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Electrophysiologic evaluation of amblyopia

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Abstract

Purpose: To compare amblyopic eyes and other eyes of the unilaterally amblyopic patients in the terms of pattern visual evoked potentials (pVEP), pattern electroretinogram (pERG) and flash electroretinogram(fERG) tests.

Methods: This study was performed at Ankara Numune Training and Research Hospital between November-2015 and August-2016. Forty-one patients above the age of 15 with anisometropic amblyopia were evaluated for their amblyopic and other eyes. The patients were tested by Metrovision brand monpack model visual electrophysiology device for pVEP, fERG and pERG tests. Mean latance and amplitudes were examined statistically.

Results: A statistically significant difference was found in decrease of P100 amplitude ($p<0.05$) and increase of P100 latency ($p<0.01$) of amblyopic eyes in all 5 patterns pVEP recorded. In pERG results P50 and N95 wave amplitudes were decreased in amblyopic eyes ($p<0.01$) but there was no statistical difference in latency period between amblyopic eyes and other eyes ($p>0.05$). In fERG results, rod response b wave amplitudes was lower and latency was increased in amblyopic eyes ($p<0.01$). However cone responses were no statistical difference in amblyopic and other eyes ($p>0.05$).

Conclusion: According to our results, amblyopia is not only a cortical pathology. Also cortico-retinal pathologies that can not be detected by routine opthalmologic examination may accompany amblyopia. pERG, fERG and pVEP are objective methods for diagnosis and follow up of amblyopic patients and valuable guides for clinicians.

Introduction

Amblyopia is the decrease of functional vision without any obvious ocular pathology in opthalmologic examination of the patient. Amblyopia is mostly unilateral but this is not a rule and bilateral involvement is also seen. Most common causes amblyopia are; occlusion therapy, media opacity, anisometropia, strabismus and uncorrected high refractive error.

Many studies are performed to highlight the mechanism of amblyopia. Electrophysiological tests are used to study the mechanism of decreased visual acuity and the location of major defects and their depth. Pattern visual evoked potential (PVEP) test results of human eyes with amblypia showed attenuated amplitudes and prolonged latencies in studies. [1-3]

Although the loss of visual acuity in amblyopia is considered to be cortical in origin, it remains unclear whether the retina is also affected in patients with amblyopia. [4-8]

Functionally, suppression of eye with amblyopia causes loss of binocular neuron function in the visual cortex [9,10]. Histopathologic changes in lateral geniculate nucleus of eyes with amblyopia were explained in previous animal and human studies. [11-15]

Ganglion cells are the third neurons of the visual pathways. Nearly 700.000- 2.000.000 ganglion cells are present in human eye. Mainly two types of ganglion cells are defined in retina. Large (Y) ganglions collect responses of various cones, have fast and temporary responses and are related with motion and three-dimensional vision. Small (X) ganglions receive outputs of different cones and are related with color, structure and shape vision. Y ganglion cells radiate to magnocellular part of the lateral geniculate nucleus whereas X ganglion cells radiate to parvocellular part. High visual acuity of fovea was provided by X ganglion cells. X ganglion cell functions are decreased in eyes with amblyopia because of deprivation of structured vision in critical period of childhood [11-17]

Electrophysiological tests provide assessment of the complete visual pathway extending from the ganglion cells to occipital cortex. PVEP is a cortical cell response to a pattern stimulation and is a sensitive indicator of optic nerve functions. Potentials arise in fotoreceptor cells and arrive to bipolar cells and then ganglion cells where they become nerve impulses. Nerve impulses arrive to lateral geniculate nucleus (LGN) from optic nerve. fERG records the changes of retinal electric potentials evoked by light stimulation. Patients without any fundus pathology also may have abnormalities in the test. PERG is a retinal cell response to pattern stimulation. This response reflects macula and ganglion cell functions. [18-20]

Early treatment of amblyopia is essential for binocular visual development and depth perception. This study aims to compare the results of electrophysiological tests for diagnosis which may shed light on the pathophysiology of amblyopia.

