Pattern Electroretinogram and Ganglionar Cells Suffering in Ocular Hypertensive Patients

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Abstract

Purpose/Objective: The purpose of this study is to evaluate the changes in pattern electroretinogram (pERG) (P50 wave, N95 wave and NP index) in patients with ocular hypertension (OH) who were treated or not. Also to detect from these changes if there are any changes in retinal ganglion cell (RGC) function and if this could be reversible.

Methods: We performed a prospective study with 126 patients (197 eyes) classified into 3 groups: Patients with OH who were treated with ocular hypotensive drops (80 eyes), patients with OH who were not treated (69 eyes) and a control group with 48 healthy eyes. We studied the changes in pERG values between initial exploration and a follow-up after 6 months.

Results: We observed a statistically significant improvement (p<0.05) in mean amplitudes in waves P50, N95 and NP index in the group of treated patients with OH. In the group of non-treated patients with OH, a sustained high intraocular pressure was statistically significant (p<0.05) associated with the worsening of the same amplitudes. These alterations were not observed in the control group. No statistical differences were found in wave latencies.

Conclusion: The finding in successive pERG of a worsening in P50, N95 waves and NP index in non-treated patients with OH would support an early hypotensive treatment to revert functional RGC alteration before a structural irreversible damage is caused.

INTRODUCTION

Primary open angle glaucoma (POAG) is the second-leading cause of blindness in the world [1]. Patients with POAG have a slowly progressive RGC loss that can produce irreversible defects in visual field when more than 40-50% of the optic nerve axons are damaged [2,3]. At present, treatment of OH in these patients is still the only proven measure we can take.

Given this evidence, in the last decades there have been studies about anatomic glaucomatous defects that help make an earlier diagnosis. Sample (1994) proposed that RGC disfunction should be studied before early anatomic changes are caused by cell death [4]. The ideal method for an early diagnosis of glaucoma should be able to detect patients with OH with incipient RGC functional defects and thus treatment could be given before damage becomes irreversible.

Our study has focused on electrophysiology techniques like pattern electroretinogram (pERG) changes in patients with OH.

pERG is done by stimulating central retina in a geometrical pattern like reversible white or black checkerboard or lines with controlled contrast and brightness and focusing on central point (5). The record has 2 responses (Figure 1):

- One made from local brightness changes and originated from the same cells as in the classic Flash electroretinogram. It is represented in the P50 wave of the pERG (positive wave around 50 ms).
Another specific of the structured stimulus generated from the RGC [6,7]. It is represented in the N95 wave of the pERG (negative wave around 95 ms).

MATERIALS AND METHODS

We performed a prospective study including 126 patients (197 eyes) attended at Hospital Sanitas La Zarzuela (Madrid) between January 2013 and June 2014. The study got approval from the hospital ethics committee. Patient data reviewed were sex, age, lateral and visual acuity. Anterior segment was evaluated by slit lamp biomicroscopy as well as gonioscopy to grade angle amplitude and possible signs responsible of OH. Fundus was explored in all patients with ophthalmoscopy and precorneal lens to evaluate glaucomatous signs in the optic disk and retinal nerve fiber layer (RNFL). Humphrey automated threshold perimetry (model HFA II, program SITA 24-2, Goldman III stimulus) was performed. Intraocular pressure (IOP) was measured with Goldman application tonometry. Optical coherence tomography (OCT) was performed (Zeiss Stratus).

Patients were classified into 3 groups: Patients with OH who were treated with ocular hypotensive drops (80 eyes), patients with OH not treated (69 eyes) and a control group with 48 healthy eyes. We studied the changes in pERG values between initial exploration and follow-up at 6-8 months. pERG parameters evaluated were N35, P50 and N95 waves and NP index (P50-N95). SPSS program was used for data recovery. Wilcoxon signed-rank test was used for statistical analysis. Inclusion criteria are showed in (Table 1).

RESULTS AND DISCUSSION

We observed a statistically significant (p<0.05) improvement in average amplitude in waves P50, N95 and NP index in the group of treated patients with OH. The group of non treated patients with OH showed a sustained high IOP with worsening of the same average amplitudes. These alterations were not observed in the control group. No statistical differences in wave latencies were found.

