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Impaired neural conduction in crossed visual pathways in patients with ocular hypertension

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PURPOSE. *To evaluate the neural conduction along crossed and uncrossed visual pathways in patients with ocular hypertension (OHT).*
METHODS. *Fifteen patients (mean age 59.1 ± 6.8 years) with OHT (IOP>22 mmHg, Humphrey 24-2 with mean deviation [MD]>–2 dB) were enrolled. They were compared to 15 age-matched controls. In OHT patients and control subjects, visual evoked potentials (VEPs) were recorded using full-field checkerboard patterns (the check subtended 15' of visual arc; contrast 80%) reversed at 2 Hz. VEP responses were simultaneously recorded in the homolateral visual cortex (HC) and in the contralateral visual cortex (CC), with respect to the stimulated eye.*
RESULTS. *In OHT patients, VEP P100 implicit times observed in HC and CC were both significantly delayed (analysis of variance, p<0.01) when compared to those of controls, and, in particular, longer in CC than in HC. The interhemispheric differences (ID: P100 implicit time in HC – P100 implicit time in CC) were significantly higher in OHT patients than controls (–3.16±1.80 msec and 1.16 ± 1.04 msec, respectively, p=0.001). In OHT patients we observed an MD hemifield difference (difference between nasal and temporal MD values) higher than in controls (–0.82±0.80 dB and 0.04±1.03 dB, respectively, p<0.01) and significantly correlated with the ID (r: 0.836, p<0.001).*
CONCLUSIONS. *The observed asymmetry in the bioelectrical cortical responses and in the visual hemifield parameters suggests that crossed visual pathways could be impaired earlier than uncrossed visual pathways in OHT patients. (Eur J Ophthalmol 2004; 14: 486-94)*

KEY WORDS. *Ocular hypertension, Visual evoked potentials, Visual field, Visual pathways*

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INTRODUCTION

Electrophysiologic evaluations, performed by pattern electroretinogram (PERG) and visual evoked potential (VEP) recordings, suggest that patients with ocular hypertension (OHT) present an early retinal dysfunction and a delay in neural conduction along the visual pathways (1, 2).

In OHT patients, it was found that the retinal dysfunction is associated with differences in nerve fiber layer thickness (the thinner the layer, the worse the visual function) (3).

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In our previous studies (1-3), and in other studies assessing VEPs in OHT patients (4-7), VEP responses were derived by means of a single electrode placed over both occipital cortices (8), and therefore did not allow the separate evaluation of neural conduction along crossed and uncrossed visual pathways.

In a recent study performed by our group (9), in order to have an index of the relative contribution of the crossed and uncrossed pathways, we compared VEPs recorded from the right (O2) (10) and left (O1) (10) cortices in response to full-field monocular stimulation. Under these conditions, VEPs recorded from the ipsilateral visual cortex to the stimulated eye should represent the activity originating from the temporal hemiretina, while the activity originating from the nasal hemiretina should be recorded over the contralateral cortex (9, 11).

Our results revealed that patients with glaucoma presented an asymmetry in the VEP responses obtained in the homolateral and contralateral cortices to the stimulated eye. It was interesting that in the early stage of glaucoma (corrected pattern standard deviation [CPSD] values of the Humphrey 24-2 perimetry, between 2 and 4 dB) the delay in neural conduction was prevalent when VEPs were recorded in the contralateral cortex to the stimulated eye. This finding could indicate that the crossed visual pathways might be more impaired than the uncrossed visual pathways in the early stages of glaucoma (9).

On the basis of this recent evidence (9), the aim of our work was to evaluate whether OHT patients show a symmetric neural conduction along crossed and uncrossed visual pathways as observed in normal subjects (9) or an asymmetric neural conduction along crossed and uncrossed visual pathways as found in the early stages of glaucoma.

PATIENTS AND METHODS

Fifteen eyes of 15 consecutive patients (mean age 59.1±6.8 years) with OHT were recruited. Each patient had significant experience with automatic perimetry (at least six previous reliable examinations within the previous year). Enrollment was conducted according to the following inclusion criteria.

