06. Accepted: 21/9/06.
Miguel Servet University Hospital. Zaragoza. Spain.
[1] Graduate in Medicine.
[2] Ph.D. in Medicine.

Correspondence:
Francesca Mayoral
Hospital Universitario Miguel Servet de Zaragoza
P.º Isabel la Católica, 1-3
50009 Zaragoza
Spain
E-mail: xescamm@hotmail.com

Conclusion: RNFL measurements performed using Stratus OCT showed differences between the study groups. OCT may be as useful as SWAP in early glaucoma diagnosis *(Arch Soc Esp Oftalmol 2006; 81: 537-544).*

Key words: Optical coherence tomography, retinal nerve fiber layer, glaucoma, short- wavelength automated perimetry, pre-perimetric glaucoma.

cuadrante inferior y el segmento horario H10. Los subgrupos de hipertensos (con o sin alteración de la PALOC), mostraron diferencias significativas sólo en el segmento horario H11.
Conclusiones: El estudio cuantitativo de la CFNR mediante OCT ha mostrado diferencias entre los grupos estudiados. La OCT puede ser tan sensible como la PALOC, y la interpretación conjunta de ambas, proporciona una valiosa información en el diagnóstico precoz del glaucoma.

Palabras clave: Tomografía óptica de coherencia, capa de fibras nerviosas de la retina, glaucoma, perimetría automatizada de longitud de onda corta, glaucoma pre-perimétrico.

INTRODUCTION

In open-angle primary glaucoma, there is a gradual loss of axons at the level of the retina's ganglion cells, which determines in turn a series of structural changes in the optic nerve head as well as alterations of the visual field (1-3).

It is one of the main causes for irreversible legal blindness worldwide, and specifically the second cause for loss of vision in patients over 40 years of age in the West (1). Efforts to prevent the gradual and silent decrease of the visual field focused on early diagnosis, which allowed for an adequate follow-up and treatment of the disease.

New digital image analysis techniques allow detecting glaucoma-related structural alterations taking place during the initial stages of glaucoma (4-8).

In this sense, low-coherence optic tomography (OCT) is a new method to assess RNFL as well as the papilla. The procedure is quick, simple and replicable (9-11). Preliminary studies performed with this technique proved its usefulness in clinical practice in the detection of RNFL loss or reduction taking place in glaucoma (7,12-14).

The purpose of the present study is to assess and compare RNFL thickness analyzed by means of an OCT in normal individuals, ocular hypertensive patients with normal short-wavelength automated perimetry (SWAP), ocular hypertensive patients with altered SWAP, and glaucoma patients in order to determine which parameters of the test yielded improved diagnostics for glaucoma-related damage.

SUBJECTS, MATERIAL AND METHODOLOGY

Ninety-eight (98) normal individuals, 285 ocular hypertensive patients, and 66 glaucoma patients were prospectively and consecutively selected from the ophthalmology services in our hospital. Out of 285 ocular hypertensive patients, the results of SWAP studies were reliable in 177 patients who made up the sample population used in our analysis. Of these, 156 yielded a normal SWAP, whereas 21 yielded an altered SWAP.

Inclusion criteria were: age between 30 and 60 years; visual acuity above or equal to 8/10; refraction defects below 5 spherical diopters and astigmatism lower than 3 diopters; transparent ocular media.

Subjects with a history of ocular trauma or surgery, systemic diseases with ophthalmic impact or inability to perform any of the tests included in the study's protocol were excluded.

All subjects underwent full ophthalmic examination, including biomicroscopy with slit lamp, measurement of intraocular pressure (IOP) by means of Goldmann's applanation tonometry, central corneal thickness pachymetry, stereopapillary photographs, conventional automated perimetry (AP), SWAP, and assessment of retinal nerve fiber layer thickness via OCT.

Informed consent was required of all the subjects included, and the study followed the guidelines contained in the Helsinki declaration. Only one eye per patient was included. In case both eyes were eligible, one was chosen at random.

APs were performed using a Humphrey Field Analyzer perimeter Model 745 (standard 24-2 SITA strategy). Perimetric defects were defined by the presence of at least 3 altered points with less than 5% probability or at least 2 altered points with less than 1% probability (15); and/or global indexes: Standard Deviation (SD) or Corrected Pattern Standard Deviation (CPSD) with less than 2% probability; and/or glaucoma hemifield test outside normal limits. A minimum of two perimetries were performed to decrease the learning effect; if any of the two failed to fulfill the validity criteria defined by the perimeter itself (false positives, false negatives and loss of fixation), the test was repeated.