Control group descriptive characteristics

We included 48 eyes of 24 healthy patients. Gender distribution was 54.2% of males (13 patients) and 45.8% of females (11 patients). Age mean was 50.63 ± 10.88 years. 52% were right eyes (25 eyes) and 48% left eyes (23 eyes). Mean basal IOP was 16.3 mmHg.

Table (2) shows average amplitudes (µV) and latencies (ms) of N35, P50 and N95 waves and NP index from pERG done at the beginning of the study (exploration 1) and at 6 months (exploration 2).

No statistically significant differences of these values between exploration 1 and 2 were found after using Wilcoxon signed-rank test for statistical analysis (Table 3).

Non-treated patients with OH group descriptive characteristics

Gender distribution was 52.5% of males (21 patients) and 47.5% of females (19 patients). Age mean was 58.88 ± 8.88 years. 49.3% were right eyes and 50.7% left eyes. 29% of patients had family history of glaucoma. Basal IOP mean was 23.88 ± 1 mmHg. Central corneal pachymetry mean was 536.26 ± 25.47 micras. Visual field index showed a MD mean of 1.28 ± 1.21 and a PSD mean of 1.86 ± 0.61. OCT analysis showed a RNFL thickness mean of 87.75 ± 6.2 µm and a cup to disk ratio mean of 0.51 ± 0.19.

Table 4 shows average amplitudes (µV) and latencies (ms) of N35, P50 and N95 waves and NP index from pERG done at the beginning of the study (exploration 1) and at 6 months (exploration 2).

Statistically significant differences of P50 and N95 waves and NP index amplitudes (µV) between exploration 1 and 2 were found after using Wilcoxon signed-rank test for statistical analysis (Table 5).

Treated patients with OH group descriptive characteristics

Gender distribution was 55% of males (22 patients) and 45%...
Table 2: Average amplitudes (μV) and latencies (ms) of N35, P50 and N95 waves and NP index from pERG done at the beginning of the study (exploration 1) and at 6 months (exploration 2) on control group.

<table>
<thead>
<tr>
<th>Exploration 1</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Exploration 2</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N35ms1</td>
<td>29,979</td>
<td>3,0561</td>
<td>N35ms2</td>
<td>30,38</td>
<td>2,818</td>
</tr>
<tr>
<td>P50ms1</td>
<td>53,042</td>
<td>6,0809</td>
<td>P50ms2</td>
<td>51,00</td>
<td>5,006</td>
</tr>
<tr>
<td>P50microV1</td>
<td>3,0192</td>
<td>0,88752</td>
<td>P50microV2</td>
<td>4,9663</td>
<td>9,630</td>
</tr>
<tr>
<td>N95ms1</td>
<td>92,854</td>
<td>6,9159</td>
<td>N95ms2</td>
<td>94,96</td>
<td>7,377</td>
</tr>
<tr>
<td>N95microV1</td>
<td>1,4696</td>
<td>0,48519</td>
<td>N95microV2</td>
<td>1,47438</td>
<td>0,470</td>
</tr>
<tr>
<td>NPMicroV1</td>
<td>4,9177</td>
<td>1,34545</td>
<td>NPMicroV2</td>
<td>4,9200</td>
<td>1,352</td>
</tr>
</tbody>
</table>

Table 3: Contrast statistical test between exploration 1 and 2 on control group.

<table>
<thead>
<tr>
<th>N35ms2 - N35ms1</th>
<th>P50ms2 - P50ms1</th>
<th>P50µV2 - P50µV1</th>
<th>N95ms2 - N95ms1</th>
<th>N95 µV2 - N95 µV1</th>
<th>NP µV2 - NP µV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z</td>
<td>-0,975</td>
<td>-1,034</td>
<td>-1,807</td>
<td>-0,606</td>
<td>-0,339</td>
</tr>
<tr>
<td>Sig. asintót. (bilat)</td>
<td>0,329</td>
<td>0,301</td>
<td>0,071</td>
<td>0,545</td>
<td>0,735</td>
</tr>
</tbody>
</table>

Abbreviations: μV: microvolts; ms: milliseconds

Table 4: Average amplitudes (μV) and latencies (ms) of N35, P50 and N95 waves and NP index from pERG done at the beginning of the study (exploration 1) and at 6 months (exploration 2) on OH group non treated.