• Intraocular pressure (IOP) >22 mmHg and <28 mm Hg (average of the two highest readings of the daily curve, from 8:00 AM to 6:00 PM, six independent readings, one every 2 hours).

• Normal automatic full threshold perimetry (24/2 Humphrey, mean defect, CPSD, and glaucoma hemifield test within the normal range of the database of the Humphrey software; fixation losses, false positive rate, and false negative rate each <20%) (see below).

• Best-corrected visual acuity of 20/20 or better

• None of the following papillary signs on conventional color stereoslides: rim notch(es), peripapillary splinter hemorrhages, increased vertical-to-horizontal cup/disk ratio, cup/disk asymmetry between the two eyes <0.2.

• Mean refractive error (when present) between –0.50 and +0.50 spherical equivalent.

• No previous history of diabetes, optic neuritis, or any disease involving the anterior visual pathways

• Pupil diameter ≥3 mm.

They were compared to 15 age-matched controls. Upon recruitment, each patient gave informed consent to the procedures. The research followed the tenets of the Declaration of Helsinki.

Visual field analysis

Static perimetry (Humphrey Field Analyzer [HFA] model 740, 24/2 achromatic full threshold strategy, StatPac-2, showing fixation losses, false positive rate, and false negative rate each less than 20%; central 24-2 threshold test) was performed twice in the month preceding the VEP examination (see below), and the second examination was considered for the statistical analysis. The main indices of the Humphrey perimetry are mean deviation (MD) and CPSD. The MD establishes the mean of the defect obtained in all tested points, considers the increasing scatter of sensitivity values according to eccentricity with respect to the data obtained in normal subjects, and therefore may represent an index of the severity of the global damage. CPSD indicates the homogeneity of defect distribution in the visual field and therefore gives information about localized damage (12).

In the visual field analysis of OHT patients and controls, MD and CPSD were both considered. In addition, both MD and CPSD were separately assessed in the temporal and nasal hemifield through the calculation of the mean of 24 single values observed in

the temporal hemifield and the mean of 28 single values observed in the nasal hemifield.

VEP recordings

In OHT and control subjects, VEP recordings were performed using the following method.

The subjects under examination were seated in a semi-dark, acoustically isolated room in front of a display, surrounded by a uniform field of luminance of 5 cd/m^2. Visual stimuli were full field checkerboard patterns (the check subtended 15$^-$ of visual arc; contrast 80%, mean luminance 110 cd/m^2) generated on a television monitor subtending 18°, and reversed in contrast at the rate of two reversals/s. The refraction of all subjects was corrected for viewing distance and mydriatic or miotic drugs were never used. Cup shaped electrodes of Ag/AgCl were fixed with collodion in the following positions: active electrode in O1 (left occipital cortex) and O2 (right occipital cortex) (10), reference electrode in Fpz; ground in the left arm. The interelectrode resistance was kept below 3KOhms. The bioelectrical signal was amplified (gain 20000), filtered (bandpass 1–100 Hz), and averaged (200 events free from artifacts were averaged for every trial) by BM 6000. Analysis time was 250 msec. Stimulation was monocular after occlusion of the other eye and the bioelectrical cortical responses were simultaneously recorded in the homolateral visual cortex (HC) and in the contralateral visual cortex (CC), with respect to the stimulated eye.

The transient VEP response is characterized by a number of waves with three subsequent peaks, of negative, positive, negative polarity: N75, P100, N145. For all VEPs, implicit time and peak-to-peak amplitude of each of the averaged waves were measured directly on the displayed records by means of a pair of cursors.

In each tested subject, the signal-to-noise ratio (SNR) of the VEP response was assessed by measuring a noise response while the subject fixated at an unmodulated field of the same mean luminance as the stimulus. A noise record of 200 events was obtained. The noise amplitudes were measured in a temporal window corresponding to that at which the response component of interest (i.e., VEP P100) was expected to peak. SNRs for this component were determined by dividing the amplitude of the component by the noise in the corresponding temporal window. In all subjects and patients, we accepted VEP responses with signal-to-noise ratio >2.