Material and methods

This study was performed at Ankara Numune Training and Research Hospital between November 2015 and August 2016. Forty-

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one patients above the age of 15 with anisometropic amblyopia were evaluated for their eye with amblyopia and without amblyopia. Patients with a best corrected visual acuity (BCVA) (by Snellen chart) of 7/10 or less in an eye with amblyopia and 10/10 or more in the other eye and refractive error (cylindrical or spherical) of ±5.0 dioptric or less were included in the study. All patients underwent detailed ophthalmic examination. Patients with any organic pathology, eccentric fixation or previous amblyopia treatment history were excluded. All participants provided their informed consents. The study was conducted in accordance with the principles of Declaration of Helsinki.

Complete ophthalmic examination was performed and the patients were questioned in terms of systemic disease. In accordance to International Society for Clinical Electrophysiology of Vision (ISCEV) standards [20], the patients were tested by Metrovision brand monpack model visual electrophysiology device for pVEP, fERG and pERG tests.

PVEP simultaneously, using high-contrast (80%) checkerboard stimuli subtending the visual arc (min arc) 120', 60', 30', 15', 7' minutes. Retinal and visual pathway functions were assessed by ERG test. Rod, cone, and flicker potentials were compared. HK loop electrodes were used for ERG tests. During pERG test, stimulation was supplied from a television screen in the shape of a chessboard. Mean latency periods and amplitudes of both the eyes with amblyopia and contralateral eyes were examined. fERG and pVEP results of 41 patients and pERG results of 31 patients were evaluated both for the eyes with amblyopia and contralateral eyes.

The results of the eyes with amblyopia and without amblyopia were compared with each other, and the standard data of the healthy individuals at the same age. Student t test and Mann-Whitney U test were used for statistical analysis. $p<0.05$ was considered to be statistically significant.

Results

According to test results, statistically significant difference was found in decrease of P100 amplitude level ($p<0.05$) and in prolongation of P100 latency period ($p<0.01$) in eyes with amblyopia in all 5 patterns pVEP recorded (Table 1). Pattern responses of patients were coherent with their BCVA. In 120' pattern all 41 amblyopia patients (100%) had responses but only 18 amblyopia patients (37%) had responses in 15' pattern. In all patterns, mean amplitude values were decreased and mean latency periods were increased in eyes with amblyopia rather than contralateral eyes.

PERG results of 31 unilateral amblyopia patients were evaluated for the eye with ambylopia and contralateral eyes. N35 waves were not statistically different in two groups both for latency periods and amplitudes ($p>0.05$) P50 and N95 wave amplitudes were decreased in eyes with amblyopia ($p<0.01$), but latency periods were not statistically different between the eyes with amblyopia and contralateral eyes ($p>0.05$) (Table 2).

Amplitude of b waves were decreased and latency periods were prolonged in eyes with amblyopia in fERG rod responses ($p<0.01$). However fERG cone responses were similar in eyes with amblyopia and contralateral eyes ($p>0.05$). Oscillatory potential amplitudes were decreased in eyes with amblyopia to a statistically different level. Flicker b latance periods were prolonged in eyes with ambylopia according to fellow eyes whereas flicker b wave amplitudes were similar in two groups (Table 3 and 4).

Tablo 1. P100 latancy time of ambliyopic and another eyes and statistically analysis.

VEP patterns	N1/N2	p100 latancy (ms)		P value
		N_1(Mean±SD)	$N_{2(}$ Mean±SD)	
120'	41 / 41	111.33 ±11.55	102.46 ±3.53	p<0.05
60'	38 /41	113.63 ±14.02	104.67 ±7.99	p<0.05
30'	33 / 41	118.78 ±11.4	108.91 ±5.83	p<0.05
15'	18 / 41	135.22 ±14.21	119.56 ±8.89	p<0.05
7'	0 /41		123.68 ±25.06	

N_1: Numbers of ambliyopic eyes , N_2: Numbers of anothers eyes

Tablo 2. P100 amplitud of ambliyopic and another eyes and statistically analysis.