<table>
<thead>
<tr>
<th>Exploration 1</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Exploration 2</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N35ms1</td>
<td>29,087</td>
<td>5,4819</td>
<td>N35ms2</td>
<td>29,81</td>
<td>5,103</td>
</tr>
<tr>
<td>P50ms1</td>
<td>52,188</td>
<td>3,8051</td>
<td>P50ms2</td>
<td>53,120</td>
<td>3,81</td>
</tr>
<tr>
<td>P50microV1</td>
<td>2,059</td>
<td>0,82353</td>
<td>P50microV2</td>
<td>1,735</td>
<td>0,670</td>
</tr>
<tr>
<td>N95ms1</td>
<td>91,130</td>
<td>13,708</td>
<td>N95ms2</td>
<td>91,24</td>
<td>17,331</td>
</tr>
<tr>
<td>N95microV1</td>
<td>1,145</td>
<td>0,84756</td>
<td>N95microV2</td>
<td>0,9025</td>
<td>0,514</td>
</tr>
<tr>
<td>NPMicroV1</td>
<td>3,429</td>
<td>1,30338</td>
<td>NPMicroV2</td>
<td>2,876</td>
<td>1,259</td>
</tr>
</tbody>
</table>

Abbreviations: μV: microvolts; ms: milliseconds

Table 5: Contrast statistical test between exploration 1 and 2 on OH group non treated.

<table>
<thead>
<tr>
<th>N35ms2 - N35ms1</th>
<th>P50ms2 - P50ms1</th>
<th>P50µV2 - P50µV1</th>
<th>N95ms2 - N95ms1</th>
<th>N95 µV2 - N95 µV1</th>
<th>NP µV2 - NP µV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z</td>
<td>-0,995</td>
<td>-1,877</td>
<td>-5,162</td>
<td>-0,790</td>
<td>-5,469</td>
</tr>
<tr>
<td>Sig. asintót. (bilat)</td>
<td>0,320</td>
<td>0,660</td>
<td>0,429</td>
<td>0,000</td>
<td>0,000</td>
</tr>
</tbody>
</table>

Abbreviations: μV: microvolts; ms: milliseconds; OH: Ocular Hypertension

Table 6: Average amplitudes (μV) and latencies (ms) of N35, P50 and N95 waves and NP index from pERG done at the beginning of the study (exploration 1) and at 6 months later (exploration 2) on OH group treated.

<table>
<thead>
<tr>
<th>Exploration 1</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Exploration 2</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N35ms1</td>
<td>30,038</td>
<td>5,46</td>
<td>N35ms2</td>
<td>28,94</td>
<td>5,302</td>
</tr>
<tr>
<td>P50ms1</td>
<td>55,100</td>
<td>5,705</td>
<td>P50ms2</td>
<td>53,68</td>
<td>5,456</td>
</tr>
<tr>
<td>P50microV1</td>
<td>1,933</td>
<td>0,84756</td>
<td>P50microV2</td>
<td>2,866</td>
<td>0,735</td>
</tr>
<tr>
<td>N95ms1</td>
<td>92,838</td>
<td>13,245</td>
<td>N95ms2</td>
<td>90,93</td>
<td>13,122</td>
</tr>
<tr>
<td>N95microV1</td>
<td>0,800</td>
<td>0,515</td>
<td>N95microV2</td>
<td>1,048</td>
<td>0,820</td>
</tr>
<tr>
<td>NPMicroV1</td>
<td>2,839</td>
<td>1,801</td>
<td>NPMicroV2</td>
<td>3,104</td>
<td>1,253</td>
</tr>
</tbody>
</table>

Abbreviations: μV: microvolts; ms: milliseconds; OH: Ocular Hypertension

Table 7: Contrast statistical test between exploration 1 and 2 on OH group treated.