Statistics

The differences between OHT patients and controls were evaluated by one-way analysis of variance (ANOVA). The correlation between visual field and electrophysiologic parameters was evaluated by Pearson test. In all statistical tests a p less than 0.01 was considered significant.

RESULTS

The electrophysiologic and visual field data of our OHT patients are presented in Table I.

Examples of VEP recordings in one control subject and in one OHT patient and relative hemi-visual field analysis are reported in Figure 1. The mean values of VEP P100 implicit time assessed in OHT patients and controls are presented in Table II.

In OHT patients, the VEP P100 implicit times observed in HC and CC were both significantly ($p<0.01$) delayed when compared to those of controls.

In all OHT patients we found an asymmetry in VEP responses in HC and CC, with VEP P100 implicit times longer in CC than in HC. The interhemispheric differences (ID: P100 implicit time in HC – P100 implicit time in CC) were significantly higher in OHT patients than controls (–3.16±1.80 msec and 1.16±1.04 msec, respectively, $p=0.001$).

Six consecutive HFA examinations were performed in OHT patients, and the last two were carried out in the month preceding the VEP examination (see Methods). A small intraindividual variability (<0.2 dB) was found in each OHT patient and, in all examinations, an MD >–2 dB and a CPSD <2 dB were observed. No changes in MD and CPSD hemifield differences (differences between nasal and temporal MD and CPSD values) were observed during the six HFA examinations of each OHT patient, and thus three OHT patients (OHT1, OHT2, OHT 4) always showed a positive difference (MD nasal > MD temporal), while the other 12 OHT patients always showed a negative difference (MD nasal < MD temporal). Individual MD hemifield differences are presented in Figure 2. In OHT pa-