SWAPs were performed using a Humphrey 745 perimeter and the 24-2 algorithm for threshold detection. Perimetric defects were defined based on: the presence of a group with at least 4 altered points with a probability level below 5% or at least 3 altered points with less than 1% probability (16).

Assessment of the optic nerve head was performed by means of subjective assessment of stereo photographs. Glaucoma-related optic neuropathy was defined by the presence of a significant thinning of the neuroretinal ring, and that of papillary notches and/or hemorrhages (17).

Healthy subjects were defined by IOPs lower than 21 Hg mm, optic nerve of regular appearance and the absence of AP defects. Ocular hypertensive patients with normal SWAPs were defined by IOPs greater than or equal to 21 Hg mm, normal optic disk appearance, AP and SWAP. Ocular hypertensive patients with altered SWAPs were defined by IOPs greater than or equal to 21 Hg mm, normal optic disk appearance and AP, and altered SWAP. Glaucoma subjects were defined by IOPs greater than or equal to 21 Hg mm, glaucoma-related optic neuropathy and altered AP.

Optical Coherence Tomography —OCT 3000—: the assessment of retinal nerve fiber layer thickness was performed using a commercial release of the OCT 3000 (Humphrey-Zeiss Instruments).

After triggering pupil dilation with 1% tropicamide, 3 circular optical scannings (which scan RNLF thickness) of 3.4 mm diameter focused on the optic disk.

Three analyses were performed on each of the eyes examined: average thickness of retinal nerve fiber layer; thickness of the fiber layer found on the 4 retinal quadrants (upper: 46-135 degrees, nasal: 136-225 degrees, lower: 226-315 degrees; and temporal: 316-345 degrees); and thickness of the fiber layer in each hour segment (30 degrees per each hour position).

Statistical analysis: ANOVA tests were used to compare all groups. To illustrate the significant differences found among groups, a Scheffé test was used. Significant differences were determined by a significance level $p<.05$.

In order to assess diagnostics improvement of OCT parameters, ROC curves (Receiver Operating Characteristics) were used. Estimates were provided for both the areas found below the curve and sensitivity values for specificity levels predetermined at 85% and 95% for each of the variables analyzed.

FINDINGS

341 eyes were included in the study (98 controls, 156 ocular hypertensive patients with normal SWAPs, 21 ocular hypertensive patients with altered SWAPs and 66 glaucoma patients). Demographic data available for these groups are shown in Table I. No statistically significant differences ($p<0.05$) were found in relation to age. AP's SD and CPSD, an improved corrected visual acuity, and central corneal pachymetry revealed differences between glaucoma patients and the remaining 3 groups. Significant differences were also found between glaucoma and control subjects regarding total RNFL thickness (Table II).

Glaucoma varied in RNFL thickness with respect to hypertensive patients (both subgroups) in all parameters except for H10, H11 and temporal quadrant where the only differences were observed with respect to hypertensive patients with normal SWAPs and in H9, where no differences were found between glaucoma and hypertensive patients.

Among control subjects and hypertensive patients with normal SWAP, significant differences were appreciated in global RNFL thickness, lower quadrants, and H10 hour segment, whereas when compared to OHTs with altered SWAPs, differences were found in global thickness on the upper, lower and temporal quadrants, as well as on H7, H10 and H11 hour segments.

Among hypertensive patients with normal and altered SWAPs, differences were only observed during H11 segment hour.

Table I. Clinical Characteristics of Study Groups

	Normal (n=98)		OHT with SWA normal (n=156)		OHT, SWAP Altered (n=21)		Glaucoma (n=66)	
	Average ± SD	P	Average ± SD	P	Average ± SD	P	Average ± SD	P
Age	59.6 ± 9.19		58.61 ± 9.15		61.43 ± 7.03		63.79 ± 9.65	
Corrected V.A.	0.90 ± 0.1	G	0.93 ± 0.09	G	0.91 ± 0.14	G	0,82 ± 0.13	N, H , P
Basal IOP	14.7± 2.23	H, P, G	23.12 ± 3.10	N	23.00 ± 2.77	N	24.22 ± 4.05	N
E/D Quotient	0.26 ±0.16	H, P, G	0.45 ± 0.10	N, G	0.50 ± 0.21	N, G	0.77 ± 0.23	N, H, P
AP's SD	-0.49 ± 1.42	G	-0.20 ± 1.13	G	-0.76 ± 1.31	G	-7.50 ± 6.25	N, H, P
AP's CPSD	1.21 ± 0.94	G	0.87 ± 0.73	G	0.94 ± 0.66	G	5.55 ± 3.93	N, H, P
Pachymeter	565.6 ± 29.34	G	572.21 ± 38.04	G	572.57 ± 50.98	G	540.02 ± 36.76	N, H, P

N: differences with respect to the normal group; H: differences with respect to OHT with normal SWAP; P: differences with respect to OHT with altered SWAP; G: differences with respect to glaucoma. OHT: Ocular Hypertensive patient; SWAP: short-wavelength automated perimetry; SD: Standard Deviation; V.A.: Visual Acuity; IOP: Intra-Ocular Pressure; E/D: Excavation/Disk expressed in deciles; AD: Average Deviation; CPSD: Corrected Pattern Standard Deviation; AP: conventional Automated Perimetry.