VEP patterns	N1/N2	p100 amplitude (mv)		P value
		N_1(Mean±SD)	N_2 (Mean±SD)	
120'	41 / 41	5.3 ±3.1	7.1±3.5	p<0.05
60'	38 /41	5.5±3.01	7.9±4.3	p<0.05
30'	33 / 41	5.31±2.5	8.72±5.8	p<0.05
15'	18 / 41	4.7±2.4	7.9±5.7	p<0.05
7'	0 /41		3.83±3.18	

N_1: Numbers of ambliyopic eyes , N_2: Numbers of anothers eyes

Tablo 3. P50 and N95 values of pERG

pERG (Mean±SD)	N_1 (n=31)	N_2 (n=31)	P value
P50 latancy	84.91 ±120	95.99 ±119.76	p>0.05
P50 amplitude	1.41 ± 0.52	2.01 ±0.61	p<0.05
N95 latancy	89.52 ±17.11	90.89 ±8.8	p>0.05
N95 amplitude	3.1 ± 0.79	4.38 ±1.4	p<0.05

N_1: Numbers of ambliyopic eyes , N_2: Numbers of anothers eyes

Table 4. Values off ERG parameters and statistically analysis.

f ERG parameters	N_1 (n=41) (mean±SE)	N_2 (n=41) (mean±SE)	P value
rod response (25db) b-wave amplitude	139 ±11	238 ±62.6	p<0.05
rod response (25db) b-wave latancy time	114.77±85.98	47,96 ±2,07	p<0.05
ossilatuar potential amplitude	19.37 ±7.01	15,64 ±3.17	p<0.05
cone response b-wave amplitude	73.75 ± 77.54	81.99 ±19.36	p>0.05
cone response b-wave latancy time	59.04 ± 77.55	38.16 ±47.69	p>0.05
flicker response	70.06 ±19.22	65.60 ±14.84	p>0.05

Discussion

Amblyopia is a common developmental visual disorder in humans. Although many studies are performed to highlight pathophysiology of amblyopia, our knowledge is still very limited. There were no studies about multi-directional electrophysiological evaluation of amblyopia in recent literature.

Electrophysiological tests can evaluate the visual system from the retinal pigment epithelium (RPE) to the occipital cortex objectively. In this study it was purposed to highlight pathophysiology of anisometropic amblyopia by electrophysiological tests and to investigate contribution of electrophysiological tests in diagnosis of amblyopia.

Cells in the striate cortex are defined as "ocular dominance columns" that are grouped into two which give electrophysiological response to each eye monocularly or to both eyes binocularly.[4,5] Hubel and Wiesel used radioactively marked aminoacids and reported that C4 part of ocular dominance columns in visual cortex were immature at birth.

Ocular dominance columns consist of 85% binocular and 15% monoocular response cells. In patients with amblyopia, it was shown that monocular response cells related to the eye with amblyopia in striate cortex and binocular response cells were decreased in number, laminar cells in LGN related to visual response were shrinked and response quality were decreased in rest of the cells [4,5].These changes could be detected by electrophysiological tests.

A large pattern (60' pattern) and a small pattern (15' pattern) are usually enough for pVEP records. Mostly, large pattern causes the parafoveal response and small pattern causes foveal response. In our electrophysiology laboratory five patterns are used for determination of visual acuity.

In study cases, 41 responses were recorded with 120' pattern and 18 responses were recorded with smaller 15' pattern. In the evaluation of patterns which could cause response, it was seen that eyes with amblyopia had lower mean amplitudes and prolonged mean latency periods than the contralateral eyes.

The results of the all patterns in anisometropic amblyopia suggest that the mean amplitude of P100 reduced in comparison with normal subjects and the mean latency was prolonged [4,21-25]. These findings confirm previous reports. Results of this study are consistent with literature and additionally more detailed because of five pattern usage.

Demer *et al.* [26] reported that VEP changes of eyes with amblyopia occurred because of inhibitor stimulation of the contralateral eye. Levi *et al.* [27] reported that decrease of P100 amplitude in eyes with amblyopia were caused by cortical neurons which get less impulse from the eyes with amblyopia. Prolonged pVEP latency periods of eyes with amblyopia may be related with prolonged conduction between retina and cortex.