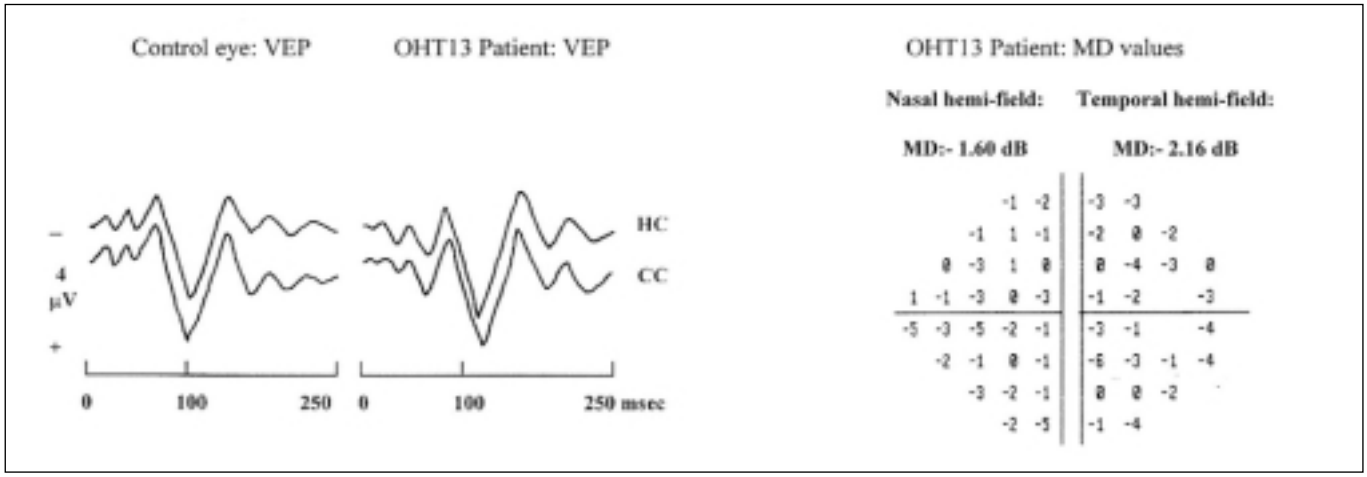

Fig. 1 - *Example of visual evoked potential (VEP) recordings performed in one control eye and in one ocular hypertension (OHT) eye (OHT13 patient, right eye, intraocular pressure: 27 mmHg) and Humphrey 24/2 perimetry (mean deviation [MD] values) observed in patient OHT13 (MD: –1.89 dB). HC = Homolateral cortex to the stimulated eye; CC = Contralateral cortex to the stimulated eye. The OHT eye shows delayed VEP responses in both HC and CC with respect to the control eye. The VEP P100 implicit time recorded in CC (119.1 msec) is longer than that recorded in HC (114.4 msec) indicating a neural conduction prevalently delayed in crossed visual pathways.*

tients, the MD hemifield difference (difference between nasal and temporal MD values) was higher than that of controls (values –0.80±0.81 dB and 0.04±1.03 dB, respectively, $p<0.01$); the CPSD hemifield difference was similar to that of controls (–0.28±0.71 dB and –0.28±0.56 dB, respectively, $p>0.05$). Mean values are reported in Table III.

In OHT patients, the MD hemifield differences evaluated in the last HFA examination and as the mean of six HFA examinations (Fig. 3) were significantly correlated with the IDs (r: 0.836, $p<0.01$ and r: 0.823, $p<0.01$, respectively); the CPSD hemifield differences, evaluated in the last HFA examination and as the mean of six HFA examinations, were significantly correlated with the IDs (r: 0.744, $p<0.01$ and r: 0.722, $p<0.01$, respectively). Other correlations between VEP and perimetric parameters are shown in Table IV.

DISCUSSION

The present study aims to evaluate the different neural conduction along crossed and uncrossed visual pathways in OHT patients. In our OHT patients, full-field VEP responses were recorded simultaneously and separately in each occipital cortex (O1 and O2) (10). This represents a novel finding with respect to previous studies (1-7) in which VEP responses were recorded by means of a single electrode centrally placed over both occipital lobes, obtaining a mass response of both visual cortices.

Our OHT patients showed longer VEP implicit times with respect to controls, suggesting the presence of an early delay in neural conduction notwithstanding the absence of perimetric alterations. In addition, in our OHT patients we found an asymmetry in the bioelectrical cortical responses of the homolateral and contralateral cortex to the stimulated eye, with a prevalent delay in neural conduction along crossed visual pathways.

Our findings could indicate that in OHT patients the different neural conduction along crossed and uncrossed visual pathways is more comparable to that observed in patients with early stages of glaucoma (in which a prevalent delay in crossed visual pathways was found (9)) than that of normal subjects in which the neural conduction along crossed and uncrossed visual pathways is symmetric. In patients with glaucoma, abnormal VEP responses result from the combined dysfunction of retinal and postretinal components (13-16), as suggested by the correlation between the reduction in nerve fiber layer (NFL) thick-

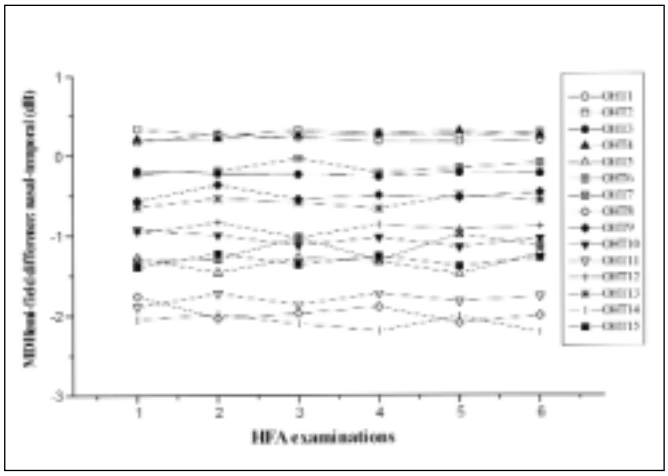

Fig. 2 - *Ocular hypertension (OHT) patients: individual hemifield mean deviation (MD) differences (difference between nasal and temporal hemifields' MD values) of Humphrey 24/2 (HFA) observed in the six visual field examinations.*