<table>
<thead>
<tr>
<th>N35ms2 - N35ms1</th>
<th>P50ms2 - P50ms1</th>
<th>P50µV2 - P50µV1</th>
<th>N95ms2 - N95ms1</th>
<th>N95 µV2 - N95 µV1</th>
<th>NP µV2 - µV1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z</td>
<td>-1,492</td>
<td>-1,792</td>
<td>-5,926</td>
<td>-0,831</td>
<td>-7,742</td>
</tr>
<tr>
<td>Sig. asintót. (bilat)</td>
<td>0,136</td>
<td>0,073</td>
<td>0,406</td>
<td>0,000</td>
<td>0,000</td>
</tr>
</tbody>
</table>

Abbreviations: μV: microvolts; ms: milliseconds; OH: Ocular Hypertension

Table 3: Contrast statistical test between exploration 1 and 2 on control group.

Table IV: Contrast statistical test between exploration 1 and 2 on control group.

Table V: Contrast statistical test between exploration 1 and 2 on OH group non treated.

Table VI: Contrast statistical test between exploration 1 and 2 on OH group treated.

Table VII: Contrast statistical test between exploration 1 and 2 on OH group treated.
of females (18 patients). Age mean was 58.53 ± 12.17 years. 51.3% were right eyes and 48.8% left eyes. 32.5% of patients had family history of glaucoma. Basal IOP mean was 24.63 ± 1.64 mmHg. Central corneal pachymetry mean was 549 ± 32.7 micras.

Visual field index showed and MD mean of 1.067 ± 1.34 and a PSD mean of 1.75 ± 0.528.

OCT analysis showed an RNFL thickness mean of 89.55 ± 9 μm and a cup to disc ratio mean of 0.53 ± 0.17.

Table 6 shows average amplitudes (μV) and latencies (ms) of N35, P50 and N95 waves and NP index from pERG done at the beginning of the study (exploration 1) and at 6 months (exploration 2).

Statistically significant differences of P50 and N95 waves and NP index amplitudes (μV) between exploration 1 and 2 were found after using Wilcoxon signed-rank test for statistical analysis (Table 7).

DISCUSSION

Primary open angle glaucoma (POAG) is a progressive optic neuropathy with a characteristic acquired loss of retinal ganglion cells (RGC). It is important to make an early diagnosis before this neurological damage becomes irreversible. Given that POAG is the second-leading cause of blindness in the world [1], early diagnosis is also an important economic factor so that early appropriate treatment would improve prognosis and prevent further consequences.

In our study, we tried to show if a sustained high IOP in patients with OH would modify RGC function detected with pERG.

Studies published to date about pERG changes in patients with confirmed glaucoma or glaucoma suspects are controversial. Some authors described a reduction in pERG amplitudes, higher in P50 wave (60% reduction) than in N95 wave (23% reduction), both in glaucoma patients and glaucoma suspects [8,9]. However, other studies concluded that the best discrimination is obtained with N95 wave amplitude (85% sensitivity and 88% specificity), followed by NP index amplitude (73% sensitivity and 85% specificity) [10-14].

In our study, we observed in the group of non-treated patients with OH a worsening in successive pERG test in mean amplitudes of P50 and N95 waves and especially in NP index; changes were statistically significant. Both waves and NP index alterations suggest that initial damage may be diffuse, so it is not limited to a particular element in the visual system (magnocellular or parvocellular). Although there are ganglion cells populations more prone to glaucomatous damage.

On the contrary, we observed that giving treatment in the group of patients with OH who were not previously treated improves mean amplitudes of P50 and N95 waves as well as NP index in successive pERG test. This finding backs up the idea that damage to RGC could be reversible at least in the beginning.

Moreover, since pERG has, in longitudinal studies, to have a predictive value for the development of visual field defects in glaucomatous eyes [15-20] and that patients with OH who developed visual field defects had an abnormal pERG 2 years before [21-24], we should do a close follow-up of patients with OH who show changes in the pERG. If worsening of the pERG amplitudes are found, early hypotensive treatment should be given as it is very likely that sooner or later this eye will suffer an irreversible visual field. Therefore, the best utility of pERG in these patients is when glaucoma is very incipient and the rest of the tests are normal.

CONCLUSION

pERG is able to detect functional RGC damage in patients with OH before white-on-white perimetry. Therefore, the worsening of successive explorations of P50 and N95 waves and NP index amplitudes in non-treated patients with OH would justify early hypotensive treatment to reverse this functional alteration before irreversible structural damage is made.

REFERENCES