The best OCT parameters to distinguish normal and perimetric glaucoma (ocular hypertensive patients with altered SWAPs) were H7, H10 and H11 hour segments, the upper and lower quadrants and RNFL global thickness (Table III), which exhibited areas underneath the curve greater than 0.65 (fig. 1). Four parameters showed sensitivity values greater than 20% for a specificity level predetermined at 90%. Setting specificity at 85% for sensitivity values of different RNFL thickness increased, although only global RNFL thickness and the upper quadrant yielded values above 40%.

DISCUSSION

Achromatic automated perimetry has been used as the reference test from a functional perspective and in order to perform diagnosis and follow-up of glaucoma. Nevertheless, in the past few years other techniques have emerged that seem to have greater

Table II. Global RNFL Thickness per Quadrants and Hour Segments per Groups

THICKNESS RNFL	Group Normal			OHT with SWAP Normal			OHT with SWAP Altered			Group Glaucomas		
	Average	SD	P	Average	SD	P	Average	SD	P	Average	SD	P
H1 (RE hours)	109.31	26.44	G	109.40	23.37	G	103.48	30.76	G	71.96	23.08	N,H,P
H2 (RE hours)	94.20	25.99	G	90.88	22.36	G	93.24	34.95	G	64.79	17.86	N,H,P
H3 (RE hours)	69.20	20.71	G	63.96	16.32	G	67.57	20.59	G	46.58	13.64	N,H,P
H4 (RE hours)	80.47	23.95	G	76.32	19.59	G	77.90	19.53	G	54.63	14.46	N,H,P
H5 (RE hours)	117.42	28.23	G	108.73	22.53	G	116.00	34.27	G	75.58	22.83	N,H,P
H6 (RE hours)	150.11	29.76	G	139.58	23.15	G	139.29	34.87	G	94.33	27.05	N,H,P
H7 (RE hours)	143.76	23.83	P,G	134.53	21.33	G	125.24	23.80	N,G	90.71	31.75	N,H,P
H8 (RE hours)	73.62	18.05	G	69.64	16.23	G	69.33	18.59	G	52.88	17.38	N,H,P
H9 (RE hours)	55.20	9.87	G	51,36	11,26		49.29	10.85		46.42	12.89	N
H10 (RE hours)	87.45	18.39	H,P,G	77.73	16.50	N,G	67.62	16.07	N	61.96	20.12	N,H
H11 (RE hours)	133.45	21.93	P,G	125.54	23.64	P,G	104.67	27.53	N,H	91.13	24.73	N,H
H12 (RE hours)	125.87	28.08	G	121.20	25.86	G	114.00	34.30	G	84.83	34.16	N,H,P
Upper	122.89	18.64	P,G	117.99	20.44	G	107.14	26.87	N, G	82.63	22.77	N,H,P
Lower	137.07	17.80	H,P,G	127.76	16.44	N,G	127.33	23.36	N,G	86.83	22.95	N,H,P
Nasal	81.64	20.66	G	77.47	16.90	G	79.67	21.88	G	54.92	13.55	N,H,P
Temporal	71.64	12.87	P,G	65.94	12.35	G	61.62	11.83	N	54.25	13.06	N,H
Global RNFL	103.32	10.86	H,P,G	97.54	11.45	N,G	93.96	16.38	N,G	69.65	13.72	N,H,P

N: differences with respect to the normal group; H: differences with respect to OHT with normal SWAP; P: differences with respect to OHT with altered SWAP; G: differences with respect to glaucoma. RTFL: Retinal Nerve Fiber Layer; OHT: Ocular Hypertensive patients; SWAP: Short Wavelength Automated Perimetry; SD: Standard Deviation; P: significant differences (p<0,05); RE hours: clockwise for the right eye.