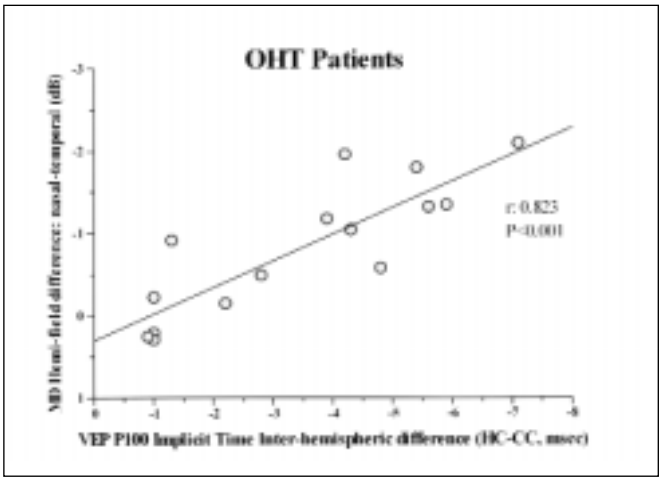

Fig. 3 - *Ocular hypertension (OHT) patients: visual evoked potential (VEP) P100 implicit time interhemispheric difference (P100 implicit time in homolateral cortex – P100 implicit time in contralateral cortex) plotted versus the mean values of the hemifield mean deviation (MD) differences (difference between nasal and temporal hemifield MD values) of six HFA examinations (Humphrey 24/2).*

ness and the decrease in PERG amplitude, and the absence of correlation between the reduction in NFL thickness and the increase in VEP implicit time (15). These electrofunctional observations are supported by the anatomic evidence of the involvement not only of retinal components (17-20), but also of other visual structures, such as the lateral geniculate nucleus (21-24).

On the other hand, the presence of abnormal PERG responses with normal values of retino-cortical time

TABLE I - CLINICAL, ELECTROPHYSIOLOGIC, AND VISUAL FIELD CHARACTERISTICS OF OCULAR

Patients	Age	IOP	VEP P100 implicit time (msec) Homolateral cortex (msec)	VEP P100 implicit time (msec) Contralateral cortex (msec)
OHT1	45	24	119.3	120.3
OHT2	61	26	117.2	118.2
OHT3	65	24	99.6	100.6
OHT4	62	25	115.3	116.2
OHT5	48	23	106.4	112.3
OHT6	61	24	121.1	123.3
OHT7	64	26	108.4	112.3
OHT8	61	25	108.6	112.8
OHT9	68	26	104.3	107.1
OHT10	62	25	121.3	125.6
OHT11	52	24	113.8	119.2
OHT12	66	26	106.1	107.3
OHT13	64	27	111.7	117.3
OHT14	62	24	111.2	118.3
OHT15	56	26	114.4	119.2

The Humphrey 24/2: A values refer to the last of the six examinations carried out. The Humphrey 24/2: B values refer to the mean of the six examinations
IOP = Intraocular pressure; VEP = Visual evoked potential; MD = Mean deviation; CPSD = Corrected pattern standard deviation

(the electrophysiologic index of postretinal neural conduction) (2) and the positive correlation between NFL thickness and VEP implicit time (3) suggest that the delayed VEP responses observed in OHT patients, differently from manifest glaucoma, may be ascribed to the selective involvement of the innermost retinal layers (ganglion cells and their fibers) without the contribution of postretinal components.

The asymmetry in VEP responses of OHT patients is consistent with the asymmetry found in the visual hemifield perimetric evaluation. In fact, our OHT patients showed MD values in the temporal hemifield higher than those of the nasal hemifield and, interestingly, the interhemispheric VEP difference and the MD hemifield difference are correlated.