Decreased P50 amplitude in pERG indicates retinal ganglion cell dysfunction in eyes with amblyopic. Arden *et al.* argued that the reduction of pERG in amblyopia occurs without a corresponding reduction in focal ERG and this reduction may differ according to the type of amblyopia.[28] Although decrease of amplitudes were related with refractive error, loss of fixation and patient compliance, these could not exclude a retinal disorder.[28] In the same study it was reported that occlusion therapy of the contralateral eyes caused decrease in pERG amplitudes by iatrogenic deprivation. Improvement of visual acuity by occlusion therapy was correlated with improvement in pERG amplitudes. pERG amplitudes were lower in cases with no visual acuity improvement by occlusion therapy [28].

Manny *et al.* described the relation between decreased P50 amplitude and retinal ganglion cell dysfunction. It is believed that ganglion cells are the main source for pERG responses.[21] On the other hand Guttob and his friends [29] and Hess *et al.* [30] stated that PERG is normal in any type of amblyopia. This study was undertaken to investigate the effect of amblyopia on both the retinal and cortical pattern responses [31].

In animal studies it was explained that changes of neurotransmitter functions in eyes with ambylopia may be related with decrease in P50 amplitudes. It is well known that neurotransmitters are active players for retinal responses. In this study P50 and N95 wave amplitudes of pERG were decreased significantly in eyes with ambylopia whereas latency periods were not statistically different than the contralateral eyes [27-30] .

Porciatti *et al.* searched in rats and found that pERG responses developed in parallel with pVEP results in postnatal period [31-32].

In our study, pERG P50 amplitudes were negatively correlated with pVEP P100 latency periods so decreased pERG P50 amplitudes were together with prolonged pVEP P100 latency periods. According to this results; decreased cortical responses were not only because of decreased number of cortical cells but also retinal dysfunction of the eyes with amblyopia.

N95 wave of pERG evaluates ganglion cell functions. In our study N95 amplitudes of eye with amblyopia were decreased which indicates that optic nerve dysfunction could accompany the retinal dysfunction in amblyopia. Decrease in pERG amplitudes could be attributed to ganglion cell dysfunction [33-35].

fERG is the record of a diffuse electrical response generated by neural and nonneuronal cells within the retina. The main components of ERG are a negative a-wave, and a positive b-wave. The a-wave appears in response to a bright flash in a dark-adapted eye, it largely reflects photoreceptor functions, but there may be a contribution from postreceptoral structures, particularly with low stimulus luminance. The b-wave, which is of higher amplitude than the a-wave in normal individuals, reflects post-phototransduction activity. It is largely produced in relation to optic nerve- (depolarising) bipolar cell function. The ISCEV standard ERG incorporates a rod-specific response to a dim light under scotopic conditions, and a standard; mixed rod–cone response to a bright white flash under dark adaptation. The latter response is dominated by rod function. A recent recommendation is an additional response to a brighter flash. The maximal ERGs shown below this stimulus demonstrate the a-wave better. Photopic ERGs are recorded both to a single flash (with adequate photopic adaptation and a rod-suppressing background) and to a 30 Hz flicker stimulus; rods are unable to respond to a 30 Hz stimulus due to poor temporal resolution. The ERG is a mass response, and therefore it is normal when dysfunction is confined to small retinal areas. This also applies to macular dysfunction; despite the high photoreceptor density, an eye with purely macular disease would have a normal ERG. [20]

Wanger *et al.* reported no difference between fERG results of the eyes with amblyopia and the contraleteral eyes of the patients but all cases had decreased pERG responses in eyes with ambylopia [35].

Slyshalova *et al.* did not find significant change in maximal rod-cone and flicker responses of fERG in eyes with amblyopia whereas some cases had lower amplitudes than normal levels in maximal rod-cone a waves and macular a and b waves [36,37]. In this study, rod response b wave and oscillatory potential amplitudes were lower and latency period was prolonged in eyes with amblyopia whereas cone and flicker responses were similar in eyes with amblyopia and other eyes. Based on the fERG results of this study, it can be speculated that rod responses and oscillatory potential amplitudes were effected but cones were not.

In literature there is no a consensus on fERG results of amblyopia cases. This can be attributed to different study designs, inclusion criteria of cases and different electrophysiology devices.

According to our results, amblyopia is not only a cortical pathology and retinal pathologies that cannot be detected by routine ophthalmic examination may accompany amblyopia. pERG, fERG and pVEP are objective methods for diagnosis and follow up of amblyopia patients and valuable guidance for clinicians.

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