Table III. Sensitivity to Different OCT Structural Parameters (RNFL Thickness) at a Predetermined Specificity Level of 85% and 90% in Normal and Hipertensive Eyes with Altered SWAPs

RNFL THICKNESS	ROC Area	Normal and OHT with altered SWAP Specif. 90% Value microns	% sens	Specif. 85% Value microns	% sens
H1 (RE hours)	.602	77	25%	79	27.5%
H2 (RE hours)	.565	63	22.5%	70	30%
H3 (RE hours)	.555	43	17.5%	51	37.5%
H4 (RE hours)	.558	52	17.5%	58	25%
H5 (RE hours)	.593	81	17.5%	86	30%
H6 (RE hours)	.599	108	25%	111	30%
H7 (RE hours)	.662	108	30%	113	32.5%
H8 (RE hours)	.558	52	20%	53	20%
H9 (RE hours)	.618	40	20%	43	25%
H10 (RE hours)	.676	62	27%	64	30%
H11 (RE hours)	.693	96	27.5%	102	30%
H12 (RE hours)	.640	83	22.5%	91	35%
Upper	.672	94	40%	96	40%
Lower	.655	107	27.5%	110	27.5%
Nasal	,564	57	22.5%	59	25%
Temporal	.621	54	30%	55	30%
Global thickness	.725	82	42.8%	87	52.3%

OHT: Ocular Hypertensive patients; SWAP: short wavelength automated perimetry; RNFL: Retinal Nerve Fiber Layer; Specif: Specificity; sens: sensitivity; RE hours: clockwise for the right eye.

sensitivity in early detection of glaucoma-related damages, such as short wavelength automated perimetry (SWAP) (18,19) which measures the activity of neuronal elements sensitive to short wavelength stimuli altered during the initial stages of the disease (20).

Furthermore, new techniques involving digital analysis have arisen, for example OCTs aimed at obtaining more accurate quantitative data related to the optic nerve and RNFL and thus less dependent on researchers subjective interpretation in order to increase their replicability (4,6).

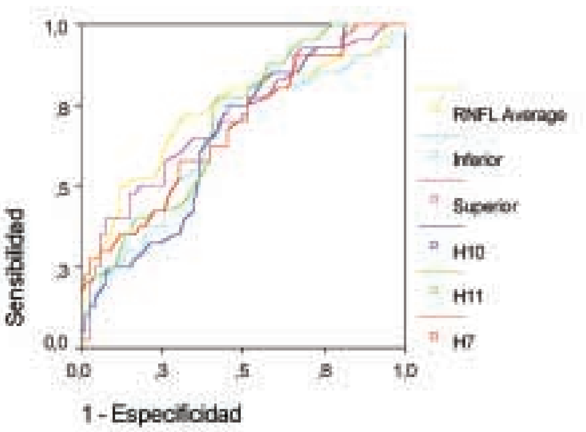

Fig. 1: ROC Curve for RNFL thickness with areas below the curve ≥ 0,60 in ocular hypertensive patients with altered SWAP.

Preliminary studies have proven the ability of OCTs to detect differences in RNFL thickness in healthy and glaucoma eyes (4,7,13,21-23). Our study also revealed this ability, as well as that of several OCT parameters, to distinguish normal and ocular hypertensive subjects, specially those hypertensive patients who begin by exhibiting visual field defects when assessed with SWAP. In these cases of early glaucoma, parameters performing best in terms of diagnosis correspond to RNFL thickness and thickness around the upper and lower poles. Most nerve fibers concentrate along this vertical axis of the optic nerve head, and thus it is easier to detect their loss around this area (increased relation excavation/vertical disc).

Using OCT-2, Mok et al (24) found differences between normal and perimetric glaucoma subjects defined by SWAP in terms of RNFL thickness on the lower-temporal and upper-temporal segments.

Many studies have established a relation between the RNFL thinning taking place in glaucoma and assessed by OCT, and areas of less visual field sensitivity and focal perimetric defects on the conventional automated perimetry (AP) (25-28).

Polo et al (19) described the relationship between changes in RNFL thickness (RNFL assessment by means of monochrome photographies) and alterations of the SWAP visual field in ocular hypertensive patients. Nonetheless, photographic analysis is a good method for assessing RNFL, requiring a transparent optical medium in order to obtain good photographies and staff trained to interpret the images adequately.

Global RNFL thickness showed a sensitivity greater than 40% with 85% and 90% specificities when detecting perimetric glaucoma. These results should not be underestimated, since that 40% would have escaped to the diagnosis yielded by a conventional automated perimetry.

Global assessment of the results obtained from conventional APs, SWAPs and OCTs boosts diagnostic performance of these tests. Readings into the data yielded should be individualized and assessed together with clinical examinations.

Quantitative studies of RNFL using OCTs have shown the differences between these particular groups. Optic Coherence Tomography may be prove to be as sensitive as SWAP in the early detection of glaucoma before the appearance of alterations through a conventional AP.

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