Some considerations should be made regarding the perimetric findings of our OHT patients. Each patient had significant experience with HFA perimetry considering that six consecutive HFA examinations had been performed since the diagnosis of OHT (more or less 1 year before). The last two examinations were carried out in the month preceding the VEP recording, and the last one was considered for the statistical analysis. These repeated HFA examinations were performed in order to reduce the learning effect and to obtain reliable HFA findings. In all HFA examinations, OHT patients showed an MD >–2 dB and CPSD <2 dB, with a very small HFA intraindividual variability (about 0.2 dB), and all HFA examinations showed the same MD hemifield difference (see Fig. 2). This led us to believe that the results observed in our OHT patients could not be due to a selection bias caused by the HFA examination used in the statistical analysis.

Considering the lack of participation of postretinal structures in the visual impairment of OHT patients (2, 3), the interpretation of the visual hemifield and VEP interhemispheric differences leads to a possible speculation regarding the early prevalent damage of the nasal retinal components from which the crossed fibers originate.

This selective damage might be related to the particular anatomic structure of this retinal sector. Indeed, the nasal area is known to have a lower cell density, consisting principally of ganglion cells with axons of great dimensions. These cells are known as M cells, and have been implicated as the initial origin of the glaucomatous damage (17, 18). The prevalent presence of M cells and the lower NFL thickness of the nasal quadrants, observed both in normal sub-

TABLE I - *(continued)*

Patients	VEP P100 implicit time (msec) Interhemispheric difference (Homolateral – Contralateral) (msec)	Humphrey 24/2: A		Humphrey 24/2:A MD difference between nasal and temporal hemifields (N–T, dB)	Humphrey 24/2:B MD Difference between nasal and temporal hemifields (N–T, dB)
		MD(dB), C	PSD(dB)		
OHT1	–1	–0.93	1.01	0.2	0.210
OHT2	–1	–0.65	0	0.29	0.290
OHT3	–1	–0.22	0.94	–0.22	–0.222
OHT4	–0.9	–1.08	0	0.25	0.255
OHT5	–5.9	–1.26	0	–1.22	–1.338
OHT6	–2.2	–0.28	1.09	–0.09	–0.148
OHT7	–3.9	–1.67	0	–1.13	–1.175
OHT8	–4.2	0.23	0.23	–2	–1.957
OHT9	–2.8	–1.22	0.37	–0.46	–0.488
OHT10	–4.3	–0.86	–0.17	–1.03	–1.037
OHT11	–5.4	0.44	0.44	–1.76	–1.795
OHT12	–1.3	–1.07	–1.07	–0.88	–0.913
OHT13	–5.6	–1.89	–1.89	–0.56	–0.577
OHT14	–7.1	–1.75	0.79	–2.21	–2.090
OHT15	–4.8	–1.25	0.37	–1.28	–1.313

jects and OHT patients (25), suggest the possibility of a greater vulnerability of this retinal sector toward the hypertensive stimulus implicated in the pathogenesis of the glaucomatous dysfunction.

Our electrophysiologic and perimetric results could be in part explained by anatomic studies evaluating the selective involvement of retinal sectors in experimental or human glaucoma. In the first published studies, the loss of fibers was initially suggested as originating from the temporal retina (17), but subsequent autopsic studies of glaucomatous patients revealed contradictory results: in half of the patients the loss was greatest in the inferior nerve sectors, while in the other half those same areas were the most preserved (18). These results might appear in contrast with our data (supposed early impairment in the nasal sector), but these morphologic findings (17, 18) were observed in more advanced stages of glaucoma than those in which our previous (13) or present electrophysiologic evaluations were assessed.

In the absence of anatomic studies evaluating the very early changes occurring in retinal structures in the presence of increased IOP, it is only possible to speculate on the different vulnerability of the nasal and temporal retinal structures during the evolution of the glaucomatous disease. In fact, the early electrophysiologic abnormalities observed in these OHT patients and in the early stages of glaucoma (9) are present in a condition in which the typical initial perimetric defects (nasal step or nasal arcuate scotoma) have not developed. The onset of the above mentioned visual field defects may indicate a dysfunction of the temporal retina that could occur in more advanced stages of glaucoma than those considered in our present and previous studies (9). It could be hypothesized that the initial dysfunction may develop in the nasal retina, but that the loss of ganglion cells producing the typical visual field defects could successively appear in the temporal retina.

In order to further study our observations, it would be interesting to evaluate the function of the innermost retinal layers (ganglion cells and their fibers) in the different retinal sectors independently. Since we believe that the stray-light effect does not allow the recording of PERGs with a hemifield stimulation (26), the functional assessment of the individual areas of the retina with this method is not possible.

The introduction of a novel technique, multifocal ERG (MERG), which allows the topographic testing of the function of the retina (27), might provide an important contribution in the assessment of the function of the different retinal sectors, and thus could be of aid

TABLE II - MEAN VALUES ± ONE STANDARD DEVIATION OF VEP PARAMETERS

Group	VEP 100 implicit time in homolateral cortex (msec)	VEP P100 implicit time in contralateral cortex (msec)	VEP P100 ID (msec)
Controls (n=15)	101.6±2.2	102.1±2.6	1.16±1.04
Ocular hypertension (n=15)	111.91±6.40*	115.33±6.65*	–3.43±2.11*

Analysis of variance with respect to control eyes: *p<0.01.
VEP ID = Visual evoked potential interhemispheric differences: P100 implicit time in homolateral cortex – P100 implicit time in contralateral cortex

TABLE III - MEAN VALUES ± ONE STANDARD DEVIATION OF HUMPHREY 24/2 PARAMETERS

Group	Humphrey 24/2 MD (dB)				Humphrey 24/2 CPSD (dB)			
	Total	Nasal	Temporal	N–T	Total	Nasal	Temporal	N–T
Controls (n=15)	–0.92±0.56	–1.19±0.65	–1.39±1.21	0.07±0.89	0.41±0.54	–0.72±0.5	–1.01±0.83	–0.28±0.56
Ocular Hypertension (n=15)	–0.89±0.62	–0.83±0.56	–1.57±0.94	–0.80±0.81*	0.14±0.78	0.59±1.04	–0.03±1.86	–0.28±0.71

Analysis of variance with respect to control eyes: *p<0.01.
N–T = Difference between nasal and temporal hemi-fields

TABLE IV - CORRELATION BETWEEN VEP P100 IMPLICIT TIMES AND HUMPHREY 24/2 PARAMETERS IN OCULAR HYPERTENSION PATIENTS

Versus	VEP 100 implicit time in homolateral cortex	VEP P100 implicit time in contralateral cortex	VEP P100 implicit time interhemispheric difference
MD full-field	r: 0.08, p=0.77	r: 0.005, p=0.98	r: 0.26, p=0.34
CPSD full-field	r: 0.42, p=0.11	r: 0.965, p=0.81	r: 0.16, p=0.55
MD in temporal hemifield	—	r: 0.157, p=0.57	—
CPSD in temporal hemifield	—	r: 0.098, p=0.76	—
MD in nasal hemifield	r: 0.536, p=0.028	—	—
CPSD in nasal hemifield	r: 0.433, p=0.11	—	—
MD hemifield difference (nasal – temporal)	—	—	r: 0.836, p<0.01
CPSD hemifield difference (nasal – temporal)	—	—	r: 0.744, p<0.01

VEP ID = Visual evoked potential interhemispheric differences; MD = Mean deviation; CPSD = Corrected pattern standard deviation

in further evaluating the early asymmetry revealed in our study. At present, there are no data in the literature regarding different MERG responses in the nasal and temporal retina of OHT or glaucoma patients.

Our study introduces the possibility of a temporal evolution of glaucomatous damage. In the early stages of the disease, the electrophysiologic and perimetric results obtained in OHT patients suggest that the dysfunction originates in the nasal retina with consequent prevalent delay in neural conduction along crossed visual pathways.

The correlation between electrophysiologic and perimetric results also suggests that, in the early assessment of patients with OHT, the evaluation of the differences between the nasal and temporal perimetric values could be useful in identifying early signs of damage.

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